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Biological removal of pharmaceuticals from hospital wastewater in a pilot-scale staged moving bed biofilm reactor (MBBR) utilising nitrifying and denitrifying processes

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Abstract

Hospital wastewater contains high concentrations of pharmaceuticals, which pose risks to receiving waters. In this study, a pilot plant consisting of six MBBRs in series (with the intention to integrate BOD removal, nitrification and denitrification as well as prepolishing COD for ozonation) was built to integrate pharmaceutical removal and intermittent feeding of the latter reactors aimed for micropollutant removal. Based on the experiments, nitrifying MBBRs achieved higher removal as compared to denitrifying MBBRs except for azithromycin, clarithromycin, diatrizoic acid, propranolol and trimethoprim. In the batch experiment, nitrifying MBBRs showed the ability to remove most of the analysed pharmaceuticals, with degradation rate constants ranging from $5.0 \times 10^{-3} \text{ h}^{-1}$ to 2.6 h^{-1} . In general, the highest degradation rate constants are from the nitrifying MBBRs while the latter MBBRs showed lower degradation rate constant. However, when the degradation rate constants were normalised to the respective biomass, the intermittently fed reactors presented the highest specific activity. Out of the 22 compounds studied, 17 compounds were removed with more than 20%.

Keywords: Pharmaceuticals; biofilm; pilot-scale; hospital wastewater; degradation

1. Introduction

Hospital wastewater with a significant load of pharmaceuticals (Santos et al., 2013; Thomas et al., 2007; Verlicchi et al., 2010) is frequently co-treated with municipal wastewater. As conventional activated sludge (CAS) is used to treat municipal wastewater, this results in insufficient pharmaceutical removal (Joss et al., 2006; Ternes et al., 2004). Hence, on-site treatment of hospital wastewater has been considered and proposed in Denmark, in order to decrease pharmaceutical input into municipal wastewater treatment plants (WWTPs) (Pauwels and Verstraete, 2006; Verlicchi et al., 2010).

A few countries in Europe, as well as in China and Japan, have started to install on-site pharmaceutical removal treatment plants, utilising either conventional wastewater treatment or membrane bioreactor (MBR) processes (Liu et al., 2010; Pauwels and Verstraete, 2006). In Denmark, where this study was undertaken, Herlev Hospital has been using advanced oxidation processes (AOPs) for MBR post-treatment, in order to ensure a more efficient eradication process (Nielsen et al., 2013). Therefore, post-treatment technologies, such as activated carbon, AOPs or nanofiltration, accompanying activated sludge reactors comprising an MBR are complemented in an overall approach.

On the other hand, a pharmaceutical removal method that relies on biological treatment, provides a more economical and environmentally friendly alternative to ozonation and activated carbon (Carballa et al., 2004; Zorita et al., 2009). Biological wastewater treatment processes are typically categorised into two categories: suspended and attached growth. Conventional activated sludge treatment used in most WWTPs is an example of suspended growth biological treatment. Despite a number of improvements reported for CAS (Andersen et al., 2003; Schaar et al., 2010), however, various micropollutants remain relatively persistent in activated sludge processes (Miège et al., 2009). On the contrary, some of these compounds have been reported to be removed with higher removal rates in attached biofilm processes compared to activated sludge (Falås et al., 2012; Zupanc et al., 2013). This suggests the possibility of further optimising the biological treatment process, using a biofilm-based

approach in which moving bed biofilm reactors (MBBRs) is one of the possibilities to exploit attached growth processes.

In the last decade, MBBRs have been known for the robustness and compactness that the technology offers with respect to nitrification in wastewater treatment. In addition, MBBRs have also been demonstrated as a promising solution to pharmaceutical removal (Escolà Casas et al., 2015; Falås et al., 2013; Hapeshi et al., 2013), with comparison studies showing that higher removal rates per unit of biomass can be obtained than with conventional activated sludge plants. Additionally, compounds such as diclofenac as well as X-ray contrast media, which are recalcitrant through CAS treatment, can be removed using an MBBR (Escolà Casas et al., 2015; Hapeshi et al., 2013; Tang et al., 2017). Furthermore, MBBRs have been applied for treating industrial wastewater, particularly wastewater from pharmaceutical industries, due to their robustness and high pharmaceutical degradation capability (Gunderson, 2012). Nevertheless, due to challenging and complex parameters involved in handling a pilot-scale staged MBBR for hospital wastewater treatment have yet to be investigated.

A follow-up study was designed based on the laboratory-scale results established by Escolà Casas et al. (2015), when they tested MBBRs in relation to the removal of pharmaceuticals. A pilot-scale treatment plant was built with the intention to integrate pharmaceutical removal into a full treatment train consisting of biochemical oxygen demand (BOD) removal, nitrification and denitrification. Assuming the nitrification was the most effective step, this step was operated intermittently, hoping that more biomass would grow in the latter stages of the reactor train. The objective of this study was to test the treatment process as a whole, aiming to achieve a higher removal of pharmaceuticals than observed in activated sludge so that the decentralised treatment of hospital wastewater may be possible in the future.

2. Materials and methods

2.1. Treatment system

A six-stage MBBR treatment plant with BOD removal, nitrifying and denitrifying properties was built to test its treatment capacity in relation to wastewater from Aarhus University Hospital in Skejby. The

MBBR comprised of six reactors, i.e.: M1 (900 L, BOD removal, denitrifying), M2 (900 L, nitrifying), M3A (900 L, nitrifying), M3B (900 L, nitrifying), M4 (500 L, denitrifying) and M5 (500 L, nitrifying), respectively. The MBBRs were operated with a filling ratio of 50% with approximately 150,000 and 80,000 Anox KTM5 carriers (AnoxKaldnes, Lund, Sweden) in the 900 L and 500 L reactors, respectively. Hydraulic retention time (HRT) for the 900 L and 500 L reactors are 1.13 h and 1.67 h, respectively. The set-up is illustrated in Fig. 1 – M1 and M4 were denitrifying (DN) reactors and thus not aerated and M4 was supported with an additional carbon source (20% ethanol) of 56 mL/h. The remaining four reactors performed nitrification (N) and other aerobic processes and were thus aerated without additional carbon sources. This on-site pilot plant was installed to minimise the input of pharmaceuticals into the municipal WWTP and it was explored whether direct discharge would be feasible. Moreover, this set-up could also minimise dissolved organic carbon (DOC) input into a post-stream ozonation polishing step. The idea behind this treatment system, with several reactors built in series, was that M1 and M4 reactors would be for nitrogen removal while M5 would polish organic matter after the denitrification processes to prepare for a possible polishing ozonation. Concerning the remaining two reactors, i.e. M3A and M3B, they were designed to nitrify and remove micropollutants. However, as described by Escolà Casas et al. (2015), latter reactors in a staged MBBR contained very little biomass, so the reactors (M3A and M3B) in this study were interchanged by switching the flow. Moreover, intermittently fed MBBRs present a new insight for the removal of pharmaceuticals, as mentioned previously. The effluent of M2 was either directed into M3A or into M3B (Fig. 1), and the flow path was switched every 12 hours. The flow rate was 800 L h⁻¹ for the 900 L reactors (M1, M2, M3A and M3B) before the return flow, while a flow of 300 L h⁻¹ was achieved for the 500 L reactors (M4 and M5) after the return flow. The wastewater was pumped from a reservoir tank (influent) and recirculated after the fourth reactor at 300 L h⁻¹ and 500 L·h⁻¹, respectively, to optimise nitrogen management in a classical recirculation approach.

The raw hospital wastewater was first pumped through a 100-micron band filter by a hose pump into a reservoir tank, before entering M1 as influent. The purpose of this reservoir tank was to maintain a continuous flow, since flow in hospital sewage pipe can have huge variations especially, during

nighttime (Klepiszewski et al., 2016). The treatment line was operated at a temperature of around 20°C, and the general parameters of the wastewater, for example pH, oxygen, chemical oxygen demand (COD) and total organic carbon (TOC), were monitored on a weekly basis.

2.2. Experimental design

Two experiments were designed and executed to test the capability of this staged treatment system, with the main focus being pharmaceutical removal. The experiments were conducted after the treatment system has achieved steady operational conditions (i.e. TOC removal, ammonium removal (nitrification), etc.) The first experiment was a batch experiment, in which the staged MBBRs were reassembled and spiked individually with a defined concentration of selected pharmaceuticals and tested for removal rates over time. This was done in order to determine removal kinetics by individual reactors. Besides, batch experiment offered to determine the potential degradation in the reactor train. The second experiment was conducted as continuous flow-through, following one body of water on its passage through the pilot plant, which was allowed to run in working conditions with actual pharmaceutical concentrations (not spiked). This approach offers an overview of the treatment system in reality, in comparison to degradation potential.

2.2.1. Batch experiment

In order to evaluate the performance of each reactor independently, the MBBR treatment system was reassembled on a smaller scale in the lab, because spiking in the 900 L and 500 L reactors would be impractical. A 3-L reactor was used to resemble each reactor, and five individual reactors were constructed (instead of the original six larger reactors, because M3A and M3B were assumed to operate identically). In each reactor, 0.9 L of hospital wastewater and 150 Anox KTM5 carriers from the respective reactor were added (representing the same filling ratio of the respective reactors). The denitrifying conditions of reactors M1 and M4 were maintained by sparging nitrogen gas (N₂), and adding nitrate (NO₃⁻) and sodium bicarbonate (NaHCO₃), to regulate pH at approximately 8. Nitrate concentration was maintained at around 20 mg N/L and replenished at least twice daily. Consecutively, each reactor was spiked with a mixed pharmaceutical solution, achieving a calculated initial concentration between 3 and 20 µg L⁻¹ for the pharmaceutically active compounds and

approximately $50 \mu\text{g L}^{-1}$ for the X-ray contrast media. Spiking was essential to enable the study of degradation kinetics over time for all of the investigated compounds. Moreover, spiking imitates predicted high concentrations in hospital wastewater, due to fluctuations. Therefore, X-ray contrast media were spiked to a higher concentration than the pharmaceutically active substances, because they are typically detected in higher concentrations (Frédéric and Yves, 2014; Wiest et al., 2018). After spiking, 10 mL samples were taken from each reactor, using a glass pipette at 1 min, 20 min, 1 h, 2 h, 3 h, 4 h, 7.5 h, 10 h, 21 h and 24 h. Whenever a water sample was withdrawn, the corresponding biomass remaining on carriers was also removed, in order to maintain a filling ratio of 50%.

2.2.2. Continuous flow experiment

This experiment was designed to examine the wastewater treatment system in a real setting. The pilot plant was not spiked, but the flow path was adjusted and fixed to the flow path (black) shown in Fig. 1. Due to fluctuating concentrations from the hospital's sewage system, the treatment plant was monitored by sampling according to the hydraulic retention time (HRT). Hence, a specific “water package” was monitored on its way through the pilot reactor system, in order to assess removal capacity. Three samples of 10 mL each were taken from each stage, one hour apart. The exact sampling intervals are detailed in Fig. 3.

2.3. Investigated pharmaceuticals

The pharmaceuticals investigated in this study can be categorised into six groups, namely analgesics (diclofenac, ibuprofen and phenazone), antibiotics (azithromycin, ciprofloxacin, clarithromycin and trimethoprim), anti-epileptic/anti-depressants (carbamazepine and venlafaxine), beta-blockers (atenolol, metoprolol, propranolol and sotalol), sulfonamides (sulfadiazine, sulfamethizole and sulfamethoxazole) and metabolite (acetyl-sulfadiazine), and X-ray contrast media (diatrizoic acid, iohexol, iomeprol, iopamidol and iopromide). They were obtained from a variety of suppliers, as listed in Escolà Casas et al. (2015). Formic acid and gradient-grade methanol were obtained from Merck (Darmstadt, Germany), while HPLC-MS-grade water was purchased from Sigma-Aldrich (Munich, Germany).

2.4. General parameters

The general parameters of the pilot plant were monitored periodically, and pH, temperature, dissolved oxygen (DO), total organic carbon (TOC), ammonium nitrogen ($\text{NH}_4^+\text{-N}$), nitrite nitrogen ($\text{NO}_2^-\text{-N}$) and nitrate nitrogen ($\text{NO}_3^-\text{-N}$) were documented. Subsamples of approximately 50ml were filtered with a 0.45 μm filter. Samples for dissolved organic carbon (DOC) were preserved in the freezer until analysis, while samples meant for COD, NH_4^+ and NO_2^- and NO_3^- were analysed the same day. COD, NH_4^+ , NO_2^- and NO_3^- concentrations were analysed on a Hach Lange DR 3900 with the application of Hach Lange cuvette tests for COD (LCK 414), NH_4^+ (LCK 303/304), NO_2^- (LCK 341) and NO_3^- (LCK 339) following the manufacturer's instructions (Hach Lange GMBH, Düsseldorf, Germany).

2.5. Biomass of attached biofilm on carriers

Ten carriers from each reactor (M1, M2, M3A/M3B, M4 and M5) were placed on an aluminium foil cup, dried overnight at 105°C and weighed. The carriers were then washed in tepid 2M NaOH and cleaned with de-ionised water. After washing, the carriers were dried again at 105°C overnight and the aluminum cup was weighed with and without carriers. The content of biomass on the carriers was calculated as the weight difference before and after cleaning the carriers. The biomass content per area was calculated, knowing that each carrier had a protective surface area of 0.00242 m².

2.6. Pharmaceutical analysis

2.6.1. Sample preparation

After each specific sampling time, 3 mL of methanol was added to the 10 mL samples and stored at a temperature of -20°C until analysis. Methanol was added to prevent any loss of the sample from glass vials breaking when stored at -20°C and to block biodegradation after sampling. Prior to analysis, the samples were left to reach room temperature and homogenised followed by centrifugation at 6000 rpm for 10 minutes. Thereafter, 900 μL of the aqueous phase was transferred to a new HPLC vial together with 100 μL internal standard solution (Acetyl-sulfadiazine ¹³C₆, Ciprofloxacin D₈, Citalopram D₆, Clindamycin D₃, Erythromycin ¹³C D₃, Ibuprofen D₃, Propranolol D₇, Sulfadiazine

$^{13}\text{C}_6$ and Trimethoprim D_3), using glass syringes. Successively, 10 μL of the batch samples and 100 μL of the continuous flow samples, respectively, were injected into the HPLC-MS/MS.

2.6.2. Determination of pharmaceuticals

The samples were analysed by means of high-performance liquid chromatography coupled to a tandem mass spectrometric detector (HPLC-MS/MS). Chromatographic separation was achieved by using a Phenomenex Synergi 4u polar-RP column (150 x 2 mm I.D., particle size 4 μm , Torrance, California, USA). The HPLC was a 3000-series from Dionex and equipped with an UltiMate 3000 pump (DGP-3600 M), an UltiMate 3000 autosampler (WPS-3000 TSL) and an UltiMate 3000 column compartment (TCC-3000 RS) at 20°C. Following HPLC separation, analytes were quantified with an AB-Sciex (Framingham, MA, USA) API 4000 triple quadrupole mass spectrometer in multiple reaction monitoring (MRM) mode, utilising electrospray ionisation in positive mode. The HPLC-MS/MS parameters, together with the MRMs, were used as described in Escola Casas et al. (2015).

2.7. Data treatment

The concentrations of the pharmaceuticals during the continuous flow-through experiment were plotted over time for both batch and continuous flow experiments. The fittings of the data for each experiment are explained in 2.7.1 and 2.7.2, respectively.

2.7.1. Batch experiment

In order to have an ideal and simplified evaluation of the data, all analysed pharmaceuticals could be fitted to single first-order degradation kinetics (Equation (1)) and utilising the software package GraphPad Prism 5.0, in which k is the degradation rate constant. A single first-order kinetic was used so that a more valid literature comparison can be obtained, since most of the data in the literature are fitted using first-order degradation kinetics. All fittings in this study were refined with least squares optimisation, without weighting, to minimise the absolute distances squared and the coefficient of determination (r^2) – as shown in Table 2. In order to yield a comparable result, the degradation rate constants (k 's) were applied regardless of the goodness of fit.

$$C = (C_0) \cdot e^{-kt} \quad (1)$$

Following the acquired degradation rate constants (k 's), an estimated overall removal for each compound for the whole reactor train was computed using the Equation (2).

Overall removal =

$$\left(1 - \left(\frac{v_i}{(1+Da_4)(1+Da_5)((1+Da_1)(1+Da_2)(1+Da_{3A})(1+Da_{3B})(v_i+v_r)-v_r)}\right)\right) \quad (2)$$

with τ_i , being the respective hydraulic retention time; v_i and v_r refer to the inflow and recirculation flow [L/h], respectively and Da_i refers to the Damköhler number which equals $k \times \tau$ at a constant liquid pressure when considering first-order reaction kinetics (William Green, 2007). The equation $Da_i = k_i \times \tau_i$ signifies the degradation rate constant of a specific reactor (k_i) and its respective hydraulic retention time (τ_i), listed in Table 1.

Due to the recirculation flow, which complicates the calculated removal, and in order to estimate removal in each reactor, a stepwise Equation (SE1 of the Supplementary Material) was used to estimate the calculated removal in each reactor (Fig. 4A).

2.7.2. Continuous flow experiment

Since the water flowing into the first reactor (M1) originated from both the influent and the return flow (Fig. 1), the pharmaceutical load into the first reactor (M1) was calculated using mass balance to resemble better the “water package” flow-through scenario (Fig. 3). During this flow-through experiment, the removal [%] was also determined and later plotted (equation 3). Two measured removals (Fig. 4B and 4C) were plotted in this case, in order to have an explicit insight into the treatment system operating in reality. The first measured removal plot (Fig. 4B) shows the total removed (in percentage of inflow) by the treatment system, in accordance with the influent concentration moving into the treatment plant at a specific time. It was plotted by applying Equation (3).

$$Removal = \left(1 - \frac{\text{Effluent concentration } (C_e)}{\text{Influent concentration } (C_i)}\right) \quad (3)$$

The second measured removal (Fig. 4C) presents an overview in this regard at each stage following the specific “water package” in which concentration from the recirculation flow was considered. Equation (4) was used to plot Fig. 4C.

$$Removal = \left(1 - \frac{\text{Concentration in each reactor } (M_i)}{\text{Concentration in the inflow to M1}}\right) \quad (4)$$

2.7.3. Uncertainty assessment of experiments

Considering compound specific uncertainties from the instrumental analysis (5%), instabilities in the reactors (15%) and variability in the feed water influencing the final results with an uncertainty of 15%, a total uncertainty of 20% can be estimated by calculating error propagation. Thus, changes exceeding 20% are only considered to be significant.

3. Results and discussion

3.1. General parameters

The working conditions of the pilot plant throughout the nine months of operation are shown in Table 1. Temperature, pH and oxygen level were maintained at a steady level throughout the running period as well as during the experiments. Chemical oxygen demand (COD) and dissolved organic carbon (DOC) removal, as well as the first step of nitrification (where ammonia is oxidised to nitrite), took place considerably in the earlier reactors, which resulted in a higher biomass in the reactors (M1 and M2) compared to the latter reactors.

3.2. Pharmaceutical removal: potential versus actual

3.2.1. Batch experiment

Concentrations obtained for the analysed compounds were plotted versus time, and fitted using first-order degradation kinetics (Equation (1)). The data of six compounds (acetyl-sulfadiazine, ibuprofen, iomeprol, sulfadiazine, sulfamethoxazole and trimethoprim) are shown in Fig. 2, which briefly summarises the treatment system (please refer to the Supplementary Material S2 for the full data of all analysed pharmaceuticals). Nitrifying MBBRs have the ability to remove most of the analysed

pharmaceuticals except for carbamazepine, diclofenac and iopamidol. Carbamazepine, a compound known to be resistant to biodegradation in wastewater (Joss et al., 2006), was expected to pass through the reactors unchanged. Diclofenac, on the other hand, was removed by up to 50% after 24 hours of treatment in the intermittently fed reactors M3A and M3B (see Supplementary Material S2). This complies with an approximate removal of 50% in two previous studies in which laboratory-scale MBBRs were utilised (Escolà Casas et al., 2015; Tang et al., 2017).

In addition to removal solely in the intermittently fed reactors, a few compounds, such as acetyl-sulfadiazine (Fig. 2), were removed or deconjugated in all reactors. In contrast, some compounds such as ibuprofen and iomeprol (Fig. 2) experienced low removal in the denitrifying reactors (M1 and M4), as studied by Torresi et al. (2016). Nonetheless, sulfonamides, namely sulfadiazine, sulfamethizole and sulfamethoxazole, were removed to a higher extent in the latter nitrifying reactors (M3A/M3B and M5), where biochemical oxygen demand (BOD) load was lower (please refer to the Supplementary Material S2). Last but not least, trimethoprim was one of the few compounds that had higher removal in the denitrifying reactors than in the nitrifying reactors (Fig. 2).

As observed in Table 2, the two reactors with the highest degradation rate constants (k) were M2 and M3A/M3B. Thus, using the k -values to postulate removal models showed that the main fraction of the pharmaceuticals was removed in M2 and M3A/M3B (Fig. 4A). The calculated removal presents overall removal by each reactor, regardless of the biomass content, based on the spiking experiment. Based on this removal model calculated using the k -values, 8 of the 22 compounds including 3 of the 4 iodinated X-ray contrast media had a near complete removal after 24 hours of MBBR treatment.

To investigate further the ability of the microorganisms present in each reactor, the k -values were normalised to the biomass in each reactor volume (k_{bio}). As a result, the k_{bio} of M3A/M3B was the highest for most compounds (Table 3), which indicates that the microorganisms in M3A/M3B were more adapted to pharmaceutical biodegradation and also that a higher fraction of these were involved in biodegradation compared to M2. Therefore, by feeding M3A and M3B intermittently, the adapted biomass was maintained at a reasonable abundance, in which case improved treatment quality was

achieved. Additionally, diclofenac removal, to a greater extent, was also achieved. Although M3A and M3B were fed intermittently, the biomass in M2 was still approximately two times higher (Table 1).

3.2.2. Continuous flow experiment

The concentration plots in Fig. 3 show an average concentration of three analysed samples, each one hour apart. The two influents in Fig. 3 represent inflows into the pilot plant and the first reactor M1, respectively. The inflow into the first reactor M1 considered the recirculation flow and was calculated by mass balancing the concentrations together with the flow rate of the pilot plant influent and the recirculation flow.

Fig. 4B was plotted according to the “water package” (connected dotted line) and presents an overview of what was removed by each reactor. On the other hand, Fig. 4C presents the total removed by the treatment system in accordance with influent concentrations flowing into the pilot plant (effluent/influent). 12 of the 17 compounds with concentrations above the LOQ (limit of quantification) were removed significantly (i.e. exceeding 20% removal). All plots for the continuous flow experiment (Supplementary Material S3) and LOQs (see Supplementary Material S4) are also presented.

3.2.3. Comparison of batch and continuous flow experiments

Using the plot shown in Fig. 4, and comparing the data from both the batch and the continuous flow experiments, the ability of each reactor to remove pharmaceuticals can be well understood. Using Equation (2) to estimate the removal in each reactor, 17 of the 22 compounds analysed in the batch experiment had an overall removal level of more than 20%. Removal in the batch experiment was generally higher than the measured removal in the continuous flow-through experiment, because wastewater does not only contain the active ingredients but also their conjugates as formed in the human body (Göbel et al., 2007; Kovalova et al., 2012). Thus, modelling can be more difficult to carry out. However, compounds excreted in their base form can be modelled straightforwardly using the degradation rate (k).

By conducting a batch experiment in which pharmaceuticals were spiked to concentrations that resembled hospital wastewater, removal capability for each reactor was discovered. In contrast, monitoring the pilot plant aided the study of the treatment system as a whole. As an example, Fig. 4B illustrates a generally higher removal in reactor M5, where BOD loading is low. This concurs with the law of nature, in that the earlier reactors obtained energy from an easily biodegradable carbon source while the latter reactor (M5) had to rely on a complex carbon source (pharmaceuticals) for energy. On the other hand, when the inflow and outflow stopped, as in the batch experiment, the biomass was rapidly consuming its primary food source and had to divert to other compounds such as pharmaceuticals. This means that more biomass leads to higher removal, since higher concentrations of pharmaceuticals are present as compared with the continuous flow experiment (Fig. 4A). Moreover, the model in Fig. 4A shows the maximum removal of 100% in a closed system in which pharmaceuticals removed in earlier reactors cannot be removed further by the latter reactors. In other words, the availability of pharmaceuticals for removal in the latter reactors was restricted by the experimental design.

3.3. Removal of pharmaceuticals in other biofilm systems

The overall degradation kinetics for most of the compounds in this study was higher in the nitrifying reactors compared to the denitrifying reactors. This concurs with a study on conventional activated sludge reactors operating under nitrifying and denitrifying conditions (Suarez et al., 2010). Since many studies, including the previous study (Escolà Casas et al., 2015), investigated and compared removal under aerobic conditions, this continuation study will apply more to discussions on denitrifying reactors. The summary for removal under denitrifying conditions is shown in Table 4.

For comparison, the data shown in Table 4 were with related treatment systems, namely Hybrid Biofilm Activated Sludge (HYBAS), MBBR, and conventional activated sludge (CAS) operating in denitrifying conditions. HYBASTM (Veolia Water Technology) is a combination of two processes, MBBR and activated sludge. It is based on integrating attached biofilm on MBBR carriers into activated sludge, in which the carriers are suspended within activated sludge in one single reactor (Christensson and Welander, 2004; Ødegaard et al., 2014). Due to data availability related to

denitrifying wastewater treatment systems focusing on pharmaceuticals, selected compounds are presented in Table 4 (refer to Fig. 4 for complete data on removals). In general, the removals measured for this MBBR study were comparable to the operated laboratory-scale MBBRs determined by Torresi et al. (2016), with the exception of atenolol, since its concentration could not be determined precisely, due to removal beyond the limit of quantification in the continuous flow experiment (please refer to the Supplementary Material S3). However, in the batch experiment, in which atenolol was spiked to a higher concentration, its removal matched the removal in the laboratory-scale MBBRs.

Moreover, when compared to CAS and HYBAS, MBBRs operating under denitrifying conditions (M1) showed a higher removal capacity, especially for trimethoprim (Fig. 2). Contrary to negligible trimethoprim removal in CAS and HYBAS (Falås et al., 2013; Su et al., 2015; Suarez et al., 2010), degradation of 23% and 78% was determined in the continuous flow and batch experiments, respectively. Additionally, clarithromycin showed also near-complete removal in the batch experiment (Table 4). Other than a higher removal than CAS and HYBAS, this study presents the robustness of MBBRs in pilot-scale. Pharmaceutical removal matched a denitrifying MBBR in laboratory-scale (Torresi et al., 2016), in which MBBRs' parameters could be easily manipulated.

In addition, degradation rate constants corrected to biomass (k_{bio}) in this study were much higher than reported in the literature (Table 3). The compounds atenolol, clarithromycin, phenazone, sulfamethoxazole and trimethoprim, for example, had ten times higher k_{bio} than reported in CAS and HYBAS. Furthermore, carbamazepine, diclofenac, ibuprofen, metoprolol and venlafaxine had similar to one fold higher k_{bio} than in CAS and HYBAS outlined in the literature (Table 3). By comparing the k_{bio} , compound-specific degradation in each reactor under nitrifying or denitrifying conditions can be identified. Besides, k_{bio} excludes any error caused by biomass differences, since DOC removal occurs considerably in the earlier reactors, resulting in a higher biomass. Consequently, a higher biomass generally marks higher degradation as well as a higher degradation rate constant (Table 2).

However, by comparing k_{bio} between different treatment systems in which all variables, for instance denitrifying/nitrifying conditions and biomass normalisation, are kept constant, a literature comparison of degradation rate constants gave more insight. The highest degradation rate constant for most of the compounds, according to data availability in the literature, showed that the reactors M3A/M3B in this study offer the most competent biofilm for pharmaceutical degradation. This includes the persistent analgesic diclofenac, which was also observed to be removed in an intermittently fed laboratory-scale MBBR (Tang et al., 2017). As a consequence, this study, which combined intermittently fed biofilm with a pilot-scale MBBR, provides a new insight into treating hospital wastewater.

Trimethoprim, an antibiotic detected at $\mu\text{g/L}$ levels in raw wastewater, was the only compound to have the highest k_{bio} in the earlier denitrifying reactor M1 (Table 3). This higher k_{bio} in an earlier denitrifying MBBR corresponds to Su et al. (2015), who found that micropollutants such as trimethoprim exhibit a higher k_{bio} with a higher DOC. Moreover, trimethoprim was also observed in the literature to have a higher k_{bio} in denitrifying conditions (Table 3). Other than biodegradation in anoxic conditions, trimethoprim treated by an oxic biological sequencing batch reactor (SBR) was observed, as well as transformation pathways, by Jewell et al. (2016). Su et al. (2015) demonstrated that trimethoprim biotransformation was affected by a readily available biodegradable substrate supply. In other words, the higher the biomass, the higher the degradation rate constant as well as the k_{bio} . Trimethoprim biodegradation can occur via co-metabolism, fortuitous metabolism and mixed substrate utilisation. Co-metabolism is commonly used to describe the transformation of a non-growth substrate by active or resting cells in the absence or presence of a primary substrate (Criddle, 1993; Stirling and Dalton, 1979). In contrast, fortuitous metabolism takes place in the absence of a growth-supporting substrate when a non-growth substrate is metabolised (Stirling and Dalton, 1979). In order for fortuitous metabolism to occur, the reactions should yield metabolites and/or intermediates that are energetically beneficial for cells to grow on, since fortuitous biotransformation of the non-growth substrate is not driven by any external energy source. Alternatively, co-metabolic activities may not generate energy that is beneficial to cells performing biotransformation. Therefore, bacterial

communities performing the co-metabolic transformation of pharmaceuticals (e.g. trimethoprim) must be capable of growing on an alternative substrate, for instance ammonia or nitrate. The third alternative to biodegradation, namely mixed substrate utilisation, occurs when bacterial cells recover electron equivalents from compounds (micropollutants) and other substrates (Joss et al., 2006).

In general, the possibility of sustainable growth solely on micropollutants (pharmaceuticals) may not seem feasible (Schmidt and Alexander, 1985), utilisation of numerous substrates as the source of energy supply for the necessity of cellular maintenance and growth seem more plausible (Kovarova-Kovar and Egli, 1998). Both ammonia oxidising bacteria (AOB) and heterotrophic bacteria are capable of co-metabolic transformation, whereas fortuitous metabolism and mixed substrate utilisation are related more closely to heterotrophic bacteria.

Other than analysing removal in each reactor separately, treating data from the treatment system as a whole is equally important. X-ray contrast media (diatrizoic acid, iohexol, iomeprol, iopamidol and iopromide) are used extensively in hospitals, in addition, these compounds are also known to be persistent throughout CAS treatment systems. However, the treatment in this pilot-scale MBBR study provides a removal rate of up to 60% compared to the previous highest removal of 31% (iopromide) in an MBR system in which the removal of other X-ray contrast media was negligible (Kovalova et al., 2012). Besides, a low removal rate (ranging from 0 to 44%) in general was observed for X-ray contrast media in other treatment systems (Cruz-Morató et al., 2014; Nielsen et al., 2013). Therefore, the ability to degrade these compounds in an MBBR suggests it may be a possible solution to treat wastewater.

As presented in Fig. 4B, the negative removal of approximately -20% can be observed for a few compounds, namely azithromycin, ibuprofen, iomeprol, sulfamethizole and sulfamethoxazole. This can be explained by the fact that compounds such as sulfamethoxazole are partially excreted as conjugates. Metabolic activity in human beings attaches a sulfo group, an acetyl group or a glucuronic acid to the compound, in order to increase solubility and facilitate excretion (Timbrell, 2009). This occurs during phase II of metabolism, described by Timbrell (2009), via sulfation, acetylation or

glucuronidation. The metabolites excreted are later deconjugated by bacterial enzymes during wastewater treatment, which actually resulted in a higher concentration of the original compound in reactor M1 of this study. Besides, some excreted pharmaceuticals are bound to faecal particles (Göbel et al., 2007) or can be formed from other compounds or metabolites (Kovalova et al., 2012). These pharmaceuticals can become available after the faecal particles have decomposed, for example; in fact, the increase in concentration in this study is assumed to be unrelated to pharmaceutical availability after the faecal particles have decomposed, because influent entering the treatment system was filtered. Sulfamethoxazole is also found to have a negative removal in a previous hospital wastewater treatment study (Escolà Casas et al., 2015).

In addition, an increase in sulfadiazine concentration can be as described above. Acetyl-sulfadiazine is known to be excreted as a conjugate, whereby deconjugation by microorganisms can occur as soon as it reaches the pilot plant. Sulfadiazine is usually metabolised in the human body through conjugation, during which products with glucuronic acid, glutathione or acetyl coenzyme A can be formed and excreted as conjugates, which later decompose to form sulfadiazine again (Kovalova et al., 2012).

Venlafaxine appeared to have a low removal (Table 4) as also reported in Falås et al. (2013). Additionally venlafaxine cannot be removed by ozonation easily as its removal requires an ozone treatment of 1.4 ± 0.2 mg-O₃/mg-DOC to achieve 90% removal (Hansen et al., 2016).

Based on the results presented in batch experiment, nitrifying MBBRs achieved higher removal, with the majority of the degradation rate constant (k) in reactors M2, M3A and M3B being the highest among the other reactors in this treatment system (Table 2). In fact, this marked a success for feeding reactors M3A and M3B intermittently in the treatment train, since the highest degradation rate constant (k) in previous studies was attributed mostly to the first reactor (Escolà Casas et al., 2015).

4. Conclusion

Pilot-scale MBBR was shown to be effective in hospital wastewater treatment. The degradation of pharmaceuticals occurs generally in parallel to COD and nitrogen removal, indicating that co-

metabolic activities are mainly involved. Low COD effluents obtained made a follow-up treatment with ozonation more feasible.

Intermittent feeding of biofilm does enhance the concentration of biomass effective against pharmaceuticals and thus the removal of pharmaceuticals. Although MBBR technology seems promising, transformation products, which may possibly be persistent, can result from the treatment process, since mineralisation through an MBBR has not been observed (Ooi et al., 2017). Further investigations are required in order to line out the degradation pathways.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at ...

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Figures and Tables

Fig. 1 – Overview of the treatment plant at Aarhus University Hospital, Skejby. Denitrification (DN) processes occur in M1 and M4, while M2, M3A, M3B and M5 perform nitrification (N) and other aerobic processes.

Fig. 2 – Concentrations of selected pharmaceuticals during the batch experiment in the reactors M1, M2, M3A/M3B, M4 and M5. First-order kinetics (Equation (1)) were fitted to the curves. Calc: expected calculated concentration for the spike.

Fig. 3 – Average concentrations and SD (n= 3 samples for each point, each sample was analysed twice) of the reactors during the continuous flow experiment. The opened circle is the concentration detected in recirculating wastewater (after M3B (fixed flow pathway during the continuous flow experiment)) into reactor M1. Influent into M1 was calculated by mass balancing the influent and recirculation concentrations as well as their respective flow rates. Horizontal dotted line represents the LOQ of the method derived from the MRM with the lowest signal.

Fig. 4 – Comparison of calculated removal from the batch experiment (Equation (2)) to measured removals in the continuous flow experiment (Equation (3) and (4)). The horizontal dotted line at $\pm 20\%$ indicates uncertainties from the experiment.

Table 1 – General parameters $\pm$ standard deviation at the pilot plant for nine months, including both sampling campaigns for the experiments. An exception to the biomass (biofilm) was not a nine-month average; instead, the biomass was determined right after the experiments, to ensure better precision. HRT= Hydraulic retention time [h]; DO=Dissolved oxygen [mgO₂/L]; TOC=Total organic carbon [mgC/L].

Reactor	HRT	Biofilm		pH	Temp.	DO	TOC	NH ₄ ⁺ -N	NO ₂ ⁻ -N	NO ₃ ⁻ -N
	[h]	[g/m ²]	[g/L]		[°C]	[mgO/L]	[mgC/L]	[mgN/L]	[mgN/L]	[mgN/L]
Influent				7.9 $\pm$ 0.3	17.7 $\pm$ 1.4	2.60 $\pm$ 1.7	137.01 $\pm$ 44.7	49.25 $\pm$ 14.2	0.06 $\pm$ 0.0	0.60 $\pm$ 0.2
M1	1.13	17.06	2.84	7.9 $\pm$ 0.3	17.9 $\pm$ 2.2	0.47 $\pm$ 0.1	55.25 $\pm$ 32.4	30.47 $\pm$ 13.7	0.06 $\pm$ 0.0	0.66 $\pm$ 0.3
M2	1.13	30.79	5.13	7.8 $\pm$ 0.2	18.2 $\pm$ 2.4	4.93 $\pm$ 2.4	16.03 $\pm$ 2.6	19.53 $\pm$ 13.1		0.41 $\pm$ 0.0
M3A	1.13	19.37	3.23	7.7 $\pm$ 0.3	18.4 $\pm$ 2.5	6.84 $\pm$ 2.4	17.66 $\pm$ 5.9	5.37 $\pm$ 6.6		12.34 $\pm$ 6.8
M3B	1.13	19.37	3.23	7.6 $\pm$ 0.3	18.3 $\pm$ 2.5	5.68 $\pm$ 3.1	19.00 $\pm$ 9.9	4.79 $\pm$ 7.2		13.67 $\pm$ 4.2
M4	1.67	14.73	2.45	7.8 $\pm$ 0.3	18.2 $\pm$ 2.7	0.62 $\pm$ 0.4	16.55 $\pm$ 3.8	6.49 $\pm$ 8.8	0.24 $\pm$ 0.2	0.87 $\pm$ 0.7
M5	1.67	19.96	3.33	8.0 $\pm$ 0.2	18.3 $\pm$ 2.8	7.14 $\pm$ 2.7	15.89 $\pm$ 2.5	4.27 $\pm$ 7.7		2.31 $\pm$ 0.4

Table 2 – Parameters from curve fitting (Equation (1)). k_i : removal rate constant [h^{-1}] $\pm$ standard deviation. Bold values refer to the highest k_i among the five reactors in the present study.

Compounds	M1		M2		M3A/M3B		M4		M5	
	$k_{M1} [\text{h}^{-1}]$	r^2	$k_{M2} [\text{h}^{-1}]$	r^2	$k_{M3} [\text{h}^{-1}]$	r^2	$k_{M4} [\text{h}^{-1}]$	r^2	$k_{M5} [\text{h}^{-1}]$	r^2
Acetyl-sulfadiazine	$19.2 \pm 5.21 \times 10^{-2}$	0.92	$11.7 \pm 1.32 \times 10^{-1}$	0.99	$9.08 \pm 2.14 \times 10^{-1}$	0.97	$21.9 \pm 1.87 \times 10^{-2}$	0.99	$11.6 \pm 1.40 \times 10^{-2}$	0.99
Atenolol	$11.8 \pm 4.35 \times 10^{-3}$	0.69	$48.5 \pm 3.06 \times 10^{-2}$	1.00	$7.94 \pm 1.42 \times 10^{-1}$	0.98	$23.0 \pm 2.25 \times 10^{-2}$	0.99	$28.4 \pm 2.03 \times 10^{-2}$	1.00
Azithromycin	$12.5 \pm 4.47 \times 10^{-2}$	0.85	$5.71 \pm 5.14 \times 10^{-1}$	0.30	$6.02 \pm 4.27 \times 10^{-2}$	0.53	$4.80 \pm 1.29 \times 10^{-1}$	0.96	$25.1 \pm 2.86 \times 10^{-3}$	0.97
Carbamazepine	$6.31 \pm 7.10 \times 10^{-3}$	0.17	$5.54 \pm 17.4 \times 10^{-3}$	0.03	$1.44 \pm 1.47 \times 10^{-2}$	0.26	$2.47 \pm 5.51 \times 10^{-3}$	0.06	$49.7 \pm 9.75 \times 10^{-4}$	0.90
Ciprofloxacin	$1.33 \pm 0.00 \times 10^{-16}$	0.00	$1.45 \pm 3.02 \times 10^{-2}$	0.06	$8.05 \pm 15.9 \times 10^{-3}$	0.08	$1.74 \pm 0.00 \times 10^{-16}$	0.00	$9.58 \pm 7.23 \times 10^{-3}$	0.40
Clarithromycin	$11.0 \pm 4.15 \times 10^{-2}$	0.85	$44.6 \pm 5.08 \times 10^{-2}$	0.99	$5.25 \pm 2.21 \times 10^{-1}$	0.90	$49.8 \pm 2.93 \times 10^{-2}$	1.00	$71.7 \pm 6.15 \times 10^{-3}$	0.99
Diatrizoic acid	$2.22 \pm 0.00 \times 10^{-16}$	0.00	$2.68 \pm 157 \times 10^{-4}$	0.00	$9.52 \pm 14.1 \times 10^{-3}$	0.13	$10.1 \pm 3.66 \times 10^{-3}$	0.73	$2.79 \pm 2.75 \times 10^{-3}$	0.26
Diclofenac	$1.72 \pm 0.00 \times 10^{-16}$	0.00	$7.08 \pm 0.00 \times 10^{-14}$	0.00	$2.42 \pm 1.16 \times 10^{-2}$	0.64	$3.36 \pm 8.13 \times 10^{-3}$	0.05	$1.45 \pm 0.00 \times 10^{-16}$	0.00
Ibuprofen	$1.13 \pm 1.57 \times 10^{-2}$	0.14	$2.63 \pm 1.12 \times 10^0$	0.97	$21.0 \pm 8.20 \times 10^{-1}$	0.95	$7.73 \pm 1.34 \times 10^{-2}$	0.97	$81.5 \pm 9.20 \times 10^{-2}$	0.99
Iohexol	$1.34 \pm 0.00 \times 10^{-16}$	0.00	$22.5 \pm 1.92 \times 10^{-2}$	1.00	$111 \pm 8.36 \times 10^{-2}$	1.00	$67.7 \pm 8.70 \times 10^{-4}$	0.96	$166 \pm 3.82 \times 10^{-3}$	1.00
Iomeprol	$1.68 \pm 0.00 \times 10^{-16}$	0.00	$18.4 \pm 1.60 \times 10^{-2}$	0.99	$76.8 \pm 8.16 \times 10^{-2}$	1.00	$5.98 \pm 5.78 \times 10^{-3}$	0.27	$11.3 \pm 1.10 \times 10^{-2}$	0.99
Iopamidol	$2.31 \pm 2.26 \times 10^{-3}$	0.21	$2.04 \pm 168 \times 10^{-4}$	0.00	$2.04 \pm 1.47 \times 10^{-2}$	0.43	$4.08 \pm 2.19 \times 10^{-3}$	0.54	$4.47 \pm 1.96 \times 10^{-3}$	0.64
Iopromide	$4.22 \pm 2.22 \times 10^{-1}$	0.42	$4.40 \pm 1.05 \times 10^{-1}$	0.97	$14.8 \pm 4.19 \times 10^{-1}$	0.96	$9.17 \pm 4.47 \times 10^{-3}$	0.61	$19.6 \pm 4.47 \times 10^{-2}$	0.96
Metoprolol	$2.22 \pm 0.00 \times 10^{-16}$	0.00	$11.6 \pm 3.12 \times 10^{-2}$	0.92	$8.94 \pm 3.72 \times 10^{-2}$	0.83	$2.67 \pm 3.66 \times 10^{-3}$	0.16	$15.1 \pm 2.76 \times 10^{-3}$	0.92
Phenazone	$1.76 \pm 0.00 \times 10^{-16}$	0.00	$24.9 \pm 6.67 \times 10^{-2}$	0.94	$5.08 \pm 2.64 \times 10^{-2}$	0.67	$1.54 \pm 0.00 \times 10^{-16}$	0.00	$5.06 \pm 1.53 \times 10^{-3}$	0.79
Propranolol	$3.68 \pm 2.19 \times 10^{-2}$	0.47	$2.57 \pm 2.31 \times 10^{-1}$	0.25	$3.35 \pm 2.90 \times 10^{-2}$	0.36	$3.02 \pm 1.63 \times 10^{-2}$	0.59	$1.43 \pm 1.33 \times 10^{-2}$	0.29
Sotalol	$1.59 \pm 2.19 \times 10^{-3}$	0.12	$6.93 \pm 3.04 \times 10^{-2}$	0.74	$4.31 \pm 2.43 \times 10^{-2}$	0.62	$1.37 \pm 1.96 \times 10^{-3}$	0.14	$189 \pm 7.97 \times 10^{-4}$	1.00
Sulfadiazine	$1.67 \pm 0.00 \times 10^{-16}$	0.00	$2.56 \pm 1.56 \times 10^{-2}$	0.51	$16.6 \pm 4.61 \times 10^{-2}$	0.94	$1.94 \pm 0.00 \times 10^{-16}$	0.00	$34.3 \pm 4.51 \times 10^{-2}$	0.99
Sulfamethizole	$2.88 \pm 2.39 \times 10^{-2}$	0.29	$12.6 \pm 4.68 \times 10^{-2}$	0.85	$9.72 \pm 2.64 \times 10^{-1}$	0.96	$10.0 \pm 7.76 \times 10^{-3}$	0.36	$69.0 \pm 2.52 \times 10^{-2}$	1.00
Sulfamethoxazole	$7.33 \pm 9.45 \times 10^{-3}$	0.15	$3.84 \pm 2.32 \times 10^{-2}$	0.52	$21.0 \pm 6.47 \times 10^{-2}$	0.93	$17.6 \pm 2.79 \times 10^{-3}$	0.94	$3.64 \pm 1.02 \times 10^{-1}$	0.94
Trimethoprim	$39.8 \pm 5.06 \times 10^{-2}$	0.98	$2.32 \pm 3.20 \times 10^{-2}$	0.14	$4.35 \pm 1.86 \times 10^{-2}$	0.74	$4.67 \pm 1.21 \times 10^{-2}$	0.89	$19.2 \pm 1.99 \times 10^{-3}$	0.97
Venlafaxine	$1.66 \pm 0.00 \times 10^{-16}$	0.00	$3.16 \pm 2.62 \times 10^{-2}$	0.35	$2.44 \pm 2.41 \times 10^{-2}$	0.29	$9.53 \pm 2.80 \times 10^{-3}$	0.81	$5.04 \pm 4.87 \times 10^{-3}$	0.26

Table 3 – Summary of degradation rate constants ($k_{\text{bio}, \text{Mi}}$) corrected to per gram of biomass per litre ($\text{L h}^{-1} \text{g}^{-1}$) in this study and a comparison with literature values. Bold values indicate the highest k_{bio} . Biomass is assessed in section 2.5.

Compounds	This study [$\text{L h}^{-1} \text{g}^{-1}$]					Literature [$\text{L h}^{-1} \text{g}^{-1}$]			Ref ¹
	$k_{\text{bio}, \text{M1}}$ Denitrifying	$k_{\text{bio}, \text{M2}}$ Nitrifying	$k_{\text{bio}, \text{M3}}$ Nitrifying	$k_{\text{bio}, \text{M4}}$ Denitrifying	$k_{\text{bio}, \text{M5}}$ Nitrifying	DNAS	Conditions ² NMBBR	DNMBBR	
Acetyl-sulfadiazine	6.76×10^{-2}	2.28×10^{-1}	2.81×10^{-1}	8.94×10^{-2}	3.48×10^{-2}	–	$3.84\text{--}76.9 \times 10^{-2}$	–	<i>G</i>
						–	$2.40\text{--}3.90 \times 10^{-1}$	–	<i>H</i>
						–	–	1.54×10^{-1}	<i>I</i>
Atenolol	4.15×10^{-3}	9.45×10^{-2}	2.46×10^{-1}	9.39×10^{-2}	8.53×10^{-2}	$2.92\text{--}3.46 \times 10^{-2}$	$2.79\text{--}3.75 \times 10^{-2}$	–	<i>A</i>
						–	$8.15\text{--}18.1 \times 10^{-2}$	–	<i>G</i>
						–	$1.30\text{--}2.90 \times 10^{-1}$	–	<i>H</i>
						–	–	2.67×10^{-1}	<i>I</i>
Azithromycin	4.40×10^{-2}	1.11×10^{-1}	1.86×10^{-2}	1.96×10^{-1}	7.54×10^{-3}	–	$1.02\text{--}3.14 \times 10^{-2}$	–	<i>G</i>
Carbamazepine	2.22×10^{-3}	1.08×10^{-3}	4.46×10^{-3}	1.01×10^{-3}	1.49×10^{-3}	$\leq 4.17 \times 10^{-3}$	$\leq 4.17 \times 10^{-3}$	–	<i>A</i>
						–	$7.73\text{--}37.0 \times 10^{-3}$	–	<i>G</i>
						–	–	$4.17\text{--}50.0 \times 10^{-3}$	<i>I</i>
Ciprofloxacin	4.68×10^{-17}	2.83×10^{-3}	2.49×10^{-3}	7.10×10^{-17}	2.88×10^{-3}	–	$3.39\text{--}21.2 \times 10^{-3}$	–	<i>G</i>
						–	$6.50\text{--}14.6 \times 10^{-1}$	–	<i>H</i>
Clarithromycin	3.87×10^{-2}	8.69×10^{-2}	1.63×10^{-1}	2.03×10^{-1}	2.15×10^{-2}	$7.50\text{--}19.2 \times 10^{-3}$	$7.50\text{--}12.1 \times 10^{-3}$	–	<i>A</i>
						–	$2.64\text{--}8.54 \times 10^{-2}$	–	<i>G</i>
						–	–	$2.50\text{--}4.17 \times 10^{-2}$	<i>I</i>
						–	–	–	<i>G</i>
Diatrizoic acid	7.82×10^{-17}	5.22×10^{-5}	2.95×10^{-3}	4.12×10^{-3}	8.38×10^{-4}	–	$1.86\text{--}19.3 \times 10^{-3}$	–	<i>G</i>
						–	–	4.17×10^{-3}	<i>I</i>
Diclofenac	6.06×10^{-17}	1.38×10^{-14}	7.49×10^{-3}	1.37×10^{-3}	4.35×10^{-17}	$\leq 4.17 \times 10^{-3}$	$\leq 4.17 \times 10^{-3}$	–	<i>A</i>
						$< 1.67 \times 10^{-3}$	–	–	<i>B</i>
						4.17×10^{-3}	–	–	<i>C</i>
						–	$2.50\text{--}15.8 \times 10^{-3}$	–	<i>D</i>
						–	$1.48\text{--}5.72 \times 10^{-2}$	–	<i>G</i>
						–	$2.20\text{--}2.30 \times 10^{-1}$	–	<i>H</i>
						–	–	–	<i>H</i>
Ibuprofen	3.98×10^{-3}	5.13×10^{-1}	6.50×10^{-1}	3.16×10^{-2}	2.45×10^{-1}	6.25×10^{-2}	–	–	<i>B</i>
						–	$0.00\text{--}6.46 \times 10^{-1}$	–	<i>D</i>
						–	$4.83\text{--}29.1 \times 10^{-1}$	–	<i>G</i>
						–	$1.31\text{--}2.91 \times 10^0$	–	<i>H</i>
						–	–	5.83×10^{-2}	<i>I</i>
Iohexol	4.72×10^{-17}	4.39×10^{-2}	3.44×10^{-1}	2.76×10^{-3}	4.98×10^{-2}	–	$3.03\text{--}9.10 \times 10^{-2}$	–	<i>G</i>
						–	–	2.92×10^{-2}	<i>I</i>
Iomeprol	5.92×10^{-17}	3.59×10^{-2}	2.38×10^{-1}	2.44×10^{-3}	3.39×10^{-2}	–	$2.51\text{--}6.70 \times 10^{-2}$	–	<i>G</i>
						–	–	2.50×10^{-2}	<i>I</i>

Iopamidol	8.13×10^{-4}	3.98×10^{-5}	6.32×10^{-3}	1.67×10^{-3}	1.34×10^{-3}	–	$3.88\text{--}11.1 \times 10^{-2}$	–	<i>G</i>
						–	–	4.17×10^{-3}	<i>I</i>
Iopromide	1.49×10^{-1}	8.58×10^{-2}	4.58×10^{-1}	3.74×10^{-3}	5.89×10^{-2}	–	$3.01\text{--}19.7 \times 10^{-3}$	–	<i>G</i>
						–	$0.60\text{--}2.10 \times 10^{-2}$	–	<i>H</i>
						–	–	3.75×10^{-2}	<i>I</i>
Metoprolol	7.82×10^{-17}	2.26×10^{-2}	2.77×10^{-2}	1.09×10^{-3}	4.53×10^{-3}	$\leq 4.17 \times 10^{-3}$	$2.88\text{--}3.17 \times 10^{-2}$	–	<i>A</i>
						–	$2.33\text{--}5.16 \times 10^{-2}$	–	<i>G</i>
						–	$8.70\text{--}21.0 \times 10^{-2}$	–	<i>H</i>
						–	–	3.33×10^{-2}	<i>I</i>
Phenazone	6.20×10^{-17}	4.85×10^{-2}	1.57×10^{-2}	6.29×10^{-17}	1.52×10^{-3}	$\leq 4.17 \times 10^{-3}$	$\leq 4.17 \times 10^{-3}$	–	<i>A</i>
						–	$8.64\text{--}35.8 \times 10^{-3}$	–	<i>G</i>
						–	$0.70\text{--}1.10 \times 10^{-2}$	–	<i>H</i>
Propranolol	1.30×10^{-2}	5.01×10^{-2}	1.04×10^{-2}	1.23×10^{-2}	4.29×10^{-3}	–	$1.26\text{--}16.9 \times 10^{-1}$	–	<i>G</i>
						–	$1.60\text{--}6.40 \times 10^{-1}$	–	<i>H</i>
						–	–	5.48×10^{-1}	<i>I</i>
Sotalol	5.60×10^{-4}	1.35×10^{-2}	1.33×10^{-2}	5.59×10^{-4}	5.68×10^{-3}	–	$2.60\text{--}5.77 \times 10^{-2}$	–	<i>G</i>
						–	$1.40\text{--}3.30 \times 10^{-2}$	–	<i>H</i>
						–	–	2.08×10^{-2}	<i>I</i>
Sulfadiazine	5.88×10^{-17}	4.99×10^{-3}	5.14×10^{-2}	7.92×10^{-17}	1.03×10^{-1}	–	$3.66\text{--}8.69 \times 10^{-3}$	–	<i>G</i>
						–	–	2.50×10^{-2}	<i>I</i>
Sulfamethizole	1.01×10^{-2}	2.46×10^{-2}	3.01×10^{-1}	4.08×10^{-3}	2.07×10^{-1}	–	$9.60\text{--}28.7 \times 10^{-3}$	–	<i>G</i>
						–	$4.30\text{--}9.20 \times 10^{-2}$	–	<i>H</i>
						–	–	$4.17\text{--}75.0 \times 10^{-3}$	<i>I</i>
Sulfamethoxazole	2.58×10^{-3}	7.49×10^{-3}	6.50×10^{-2}	7.18×10^{-3}	1.09×10^{-1}	1.71×10^{-2}	–	–	<i>E</i>
						–	$7.88\text{--}17.5 \times 10^{-3}$	–	<i>G</i>
						–	$1.00\text{--}1.60 \times 10^{-2}$	–	<i>H</i>
						–	–	$4.17\text{--}70.8 \times 10^{-3}$	<i>I</i>
Trimethoprim	1.40×10^{-1}	4.52×10^{-3}	1.35×10^{-2}	1.91×10^{-2}	5.77×10^{-3}	$\leq 4.17 \times 10^{-3}$	$\leq 1.25 \times 10^{-2}$	–	<i>A</i>
						$3.75\text{--}5.42 \times 10^{-2}$	–	–	<i>F</i>
						–	$2.84\text{--}6.29 \times 10^{-2}$	–	<i>G</i>
						–	$1.10\text{--}1.70 \times 10^{-2}$	–	<i>H</i>
						–	–	1.79×10^{-1}	<i>I</i>
Venlafaxine	5.85×10^{-17}	6.16×10^{-3}	7.55×10^{-3}	3.89×10^{-3}	1.51×10^{-3}	$\leq 4.17 \times 10^{-3}$	$6.25\text{--}8.33 \times 10^{-3}$	–	<i>A</i>
						–	$4.02\text{--}14.5 \times 10^{-3}$	–	<i>G</i>
						–	$1.30\text{--}1.90 \times 10^{-2}$	–	<i>H</i>
						–	–	$4.17\text{--}79.2 \times 10^{-3}$	<i>I</i>

¹References: A=Falås et al., 2013 (rate constants: L h⁻¹ gTS⁻¹); B=Suarez et al., 2010 (rate constants: L h⁻¹ gVSS⁻¹); C=Plósz et al., 2012 (rate constants: L h⁻¹ gTSS⁻¹); D=Falås et al., 2012 (rate constants: L h⁻¹ gTS⁻¹); E=Plósz et al., 2010 (rate constants: L h⁻¹ gTSS⁻¹); F=Su et al., 2015 (rate constants: L h⁻¹ gCOD⁻¹); G=Escollà Casas et al., 2015a (rate constants: L h⁻¹ g⁻¹); H=Tang et al.,

2017 (rate constants: $\text{L h}^{-1} \text{g}^{-1}$); I =Torresi et al., 2016 (rate constants: $\text{L h}^{-1} \text{g}^{-1}$); ²Abbreviations: DNAS=Denitrifying Activated Sludge; NMBBR=Nitrifying MBBR; DNMBBR=Denitrifying MBBR

Table 4 – Overall removal percentage [%] comparison in MBBRs performing denitrification processes in the present study and in the literature.

Compounds	Removal after 24h treatment in M1 & M4 (batch experiment) [%]	Measured removal [%]			
		Denitrifying MBBRs (M1 & M4)	Lab-scale anoxic CAS (Suarez et al., 2010)	HYBAS (including both oxic and anoxic) (Falås et al., 2013)	Lab-scale post-denitrifying MBBRs (Torresi et al., 2017)
Atenolol	62 ± 33	16 ± 14	N/A	~25 ± 10	~70 ± 15
Carbamazepine	2 ± 9	25 ± 1	1 ± 10	~0	~10 ± 15
Clarithromycin	96 ± 2	10 ± 4	N/A	~0 ± 20	N/A
Diclofenac	6 ± 3	13 ± 13	2 ± 5	~20 ± 20	N/A
Ibuprofen	67 ± 21	-8 ± 10	37 ± 26	N/A	N/A
Iohexol	1 ± 11	4 ± 1	N/A	N/A	~10 ± 7
Iomeprol	12 ± 19	-4 ± 20	N/A	N/A	~5 ± 10
Metoprolol	9 ± 6	6 ± 2	N/A	N/A	~10 ± 7
Sotalol	9 ± 7	< LOQ	N/A	N/A	~5 ± 20
Sulfamethoxazole	33 ± 2	-9 ± 22	–	N/A	~15 ± 35
Trimethoprim	78 ± 23	23 ± 26	–	~0 ± 20	~50 ± 20
Venlafaxine	16 ± 10	7 ± 6	N/A	~0 ± 10	N/A

Highlights

- Pharmaceuticals from hospital wastewater are removed using pilot-scale MBBR.
- Removal above 20% was observed for each of 17 of the 22 compounds analyzed.
- 8 compounds had a near complete removal after 24 hours of treatment.
- This includes iodinated X-ray contrast media, which used extensively in hospitals.