Removal of cytostatic drugs from wastewater by an anaerobic osmotic membrane bioreactor

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Abstract

Cytostatic drugs, mainly used as chemotherapy compounds, can pose serious threats to aqueous ecosystem and human health once released into the natural environment. We investigated the use of an anaerobic osmotic membrane bioreactor (AnOMBR) for removing cytostatic drugs from wastewater. The AnOMBR utilizes a dense forward osmosis (FO) membrane in an anaerobic digester with prolonged sludge retention time (60 days). The high rejection of the FO membrane combined with the extended organic retention time in the reactor ensured high removal rates (more than 95.6%) for all the eight cytostatic drugs investigated. With regard to their removal routes in the AnOMBR, the eight cytostatic drugs can be divided into several groups. Doxorubicin, Epirubicin and Tamoxifen were nearly completely removed through the adsorption of anaerobic sludge, while Methotrexate and Cyclophosphamide were mainly removed by biodegradation and FO rejection, respectively. In addition, Mitotane, Azathioprine and Flutamide were removed by both biodegradation and adsorption. This work provides critical insights into the removal mechanisms of high-retention AnOMBRs.

Keywords: Cytostatic drugs; Osmotic membrane bioreactor; Forward osmosis; Anaerobic bioreactor; Wastewater treatment

1. Introduction

Trace organic compounds (TOrCs) including personal care products, endocrine-disrupting chemicals, pharmaceutically active compounds, disinfection byproducts and industrial chemicals have gained increasing concerns for their significant threats to the environment and human health [1,2]. Among the different types of TOrCs, cytostatic drugs (also known as antineoplastic drugs) are a broad group of chemotherapy compounds mainly applied for tumor treatments [3,4]. These drugs and their human metabolites can directly enter into the water cycle from the hospital effluent, household wastewater, production discharge and drug waste disposal [3-7]. As a final barrier, wastewater treatment plant plays a critical role in preventing their discharge to the environment [3].

Previous studies have demonstrated that the conventional wastewater treatment technologies such as activated sludge process are not able to achieve a satisfactory removal of cytostatic drugs on the basis of biodegradation and adsorption to biomass [3,8]. Membrane bioreactors (MBRs) have been applied as an alternative technology for removing cytostatic drugs [9-12]. Their removal efficiency varied among different cytostatic compounds, and those more hydrophilic and less biodegradable compounds are likely to appear in the treated effluent. For example, up to 90% of hydrophobic anthracyclines were removed primarily due to adsorption to sewage sludge [11], while only moderate elimination was achieved in the same system for the more hydrophilic cisplatin and carboplatin (51% and 63%, respectively) [9]. Kovalova et al. [12] observed a low elimination efficiency (< 20%) for cyclophosphamide through a MBR system fed with hospital's sanitary wastewater. In order to address the low removal of more hydrophilic and less biodegradable cytostatic drugs, dense reverse osmosis (RO) membrane or tight nanofiltration (NF)

membrane has been applied [3]. Previous studies have reported that thin film composite NF and RO membranes can efficiently reject most of the negatively-charged pharmaceuticals, while the rejection of neutral compounds mainly depends on their molecular weights [13-16]. However, related studies for cytostatic drugs are very limited [3], which indicates the need for further research efforts.

Recent achievements in the membrane technology have demonstrated forward osmosis (FO) as an effective alternative to conventional membrane processes for seawater desalination and water reclamation [17-19]. A typical FO membrane has a dense active layer with rejection properties on pair with RO membranes and is able to retain organic matter including small molecular compounds as well as nitrogen and phosphorus [17-22]. A recent review reports the FO removal of some 70 TOrCs [1]. Nevertheless, TOrCs are merely physically concentrated (as in the case of RO and NF) rather than chemically or biologically degraded.

We are inspired by the latest development of osmotic membrane bioreactors (OMBRs), where a dense FO membrane is used to retain dissolved organic matter in addition to suspended solids and biomass [23-34]. Due to the high retention nature of FO membrane, the residence time of TOrCs can theoretically approach the sludge retention time (SRT) in an OMBR, instead of the hydraulic retention time (HRT) as in a conventional MBR. This extended TrOC exposure time, i.e., trace organic retention time (TrORT), to the biological treatment may result in a synergistic effect on TrOCs' removal and degradation, an exciting possibility yet to be systematically investigated. The recent development of anaerobic osmotic membrane bioreactors (AnOMBRs) with prolonged SRT (e.g., ~ 60 d) may further enable enhanced TrOCs removal, which is on top of their efficient organic carbon removal (> 96%), biogas recovery (0.21 L/g COD), and nutrient removal (nearly

100% total phosphorus and 62% ammonia-nitrogen) [35-41].

In the current study, we applied an AnOMBR for cytostatic drugs removal. To the best knowledge of the authors, this is the first study for investigating the removal mechanisms of cytostatic drugs and their impacts on the performance of AnOMBRs. Our study provides important implications to the application and operation of AnOMBRs.

2. Materials and Methods

2.1 Experimental Set-up and Operating Conditions

A laboratory-scale AnOMBR with an effective volume of 3.6 L was operated at 25 °C. The AnOMBR was equipped with temperature, conductivity, pressure, pH and oxidation-reduction potential (ORP) monitoring units (Mettler-Toledo M200 system) following our previous studies [35,37]. A flat-sheet FO membrane made of thin-film composite (TFC) polyamide (Hydration Technologies Inc.) with 0.025 m^2 was submerged in the bioreactor. The membrane was oriented with the dense active layer facing the reactor and the support side facing the draw solution. The support layer was made of polysulfone, and its thickness was approximately 47.2 μm. The influent pump was controlled by a water level sensor to maintain a constant water level in the reactor. Produced biogas was recycled with a recirculation rate of 2 L/min to mix the biomass and to alleviate membrane fouling. A 0.5 M NaCl solution was used as the draw solution (with the conductivity in a range of 45.0-45.5 mS/cm), whose concentration was maintained constant by a conductivity controller connected to a 5 M NaCl solution tank. The flow rate of draw solution was kept at 0.4 L/min to minimize the effect of external concentration polarization. The permeate flux was derived by mass balance to account for the mass of 5 M NaCl dosed into the draw solution tank, and then normalized for the membrane area. During the entire AnOMBR operation, the SRT

was kept at 60 days, and the HRT was in a range of 15-40 h depending on the membrane flux.

The influent water of the AnOMBR was synthetic domestic wastewater, and its composition was summarized in Table S1. The total organic carbon (TOC), ammonia nitrogen (NH_4^+-N), total nitrogen (TN) and total phosphorus (TP) of the synthetic wastewater were 127.5 ± 12.7, 15.3 ± 1.0, 40.3 ± 1.2 and 5.3 ± 0.5 mg/L, respectively. Its conductivity and pH were 1.1 ± 0.1 mS/cm and 7 ± 0.1, respectively. The seed sludge was collected from a local wastewater treatment plant (Ulu Pandan Water Reclamation Plant, Singapore). Before the seed sludge was put into the reactor, it was cultivated in a fermentation flask with an effective volume of 5 L by the synthetic wastewater for about 30 days at the temperature of 25 ± 0.5 °C. The initial mixed liquor suspended solids (MLSS) in the AnOMBR was controlled at about 5 g/L. During the operation of the reactor, the conductivity of its mixed liquor will slowly increase. In the current study, the supernatant was discharged when the conductivity in the bioreactor reached about 20 mS/cm for controlling the salinity in the reactor, after which the FO membrane module was replaced with a new one and then a new operation cycle was started. Before adding cytostatic drugs into the bioreactor, the AnOMBR was operated for 78 days.

2.2 Cytostatic Drugs Addition

A group of 8 cytostatic drugs of high environmental relevance was tested in this study, including cyclophosphamide (CP), azathioprine (Aza), methotrexate (Met), doxorubicin (Dox), epirubicin (Epi), flutamide (Flu), mitotane (Mit), and tamoxifen (Tam), supplied by Sigma-Aldrich (Singapore) with high purity (≥ 98%). The internal standard cyclophosphamide-d_8 (CP-d_8) was obtained from TLC PharmaChem (Ontario, Canada). Individual stock solution of 1.0 g/L was prepared in HPLC-grade methanol (Merck, Singapore) and stored at -20 °C. A working solution

containing 1 mg/L of each compound was then prepared in deionized water, and then dosed into the AnOMBR system at two concentration levels of 100 ng/L and 100 µg/L on days of 84 and 87, respectively. The main physicochemical properties of target compounds are summarized in Table 1. The cytostatic drugs at each concentration level were continuously added into the reactor for 3 days, and the water samples including influent water, sludge supernatant and FO permeate and sludge samples in the bioreactor were collected before and after each adding experiment.

2.3 Batch Experiment Design

In order to distinguish the adsorption and biodegradation of biomass for the 8 cytostatic drugs in the AnOMBR, a batch experiment was carried out simultaneously. In the batch test, five 5 L glass beakers with 3 L mixed liquor were operated simultaneously at 25 ± 0.5 °C for 48 h following the three treatments (I, II and III) summarized in Table 2. All reactors were placed in a dark chamber to avoid possible photolysis. The same seed sludge used in the AnOMBR was applied in the batch test. The specific properties of the anaerobic sludge used in the batch test are listed in Table S2, which were similar as the anaerobic sludge in the AnOMBR before adding cytostatic drugs. The synthetic wastewater in the batch test was also same as the influent water of the AnOMBR. The cytostatic drugs were added with an aqueous stock solution mixture containing 1 mg/L of each cytostatic drug to obtain a final concentration of 100 µg/L. The mixing was supplied by the magnetic stirrers at 150 rpm. Water samples of sludge supernatant were collected from the batch reactors at the end of the experiment.

The removal routes for TOrCs in biomass are considered to be adsorption (A), biodegradation (B), volatilization (V) and hydrolysis (H) [3,42,43]. For Treatment I, R1 and R1′ were duplicate reactors in which all four removal routes occurred. For Treatment II, in duplicate reactors R2 and

R2′, biodegradation was excluded because the sludge was inhibited by NaN_3 (purity ≥ 99.5%, Sigma-Aldrich, Singapore). In Treatment III (R3), only volatilization and hydrolysis accounted for the elimination of cytostatic drugs. According to the experimental results, the parts removed by biodegradation (R_b) and adsorption (R_a) can be calculated based on differences between treatments as follows:

$$R_b = R_{\mathrm{I}} - R_{\mathrm{II}} \quad (1)$$

$$R_a = R_{\mathrm{II}} - R_{\mathrm{III}} \quad (2)$$

Based on the above equations, the removal rate of the drugs due to the biodegradation (η_b) and adsorption (η_a) in the batch test can be obtained in equ. (3) and (4), respectively.

$$\eta_b = \frac{R_b}{C_0} \times 100\% \quad (3)$$

$$\eta_a = \frac{R_a}{C_0} \times 100\% \quad (4)$$

where R_I, R_{II}, R_{III} are the reduced concentration of drugs in reactors of I, II and III, respectively, and C_0 is the initial concentration of the drugs in the mixed liquor.

2.4 Analysis of Cytostatic Drugs

The concentrations of cytostatic drugs in the feed water, sludge supernatant, and effluent samples were determined by solid-phase extraction (SPE) and liquid chromatography tandem mass spectrometry (LC-MS/MS) (LC-MS 8030, Simadzu, Japan) based on our previous methods [44]. In brief, sample extraction was performed with Strata-X SPE cartridges (6cc, 200 mg) (Phenomenex, Torrance, CA, USA) and high recovery rates (82%-121%) was obtained for all target compounds at pH 2. The target compounds were concentrated by 10-100-fold in different samples according to their dosage levels in the AnOMBR system. Aliquots of internal standard

solution were then spiked into each sample extract (1 mL) to obtain a spiking level of 100 µg/L. Cytostatic drugs were chromatographically separated using a Luna 3µ C18 (2) column (75 mm × 2.0 mm id, 3 µm) preceded by C18 guard column (4 mm × 3 mm id) (Phenomenex, Torrance, CA, USA) and eluted with gradient methanol-water binary phases (+ 0.1% formic acid). MS quantification was conducted in multiple-reaction monitoring (MRM) mode using two most intense ion transitions for both quantification and qualification purposes. The method detection limits for the target compounds were between 0.33 (Tam) and 14.7 ng/L (Mit).

2.5 General Analytical Methods

MLSS and mixed liquor volatile suspended solids (MLVSS) were measured according to standard methods [45]. Chemical oxygen demand (COD), NH_4^+-N, TN and TP concentrations were determined by the USEPS Reactor Digestion Method (HACH 2125915/2415815), Amver Salicylate Method (HACH 2606945), Persulfate Digestion Method (HACH 2714100/2672245) and Molybdovanadate Method (HACH 2767245), respectively. TOC was determined using a total organic carbon analyzer (Shimadzu, TOC-VCSH). The biogas generation rate was determined by liquid-displacement method, and the composition was analyzed by using GC equipped with thermal conductivity detector (GC-TCD) (Shimadzu, Singapore), where a J&W 113-4362 column (0.32 mm×60 m, 0 µm particle size) and Agilent 19095 P-MS6 column (0.53 mm×30 m, 50 µm particle size) were used [35]. Volatile fatty acids (VFAs) were analyzed by PerkineElmer HPLC system with H^+ cation exchange column (HAMILTON, 305 × 7.8 mm, 8-10 µm) and UV-Vis detection at 210 nm [35]. The specific methods for soluble microbial products (SMP) and bound extracellular polymer substances (BEPS) extractions from the sludge have been reported in previous literature [46]. Both SMP and BEPS extractions were normalized as the sum of protein

and polysaccharide, which were determined by modified Lowry method and phenol-sulphuric acid method, respectively [46]. Particle size distribution of sludge was analyzed by using laser scattering (Mastersizer 2000, Malvern). All the above analyses were conducted at least three times, and their mean values were reported.

3. Results and Discussion

3.1 Water Flux and Salt Accumulation in AnOMBR

The FO water flux and the conductivity in the AnOMBR are shown in Fig. 1. In each cycle, the salinity increased with the operation time, e.g., from an initial value of around 1.2 mS/cm to a final value of about 21 mS/cm in Cycle 1. The salinity build-up, attributed to the retention of solutes from the influent and reverse salt transport from the draw solution [35,37], was accompanied with a significant decrease in water flux. The rate of the flux decline (~ 0.31 LMH/d) in current study was slightly faster than that reported in our previous studies (~ 0.27 LMH/d) in AnOMBRs using cellulose triacetate (CTA) FO membranes [35,37], which can be partially explained by the greater fouling propensity of the TFC FO membrane used in the current study (as a result of its much rougher membrane surface) [30,47]. The biofouling induced by the polysaccharides, proteins and microorganisms played a dominant role in the fouling of TFC FO membrane [40], and its permeability could be effectively recovered by the chemical cleaning using H_2O_2 [39]. Nevertheless, there was no abrupt salt leakage in the TFC membrane indicating a good stability in current study, unlike CTA membrane that can be easily damaged by biodegradation and hydrolysis during the operation of AnOMBR [35].

3.2 Removal of Cytostatic Drugs

The AnOMBR achieved consistently high overall removals of the 8 cytostatic drugs studied

(Fig. 2). Dox, Epi, Flu, Mit and Tam were completely removed from the AnOMBR effluent irrespective of their dosing concentration. While Aza and Met achieved nearly 100% removal at a dosing concentration of 100 µg/L, their removal rates were lower (97.8% and 99.2%, respectively) at a lower dosage of 100 ng/L. A similar trend was observed for the removal of CP: its removal rate decreased from 99.3% to 95.6% as the dosing concentration decreased from 100 µg/L to 100 ng/L. The lower removal obtained at a dosing concentration of 100 ng/L might be caused by partial sorption of the compounds by the soluble organic compounds in the supernatant. Despite of the limited publications on the removal of cytostatic drugs, it is apparent that the removal of CP in the AnOMBR was much higher compared with those in conventional MBRs (ranging from 20% to 80%) [10,12]. This improved removal was attributed to the high rejection of FO membrane: the small-molecular-weight cytostatic drugs can be retained by an FO membrane whereas they leak through the porous ultrafiltration/microfiltration membranes used in conventional MBRs [3]. The prolonged exposure of the cytostatic compounds in the AnOMBR can further enhance their removals by the biomass through a combination of adsorption and biodegradation. Indeed, the AnOMBR was able to achieve much higher removal of CP compared to typical NF membranes (about 30% removal) and RO membranes (~ or > 90%) [14,16]. The combined physical retention and biological removal in the AnOMBR makes it a more attractive technology for removing cytostatic drugs compared to conventional MBRs (mainly by biological removal) and NF/RO (mainly by physical rejection).

3.3 Removal by anaerobic sludge

In order to better understand the removal mechanisms of the cytostatic drugs in the AnOMBR, their removals by the anaerobic sludge (Fig. 3) and by the rejection of FO membrane (Fig. 4) were

analyzed. As shown in Fig. 3(a), the anaerobic sludge exhibited significantly different results on the removal of eight cytostatic drugs. Regardless of the dosage level, more than 90% of Dox, Epi, Tam, Mit, Aza and Flu were removed by the anaerobic sludge. However, at the dosage level of 100 ng/L, the removal efficiency of Met was approximately 60.9%, and only 30.2% of CP was removed by the anaerobic sludge. The different results on cytostatic drugs removal might be owing to their different adsorption and biodegradability in the anaerobic sludge [3].

Additional batch experiments were performed to resolve the removal of cytostatic drugs by biodegradation and by adsorption to sludge in accordance to Table 2 [48-51]. It should be pointed out that the volatilization and hydrolysis for cytostatic drugs removal can be neglected in the anaerobic sludge based on the fact that no reduction of cytostatic drugs concentration occurred in Treatment III. According to the different results on biodegradation and adsorption, the cytostatic drugs were divided into several groups:

- Group I (Dox, Epi and Tam). These cytostatic drugs were nearly completely removed through the adsorption of anaerobic sludge. These compounds are all positively charged, which may promoted to their adsorption to the negative charged sludge due to electrostatic attraction.
- Group II (Met). The hydrophilic neutral compound Met was mainly removed by biodegradation. It suggests that Met belongs to the easily degradable cytostatic drugs. Furthermore, the lower adsorption of Met in the anaerobic sludge might be due to its much lower Log D value of -5.22 (see Table 1).
- Group III (Mit, Axa and Flu). These compounds were removed by both biodegradation and adsorption. High combined removal can be generally obtained in the batch tests (Fig.

3b), which are in good agreement with their high removal in the bioreactor (Fig. 3a).

- Group IV (CP). A much low removal (approximately 50%) was achieved in the batch test, and only adsorption played a role in its removal by the anaerobic sludge. The low bio-removal of CP was consistent with the results shown in Fig. 3(a) and a previous study [12].

3.4 Rejection by FO

Another important mechanism for cytostatic drug removal from the AnOMBR is their rejection by the FO membrane. Fig. 4 presents the FO rejection of the 8 cytostatic compounds on the basis of the effluent concentration and the supernatant concentration. High removals of > 95% were achieved for compounds with molecular weight around or greater than 370 Da (Dox, Epi, Met, and Tam). This result is of no surprise, noting that the molecular weight cutoff of the FO membrane was between 200-300 Da on the basis of poly(ethylene glycol) rejection [44] such that these compounds can be adequately removed by size exclusion. Consistent to the size exclusion mechanism, neutral compounds with low MW were not well rejected (69.2% for Aza [MW = 277 Da] and ~ 0% for Flu [MW = 130 Da]). However, the neutral hydrophobic compound Mit had nearly no retention by the FO membrane, even though it has a relatively large MW of 322 Da. The low retention of Mit can be attributed to its hydrophobic interaction with the FO membrane (Log D = 5.84) [3,44].

The negatively charged CP had a rejection of 99.0% by the FO membrane (Fig. 4). In the current study, although CP was poorly removed by the anaerobic sludge (Fig. 3), its high rejection by FO membrane ensured a near complete removal from the treated effluent. Previous studies have demonstrated the high rejection of TFC FO membrane for other negatively charged TOrCs as

a result of their electrostatic repulsion from the also negative charged membrane surface [1,3,52,53]. Based on the above results, it can be concluded that the rejection of FO membrane was a dominant factor during the removal of CP by the AnOMBR, while the anaerobic biomass played a more important role in the removals of other cytostatic drugs.

3.5 Impacts of Cytostatic Drugs on Reactor Performance

The AnOMBR in current study achieved high TOC and TP removals (Fig. S1 and Section S1). When the cytostatic drugs were added into the AnOMBR, the TOC concentration in the sludge supernatant suddenly increased, while there were no impacts on the removals of nitrogen and phosphorus. In current study, the VFA only includes acetic and propionic. During the operation of AnOMBR before the drug addition, the acetic varied in the range of 0-20 mg/L, and the propionic concentration was less than 0.5 mg/L at all time (similar to that reported for a CTA membrane based AnOMBR operated at 25°) [35]. However, after adding cytostatic drugs, the acetic concentration increased from 13.5 mg/L to about 35 mg/L, which agreed with the increase of TOC concentration in the supernatant (see Fig. S1). Methane production (see Fig. 5 (a)) was in the range of 0.18-0.23 L CH_4/g COD before drug addition, consistent with our previous study [35]. However, this value dropped to 0.16 L CH_4/g COD upon drug addition, which implies an inhibitory effect of the cytostatic drugs on methanogenesis. The increase of TOC and VFA and the reduction of methane yield after adding cytostatic drugs were due to the ecotoxic and genotoxic effects of cytostatic drugs on microbial activity. Previous studies have demonstrated that cytostatic drugs had negative effects on the microbial community and activity due to their direct chemical stress [54] and the transformation product through their biodegradation [55].

The cytostatic drugs not only disrupted the microbial metabolism, but also affected the sludge

properties. After cytostatic drugs addition, the mean floc size of sludge (Fig. 5 (b)) decreased from 92 to 80 μm, and both the SMP and BEPS dramatically increased. It has been reported that cytostatic drugs induced the increase of EPS concentration of sludge, especially protein and polysaccharide [56], likely caused by a stress response mechanism [57]. Despite the detrimental effects of the cytostatic drugs, good quality of effluent was still maintained in the AnOMBR (see Fig. S1).

4. Conclusions

In this study, the AnOMBR was applied for removing cytostatic drugs from wastewater. The results indicated that AnOMBR exhibited excellent removal for all cytostatic drugs owing to the anaerobic sludge and FO rejection. The anaerobic biomass played a more important role in the removals of Dox, Epi, Flu, Mit, Tam, Aza and Met. On the contrary, the FO membrane rejection was the dominate factor for removing CP. Further analyses demonstrated that Dox, Epi, Tam and CP were removed just through the adsorption, while Met could only be removed by the biodegradation. With regard to the Mit, Axa and Flu, both biodegradation and adsorption resulted in their reduction in the anaerobic sludge. Moreover, the cytostatic drugs adversely affected the methane yield accompanying with an increase of VFAs, indicating an inhibition of cytostatic drugs to the microbial activity in the AnOMBR. Despite the toxic effects on the microbial metabolism, the cytostatic drugs also influenced the sludge properties (e.g., a reduction of particle size and an increase of EPS).

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Appendix A. Supplementary information

Detailed information on additional tables, figures and descriptions on performance of the TFC FO membrane in the AnOMBR can be found in the Supporting Information.

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CAPTIONS

Figures

Fig. 1. Variations of water flux (a) and salinity (b) in terms of conductivity in the mixed liquor during the operation of AnOMBR (low and high drug additions on days of 84 and 87, respectively).

Fig. 2. Overall removals of 8 cytostatic drugs at low and high concentration levels by the AnOMBR. The molecular weight and the charge of each compound are provided in parentheses.

Fig. 3. Removals of 8 cytostatic drugs by the anaerobic sludge in the AnOMBR (a) and in the batch experiment (b). The molecular weight and the charge of each compound are provided in parentheses.

Fig. 4. Rejection of 8 cytostatic drugs at the concentration of 100 μg/L by FO membrane. The molecular weight and the charge of each compound are provided in parentheses.

Fig. 5. Evolution of methane yield (a), mean flocs size (D50) (b), polysaccharide and protein contents in SMP (c) and BEPS (d) during the operation of AnOMBR.

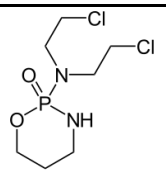
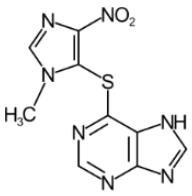
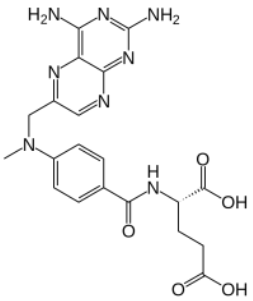
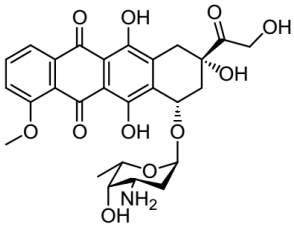
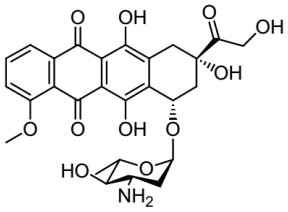
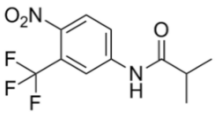
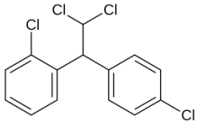
Tables

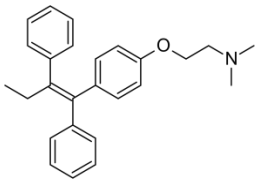
Table 1 Major characteristics of target cytostatic compounds in this study.

Table 2 Batch experiment on the adsorption and biodegradation of anaerobic biomass for cytostatic drugs.

Table

Table 1 Major characteristics of target cytostatic compounds in this study.

Compound	Therapeutic action	Chemical structure	MW	Log D	pKa	Charge@ pH 7	IARC carcinogenicity
Cyclophosphamide (CP)	alkylating agent		260.0	0.53	2.8	Negatively charged	Group 1
Azathioprine (Aza)	antimetabolite		277.3	-0.04	8.2	Neutral	Group 1
Methotrexate (Met)	antimetabolite		454.4	-5.22	3.8	Neutral (Zwitter-ionic)	Group 3
Doxorubicin (Dox)	cytotoxic antibiotic		543.5	-0.79	8.2	Positively charged	Group 2A
Epirubicin (Epi)	cytotoxic antibiotic		543.5	-0.79	7.7	Positively charged	non-listed
Flutamide (Flu)	hormone antagonist		276.2	3.14	13.1	Neutral	non-listed
Mitotane (Mit)	hormone antagonist		320.0	5.84	N.A.	Neutral	Group 2B

Tamoxifen (Tam)	hormone antagonist		371.5	5.51	8.9	Positively charged	Group 1

Table

Table 2 Batch experiment on the adsorption and biodegradation of anaerobic biomass for cytostatic drugs.

Treatment	Reactor	Anaerobic sludge	Synthetic wastewater	Cytostatic drugs (100 μg/L)	0.1% NaN_3[a]	Removal routes
I	R1 and R1′	+[b]	+	+	−	B+A+V+H[d]
II	R2 and R2′	+	+	+	+	A+V+H
III	R3	−[c]	+	+	+	V+H

[a] NaN_3 was used to inhibit the sludge biodegradation activity. [b] "+" indicated "with" or "presence". [c] "—" indicated "without" or "absence". [d] B-biodegradation, A-adsorption, V-volatilization, H-hydrolysis.

Figure

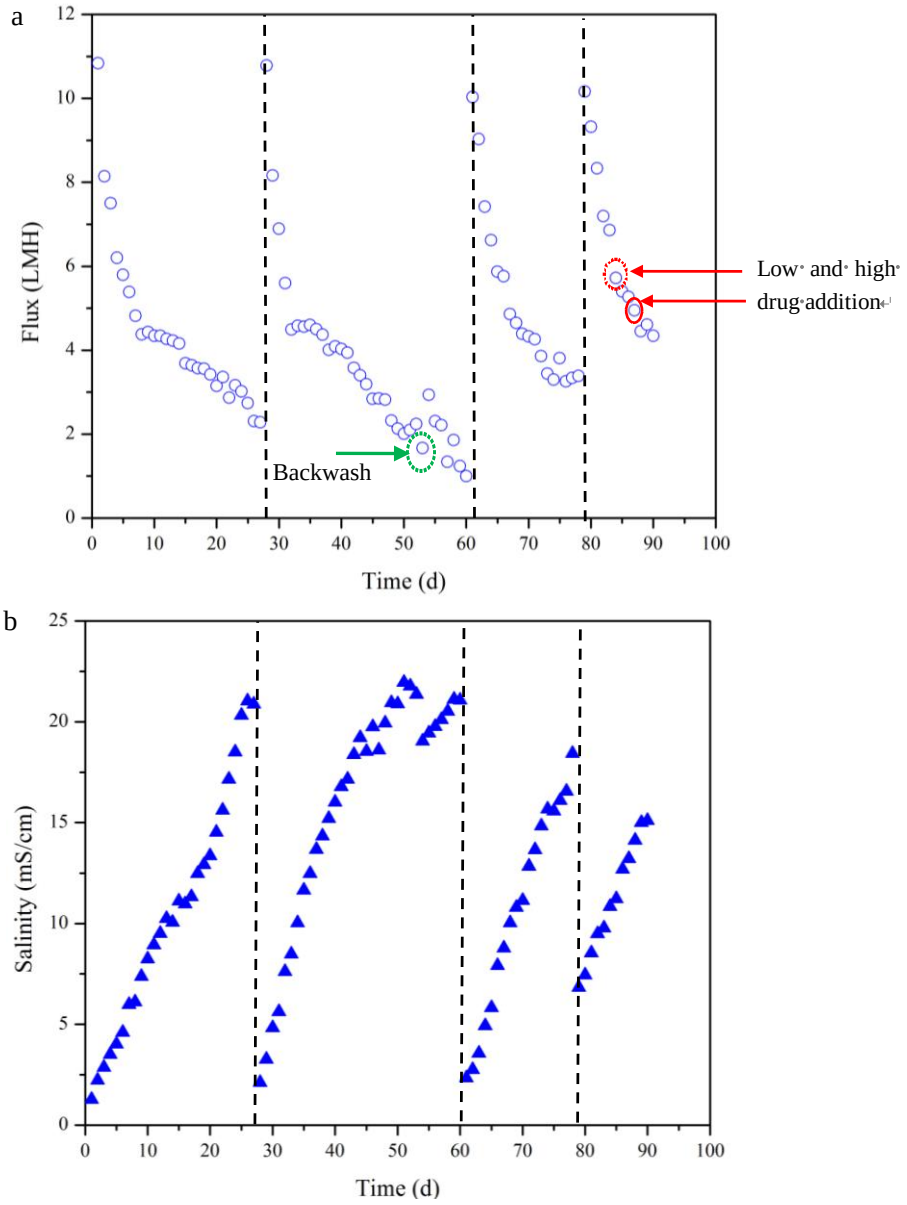


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Figure

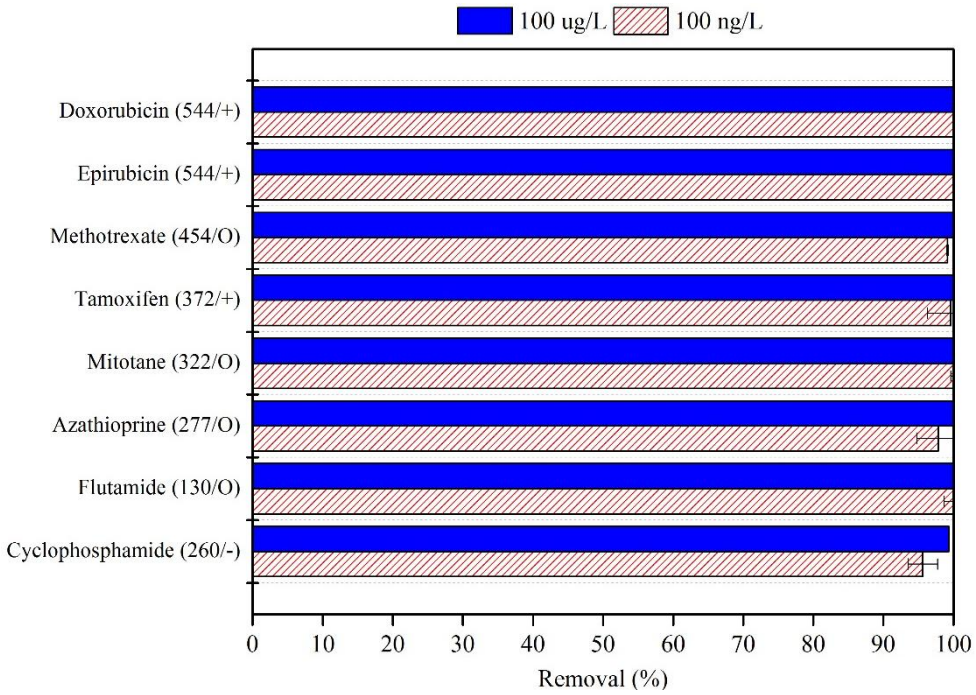

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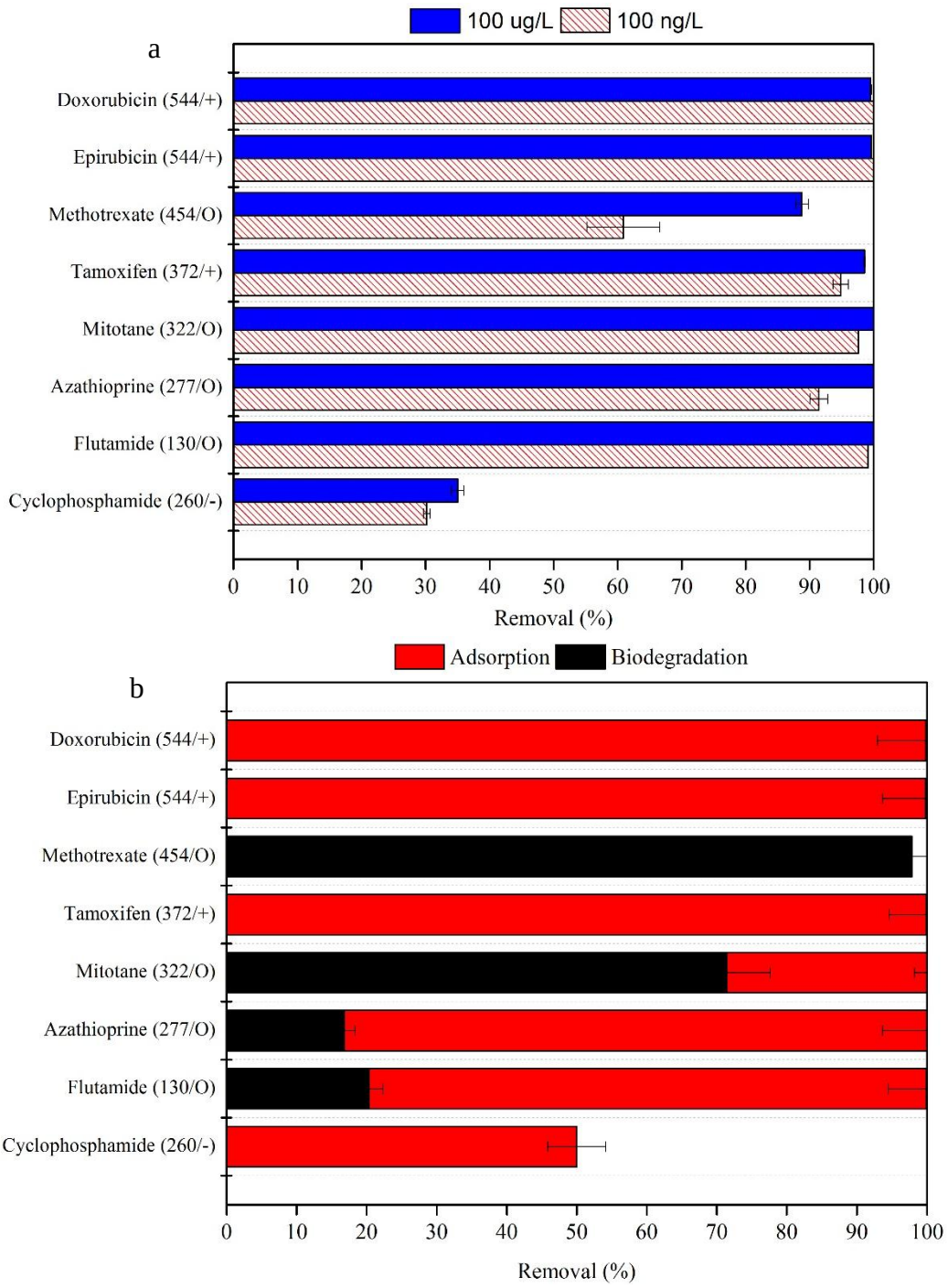
Figure



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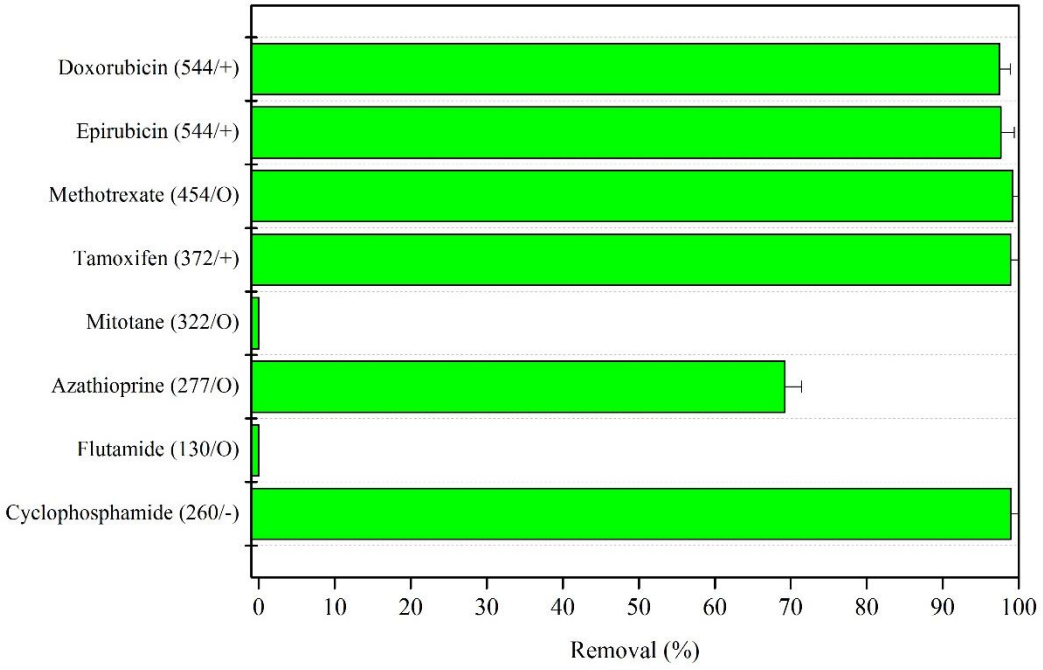

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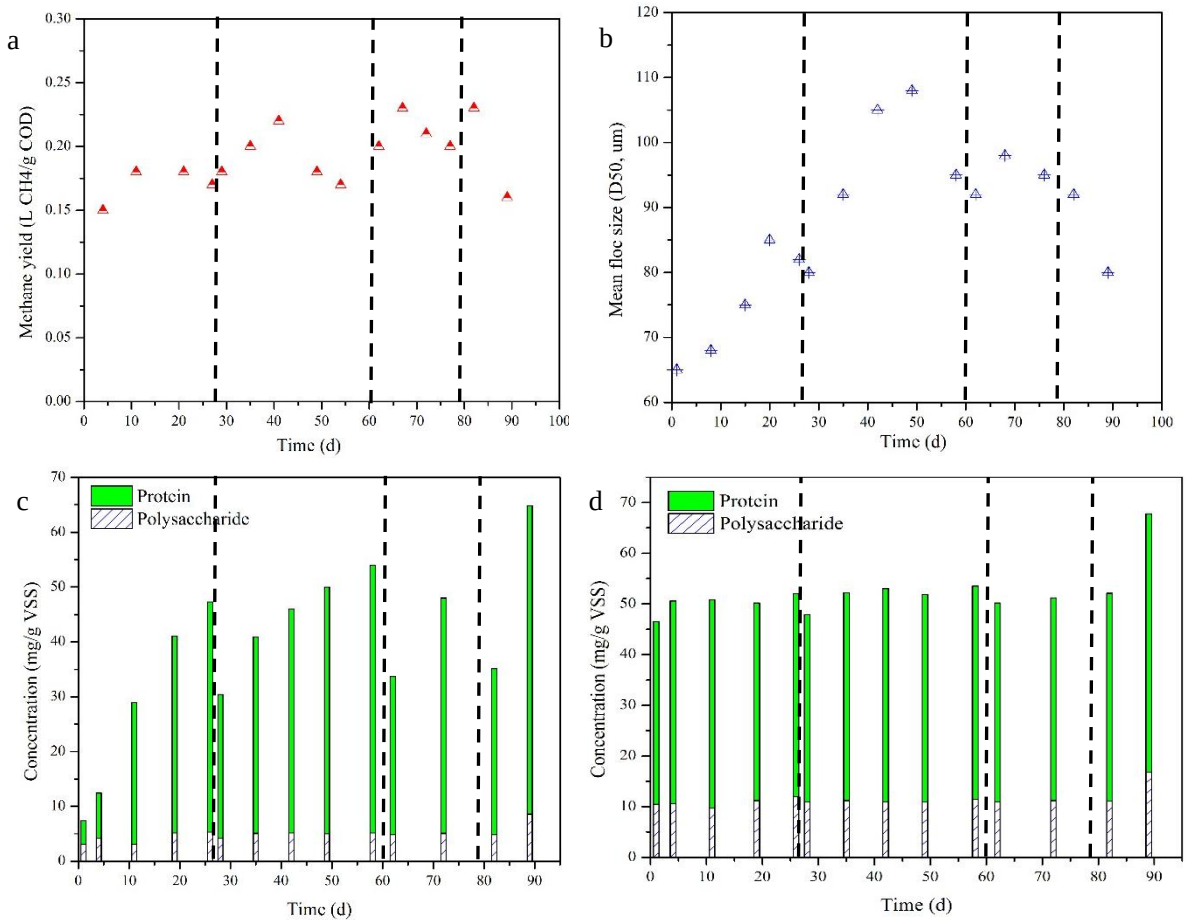

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Supplementary Material

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