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PHARMACEUTICALLY ACTIVE COMPOUNDS REMOVAL FROM SURFACE WATER BY MEMBRANE PROCESSES

Carolina Fonseca Couto

Belo Horizonte

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Supervisor: D. Sc. Míriam Cristina Santos Amaral Moravia

Co-Supervidor: D. Sc. Lisete Celina Lange

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Co-Orientador: D. Sc. Lisete Celina Lange

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UNIVERSIDADE FEDERAL DE MINAS GERAIS
Escola de Engenharia
Programa de Pós-Graduação em Saneamento, Meio Ambiente e Recursos Hídricos
Avenida Antônio Carlos, 6627 - 4º andar - 31270-901 - Belo Horizonte – BRASIL
Telefax: 55 (31) 3409-1882 - posgrad@desa.ufmg.br
http://www.smarh.eng.ufmg.br

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PHARMACEUTICALLY ACTIVE COMPOUNDS REMOVAL FROM SURFACE WATER BY MEMBRANE PROCESSES

CAROLINA FONSECA COUTO

Tese defendida e aprovada pela banca examinadora constituída pelos Senhores:

Profa MIRIAM CRISTINA SANTOS AMARAL MORAVIA

Profa LISÉTE CELINA LANGE

Prof. EDUARDO COUTINHO DE PAULA

Profa FABIANA VALÉRIA DA FONSECA

Prof. LUCIANO MATOS QUEIROZ

Prof. RITA RIBEIRO

Aprovada pelo Colegiado do PG SMARH

Prof. Antonio Teixeira de Matos
Coordenador

Versão Final aprovada por

Profª. Miriam Cristina Santos Amaral Moravia
Orientadora

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ABSTRACT

Pharmaceutically active compounds (PhACs) are a real threat all around the world as well as in Brazil. Conventional water and wastewater treatment are not efficient in the complete removal of these kinds of organic micropollutants of emerging concern ending up in the release of these compounds in the environment. This work aims to investigate the PhACs removal from surface water by membrane processes. Betamethasone and fluconazole, among the 28 assessed PhACs, were the most recurrent during monitoring of the Doce river located in Minas Gerais, which is used for drinking water catching and raw sewage disposal. The results show that the PhACs rejection by nanofiltration (NF) and reverse osmosis (RO) membranes is dependent of permeate recovery rate (RR) adopted The PhAC is completely retained at low RR, but increasing the RR above 40% and 60% for NF and RO respectively resulted in the membrane retention loss. The mechanism of NF and RO PhACs rejection involves size exclusion and hydrophobic interactions. Direct contact membrane distillation (DCMD)showed a rejection >99% for both fluconazole and betamethasone even at high RR (70% RR). The retention of PhACs by MD membrane occurs predominantly by membrane rejection which is mainly governed by volatility and, to a lesser extent, by hydrophobia. DCMD did not show any tendency of fouling, while NF and RO show flux decline mainly due to membrane fouling, which was more evident in RO. Operational cost was estimated at 0.50, 0.43, and 1.96 US$/m^3 for NF, RO and MD respectively. A factorial design 2^3 was used to assess the influence of natural organic matter and Ca and Fe ions on DCMD in order to achieve rejection of 25 PhACs in water. DCMD provided safe water with high PhACs removal (>98%) in all studied cases. The PhAC retention was not affected by HA, Ca and Fe ions in the concentration range evaluated (20-80 for HA, 12-200 for Ca and 12-200 for Fe), except for betamethasone. Permeate flux was not significantly influenced by HA concentrations and was associated to the presence of Fe and Ca. The mathematical model proposed here explained 63,7% of the total response variation, indicating a reasonable adjustment to the DCMD. Thus, in general, MD is less influenced by the feed composition than NF or RO, implicating in higher PhACs rejections, and although the cost was much higher than RO or NF, the possibility of utilization of renewable energy turns this process very promising for producing drinking water with much smaller concentrate production.

Keywords: Membrane separation processes, pharmaceutically active compounds, nanofiltration, reverse osmosis, membrane distillation.

RESUMO

Fármacos são uma ameaça real em todo o mundo e no Brasil. O tratamento convencional de água e águas residuárias não é eficiente na remoção completa desses micro poluentes orgânicos, acabando com a liberação desses compostos no meio ambiente. Este trabalho tem como objetivo investigar a remoção de fármacos em águas superficiais por processos de separação por membrana. Betametasona e fluconazol, dentre os 28 fármacos avaliados, foram os mais recorrentes durante o monitoramento do rio Doce, localizado em Minas Gerais, que é usado para captação de água potável e lançamento de esgoto bruto. Os resultados mostram que a rejeição de fármacos por membranas de nanofiltração (NF) e osmose inversa (OI) é dependente da taxa de recuperação de permeado (RR) adotada. O fármaco é completamente retido em RR baixo, mas aumentando o RR acima de 40% e 60% para NF e OI respectivamente resultou na perda de retenção da membrana. O mecanismo de rejeição de NF e OI envolve a exclusão por tamanho e interações hidrofóbicas. A destilação por membrana de contato direto (DCMD) mostrou uma rejeição >99% tanto para o fluconazol quanto para a betametasona, mesmo com alta RR (70%). A retenção de fármacos pela membrana MD ocorre predominantemente pela rejeição da membrana, que é principalmente governada pela volatilidade. DCMD não mostrou qualquer tendência de incrustação, enquanto NF e OI mostram declínio de fluxo principalmente devido a incrustação de membrana, que foi mais evidente na OI. O custo de operação foi estimado em 0,50, 0,43 e 1,96 US $ / m^3 para NF, OI e MD, respectivamente. Um planejamento fatorial 2^3 foi utilizado para avaliar a influência da matéria orgânica natural e dos íons Ca e Fe na DCMD, visando à rejeição de 25 fármacos em água. O DCMD forneceu água com alta remoção de fármacos (> 98%) em todos os casos estudados. A retenção de fármacos não foi afetada pelos íons ácidos húmicos (HA), Ca e Fe na faixa de concentração avaliada (20-80mg/L para HA, 12-200mg/L para Ca e 12-200mg/L para Fe), exceto para betametasona. O fluxo de permeado não foi influenciado significativamente pelas concentrações de HA e esteve associado à presença de Fe e Ca. O modelo matemático proposto explicou 63,7% da variação total da resposta, indicando um ajuste razoável ao DCMD. Assim, em geral, o MD é menos influenciado pela composição da alimentação do que a NF ou OI, implicando em maiores rejeições de fármacos, e embora o custo seja muito maior que OI ou NF, a possibilidade de utilização de energia renovável torna este processo muito promissor para produção de água potável com menor produção de concentrado.

Palavras-chave: Processos de separação por membranas, fármacos, nanofiltração, osmose inversa, destilação por membrana.

SUMMARY

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LIST OF SYMBOLS AND ABREVIATIONS

A	Filtration area
AOP	Advanced oxidation process
CP	Concentration polarization
D_h	Cell hydraulic diameter
D_i	Diffusion coefficient
EC	Electrical conductivity
F_{df}	flux decline due to fouling
R_{cc}	hydraulic resistance after chemical cleaning
R_f	Hydraulic resistance of the fouling layer
R_{fr}	Reversible fouling layer
R_{fir}	Irreversible fouling layer
J_{sd}	Effluent flux
J_w	Water flux
MBR	Membrane bioreactor
MF	Microfiltration
MD	Membrane Distillation
MSP	Membrane separation process

MWCO	Molecular weight cut-off
NF	Nanofiltration
NOM	Natural organic matter
PhAC	Pharmaceutically Active Compound
Q	feed flow rate
Re	Reynolds number
r_{int}	logarithmic mean radius difference
R	Rejection
R_m	Hydraulic resistance of the membrane
RO	Reverse osmosis
SEC	Specific energy consumption
S_c	Schmidt number
S_h	Sherwood number
TMP	Transmembrane pressure
UF	Ultrafiltration
TS	Total solids
TVS	Total volatile solids
TDS	Total dissolved solids

T_{fd}	Total flux decline
WP	Water permeability
WTP	Water treatment plant
WWTP	Wastewater treatment plant
$\Delta\Pi$	Trans-membrane osmotic pressure difference
μ_w	Water viscosity

1. INTRODUCTION

1.1. Contextualization and problem

In recent years, pharmaceutical products, such as, analgesics, anti-inflammatory drugs, antibiotics, lipid regulators, beta-blockers and X-rays contrast media, have become more and more a part of the daily routine life, being used in human and animal for health treatment, in order to improve life quality and to increase their life span worldwide.

PhACs can reach the aquatic environment in excrements through sewer systems after veterinary and human usage (CAMACHO-MUNOZ *et al*., 2014). Also, the improper disposal of expired medication can also contribute to this contamination. Thus, without an efficient treatment, these pollutants are being discharged with the effluent into the water bodies (YAN *et al*., 2014).

More than 200 PhACs have been detected from ng/l to μg/l concentrations in surface, ground water and sewage, and they were recognized as potential environment threats (PETRIE *et al*., 2015; TAHERAN *et al*., 2016; CAMACHO-MUNOZ *et al*., 2014). Due to their increase in production, usage and continuous discharged to the environment and their potential ecological effect, PhACs have been attracting global attention (SADMANI *et al*., 2014).

However, their actual effect and interaction with the environment is still not well known and understood, also PhACs are not currently covered by the water quality regulations (MA *et al*., 2017) opening a gap on the knowledge on thresholds of residues in environment and human health.

Due to a large spectrum of pollutants from industrial, domestic and farming activities that arrives, diluted in water, in conventional wastewater treatment plants (WWTPs), they are not specially designed to remove PhACs (GRACIA-IVARS *et al*, 2017). The complete removal of PhACs during conventional WWTP is quite a challenge due to several factors such as low volatility, different hydrophobicity, complex structures, extremely low concentration, influencing the microorganisms, interaction with other solutes and the separation medium (membrane, sludge, etc.) (KEEN *et al*., 2012) and low concentrations levels of PhACs. Since they are not completely eliminated during treatment processes, and complex outlets may be formed PhACs are discharged into waterbodies (YOON *et al*., 2010).

Conventional drinking water treatment plants (WTP) using surface water mainly aims to remove natural organic matter and microorganisms from the water (VERGILI, 2013). It has been reported that some PhACs show to be persistent throughout the drinking water treatment process mostly due to the PhACs small size and polarity, which makes them highly soluble in water and very mobile in the environment, and extremely difficult to remove by treatment (GABARRON *et al*., 2016, VERLIEFDE *et al*., 2009). Thus, PhACs can return to human body through water cycle and food chain which may potentiate the human health risks (AMON, 2011).

In face of such limitations associated to conventional treatment processes, the necessity to achieve PhACs removal has led to explore alternatives technologies, among them can be highlighted membrane separation processes (MSP) (GRACIA-IVARS et al, 2017; SADMANI *et al*., 2014; NGUYEN *et al*., 2013; PARK *et al*., 2017; HUBNER *et al*., 2015).

MSP such as membrane distillation (MD), reverse osmosis (RO), nanofiltration (NF), ultrafiltration (UF), and microfiltration (MF) applied at pilot- and full-scale installations are being successfully applied either as a single process or as a combination of different membrane techniques in domestic or industrial wastewater reclamation in order to achieve a high quality permeate by efficiently removing a large spectrum of pollutants, microorganisms, salts, organic micropollutants, proteins, sugars or inorganic ions. To increase its efficiency and to reduce problems with fouling, it is possible to integrate membrane systems using low pressure driven membranes such as ultrafiltration (UF) and microfiltration (MF) with NF/RO membranes reaching high treatment efficiency for the removal of salts, metals, endocrine disrupting compounds, pharmaceuticals, personal care products and other emerging contaminants (DOEDERER *et al*., 2014).

Despite their high efficiency in removing compounds even in trace concentration, a major drawback is that filtration processes are basically designed to concentrate but not to degrade pollutants and require the disposal of wastes stream. And since the rejection of PhACs depends on the concentration of them in the feed stream, if it increases, the efficiency in the removal of pharmaceutically active compounds by the membrane may decrease, reducing the overall efficiency. Thus, the concentrate generated of one of the MSP applications, requires further treatment in order to break down PhACs molecules and eliminate the threat, increasing its efficiency.

Membrane separation processes, in particular the nanofiltration (NF) and reverse osmosis (RO) processes, are recognized as effective and reliable forms of being applied, mainly, in the treatment of supply water either as a polishing step or in raw water purification (YANGALI-QUINTANILLA *et al*., 2010; SADMANI *et al*., 2014). However, NF-based treatments are still limited primarily to bench scale (AZAIS *et al*., 2014). Unlike the reverse osmosis processes, NF, in addition to having a greater permeate flux and being able to work at lower pressures, does not promote the complete removal of ions, being a preferable process to RO in cases where there is no such need, since it is expected of showing effective removal organic pollutants (BRUGGEN *et al*., 2008), demonstrating promising results on rejection of PhACs and EDCs.

Membrane distillation (MD) is a low temperature distillation process that involves the transport of water in the vapour phase from a feed solution through a microporous and hydrophobic membrane to the distillate (product) side. Direct contact membrane distillation (DCMD) is probably the most widely studied MD system configuration due to its simple operation (WIJEKOON *et al*., 2014). In DCMD, the feed solution is maintained at a higher temperature than the distillate; thus, creating a vapour pressure difference between the feed and distillate. The membrane separates the liquid phase of the feed and distillate streams but allows water vapour to transport freely through its dry microporous pores. In MD, the membrane material must be hydrophobic to prevent wetting of the pores by liquid feed or distillate under standard operating conditions.

Because mass transfer can occur only in the gas phase, MD can offer complete rejection of all non-volatile solutes such as inorganic salts and pathogenic microorganisms. As a result, to date, much of the effort in MD research has focused on desalination applications (CURCIO; DRIOLI, 2005).

Unlike pressure driven membrane processes, due to the absence of hydraulic pressure, MD is less susceptible to membrane fouling (ALKHUDHIRI *at al*., 2013). Even when a fouling layer does form on the membrane surface, it is expected to be less compacted and can be easily removed (ALKHUDHIRI *at al*., 2013).

Although, the application of MSP has been proved to be efficient in PhACs removal, there is still lack of knowledge of the best feasible applicable technology for drinking water treatment

processes in order to archive PhACs removal associated with the best technically, economically and environmentally friendly technology.

1.2. Justification

This proposal addresses issues that are at the frontier of knowledge and that can make a major contribution to the advancement of technologies for the treatment of water and effluents considering the growing concern with pharmaceutical products present in aquatic environments as well as the low efficiency of the classic processes of treatment of water and domestic effluents in the removal of these components.

The great need in the identification and quantification of these compounds is directly related to the possibility of causing adverse effects in aquatic animals as well as in the domestic consumers of the treated waters. The efficiency of removal of these compounds with viable technologies is of paramount importance for population safety.

As far as the knowledge goes, there are no published papers identifying and quantifying the miscellany of drugs present in the supply waters of the five regions of Brazil. There is no knowledge of the relationship between population habits as well as the treatments used and the presence of these chemicals in the waters. There is a growing increase in research in order to obtain the removal of these drugs, especially in supply waters around the world, however, there are only a few Brazilian efforts in this regard. In addition, the vast majority of papers focus on synthetic samples with only one compound, thus identifying the need for research development focusing on this deficiency.

The interest in the use of membrane separation processes associated or not with other processes directed to the treatment of waters and effluents is increasing, due to the great potential of improvement of efficiency when compared to the traditional technologies, especially when considering the facility of installation, reduction of the area, as well as trends in reducing its cost.

This work will also contribute significantly to increasing national knowledge on monitoring of water source drugs and supporting studies that can assess their potential effects on aquatic organisms. In addition, it will assist water users, health authorities and companies responsible

for the management of water resources and treatment of water for human consumption in decision making.

1.3. Hypothesis

H1: There are PhACs in surface water in Doce River, since untreated wastewater is discarded in the river;

H2: Reverses osmosis, nanofiltration and membrane distillation are able to completely reject PhACs, although due to its robustness, MD is more effective;

H3: Membrane distillation is a process less susceptible to fouling, and even submitted to extreme conditions of fouling feature will contribute to a higher PhACs rejection.

1.4. Objectives

1.4.1. General

Investigate the PhAC removal from surface water by membrane processes.

1.4.2. Specifics

• Evaluate and compare technically, economically and environmentally the performance of nanofiltration, reverse osmosis and membrane distillation in the removal of drugs in supply waters;

• Evaluate the effect of organic matter concentration on the performance of membrane distillation processes;

• Evaluate the effect of ion concentration on the performance of membrane distillation processes.

1.5. Structural form

Besides this introduction (Chapter 1) and the final considerations (Chapter 7), this thesis is structured in five chapters in an article format. The choice of an article format indicates that each chapter is interdependent and can be read separately. Each specific objective relates to one chapter. **Chapter 2** is literature reviews, which brings the actual knowledge about the presence and removal of PhACs in the environmental applying different membrane separation processes; **Chapter 3**, attending the first specific objective, assess and compare the application of different technologies in order to remove and promote a safer drinking water. The better treatment will be chosen from a technical, economic and environmental assessment. **Chapter 4 and 5** attends the second and third specific objectives, addressing the application of membrane distillation on the removal of PhACs using organic matter and salts, respectively, as a foulant.

1.6. Achievement

Table 1 shows the main achievement of this thesis.

Table 1- Summary of main achievement of this thesis

Chapter	Title	Status	Journal	Impact factor
Appendix 1	Occurrence, fate and removal of pharmaceutically active compounds (PhACs) in water and wastewater treatment plants – a review	Submitted.	Environmental Science Pollution Research	2.6
2	A critical review on membrane separation processes applied to remove pharmaceutically	Accepted	Journal of Water Processing Engineering	-

	active compounds from water and wastewater			
Appendix 2	Occurrence of pharmaceuticals active compounds in water supply systems in Brazil	Submitted.	Chemosphere	4.2
3	Assessing potential of nanofiltration, reverse osmosis and membrane distillation drinking water treatment for pharmaceutically active compounds (PhACs) removal	Submitted.	Separation and Purification Technology	3.9
4	Effect of humic acid concentration on pharmaceutically active compounds (PhACs) rejection by direct contact membrane distillation (DCMD)	Submitted.	Separation and Purification Technology	3.9
5	The use of factorial design in the analysis of membrane distillation' rejection of pharmaceutically active compounds (PhACs) as a function of organic matter and salts	Finished. Ready for submission.	Chemical Engineering Journal	6.7

This thesis is a part of a much bigger project sponsored by National Health Foundation (FUNASA) which aims to evaluate the occurrence of drugs in raw and treated waters (ETA's and ETE's effluent and effluent), with representation in the 5 Brazilian regions, with a respective removal and half-life rate for each compound found, in addition to establishing risk indicators ecotoxicological, with a view to technically and scientifically subsidize the decision-making of the actions of monitoring the quality of water for human consumption and the revision of Portaria MS nº 2.914 / 2011.

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2. A CRITICAL REVIEW ON MEMBRANE SEPARATION PROCESSES APPLIED TO REMOVE PHARMACEUTICALLY ACTIVE COMPOUNDS FROM WATER AND WASTEWATER

2.1. Introduction

In recent years, pharmaceutical products, such as, analgesics, anti-inflammatory drugs, antibiotics, lipid regulators, beta-blockers and X-rays contrast media, have become more and more a part of the daily routine life, being used in human and animal for health treatment, in order to improve life quality and to increase their life span worldwide. This scenario is due, specially, to improvements in health standards which implies in a consumption increase of pharmaceutically active compounds (PhACs) (VERLICCHI *et al*., 2012).

PhACs reach water systems from different sources such as human excretion (sewage), wrongful disposal, landfill leachate, drain water, or from industries (ARCHER *et al*., 2017). Although it has been reported that PhACs are found in the environment at low concentration (ng/l to μg/l range), the constant production, consumption and therefore discharge to the environment, PhACs has been raising global attention and concern.

Over 200 different PhACs were observed in surface, ground water and sewage (PETRIE *et* al., 2015; TAHERAN *et al*., 2016) and it is still unclear the levels and effects as well as the fate of these compounds in the human health and wildlife, however it has been found their potential to cause aquatic toxicity, development of resistance in pathogenic microbes; genotoxicity and endocrine disruption (KHETAN; COLLINS, 2007; MARTÍN *et al*., 2012; TAHERAN *et al*., 2016). Also, the release of PhACs in the environment is not regulated and covered by the existing water quality (MA *et al*., 2017).

The presence of PhACs in the environment and their impact on human and wildlife health may be far more extent than it is reported, since the analytical methods for the quantification and monitoring of these compounds, so as to understand and determine their fate and behaviour

within the environment are expensive, complicated and time consuming which may compromise the knowledge of the full extent of PhACs impact.

A large spectrum of pollutants from industrial, domestic and farming activities arrives, diluted in water, in conventional wastewater treatment plants (WWTPs). Their main goal is to remove organic matter and nutrients from the effluent in the order of g/L to mg/L, thus, the complete removal of PhACs during conventional WWTP is quite a challenge due to several factors such as low volatility, different hydrophobicity, complex structures, extremely low concentration, influencing the microorganisms, interaction with other solutes and the separation medium (membrane, sludge, etc.) (KEEN *et al*., 2014). Since they are not completely eliminated during treatment processes, and complex outlets may be formed, PhACs are discharged into waterbodies (YOON *et al.*, 2010). According to Archer *et al.* (2017), the concentration of some PhACs in the effluent has increased during the treatment in WWTPs, if compared with the influent, as a consequence of their transformation into conjugates.

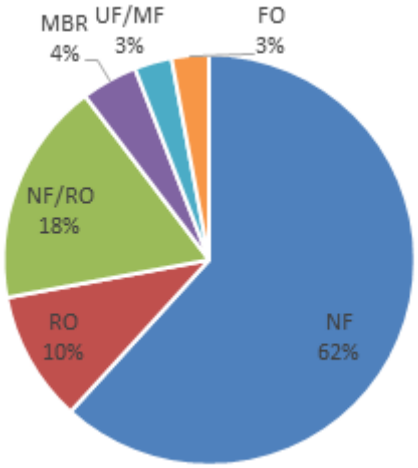
It has been reported that some PhACs show to be persistent throughout the drinking water treatment process mostly due to the PhACs small size and polarity, which makes them highly soluble in water and very mobile in the environment, and extremely difficult to remove by conventional treatment (GABARRON *et al*., 2016, VERLIEFDE *et al.*, 2009). Thus, PhACs can return to human body through water cycle and food chain which may potentiate the human health risks (AMON, 2011).

In face of such limitations associated to conventional treatment processes, the demand to achieve PhACs removal have led to explore alternatives technologies, among them can be highlighted membrane separation processes (MSP) due to their high efficiency in removing organic matter, salts, metal, and therefore, PhACs and other emerging contaminants (SADMANI *et al*., 2014;HAN *et al*., 2017; DOEDERER *et al*., 2014).

Despite their high efficiency in removing compounds even in trace concentration, a major drawback is that filtration processes are basically designed to concentrate but not to degrade pollutants and require the disposal of wastes stream. And since the rejection of PhACs depends on the concentration of them in the feed stream, if it increases, the efficiency in the removal of pharmaceutically active compounds by the membrane may decrease, reducing the overall efficiency. Thus, the concentrate generated in one of the MSP applications requires further treatment in order to breakdown PhACs molecules and eliminate the threat, increasing its efficiency. Thus, this paper reviews the potentials and challenges of the removal of PhACs

from water and wastewater by membrane separation processes, the treatment options for membrane concentrate rich in PhACs and future prospects. Several review papers were published about removal of PhACs contaminants through membrane, however, a general overview of the application and the rejection of PhACs, including all membrane separations processes, as well as membrane distillation, is still needed. Thus, a research on Scopus was done in order to rise how many studies have been carried out in the last decade (2008-2018) about the subject, using the key words PhACs, pharmaceutically active compounds, microfiltration, ultrafiltration, microbioreactor, nanofiltration, reverse osmosis and membrane distillation. It was found 78 published papers on the subject. The majority of the studies are focused on the application of NF and RO (Figure 1). Therefore, it was selected papers published no earlier than 2000.

Figure 1 - Distribution of papers published in the last decade (2008-2018) about the application of membrane separation processes for the removal of PhACs



2.2. Membrane separation processes (MSP) toward PhACs removal from water and wastewater

Membrane separation processes (MSP) have become an important alternative to produce good quality water reaching the drinking water standards due to their higher removal rate of low molecular weight organic pollutants, minimizing the risk associated to the source and its contaminants as well as its modularity and ability to integrate with other systems. Microfiltration (MF), ultrafiltration (UF) and membrane bioreactor (MBR) which is the association of MF or UF with a biological treatment, are mainly applied to the treatment of raw

effluent (GARCIA-IVARS *et al*., 2017; RADJENOVIC *et al*., 2009; SNYDER *et al*., 2007) and nanofiltration (NF) and reverse osmosis (RO) as a polishing step in order to produce water for reuse. NF, RO and membrane distillation (MD) can also be considered as advanced treatment which generates water with high quality (HAN *et al*., 2017; SADMANI *et al*., 2014; LIN, 2017)

It has been reported that membranes have three mechanisms of removing micropollutants which is either by size exclusion, electrostatic repulsion or adsorption (GEANIYU *et al*., 2015 SIRES and BRILLAS, 2012; VERLIEFDE *et al*., 2009). Thus, the prediction of the PhACs removal efficiency is quite difficult because it is dependent on physico-chemical properties of the compound, membrane properties such as pore size, molecular weight cut-off and zeta potential, membrane-solute interactions and also influent matrix (TAHERAN *et al*., 2016).

2.2.1. MF and UF membranes

The application of microfiltration (MF) and ultrafiltration (UF) technology is limited to their pores size and molecular weight cutoff (MWCO) which is larger than the molecular weight (MW) of most PhACs (MWCO ranging from 200-1 KDa for MF and UF). This factor plays a major role in the rejection of PhACs considering that MF and UF technology is based on the separation mainly associated to the size difference. Also, associated to the high solubility of pharmaceutical compounds, the MF and UF efficiency is considered very little or none in removing dissolved solutes in the aquatic media (Table 2) Yoon *et al.* (2007) evaluated the interactions between PhACs and UF membrane which membrane had a molecular weight cut-off value of 100 kDa and the investigated pharmaceuticals had a molecular weight less than 0.4 kg/mol (0.4 kDa). The UF membrane was not able to block PhACs passage. Similar results can be observed in the study conducted by Snyder *et al*. (2007).

Besides size exclusion, membrane surface adsorption is another one of the major mechanisms for UF to remove dissolved pollutants. The pharmaceutical adsorption on the membrane surface is related to the Log K_{ow} value. When this value is low (usually log K_{ow}<2.8), pharmaceuticals have low lipophilicity and high hydrophilicity, which indicates that these contaminants are not likely to be adsorbed on the membrane surface, and therefore, pass through the membrane barrier with the permeate (SHENG *et al*., 2016, FERNÁNDEZ *et al*., 2014, YOON *et al*., 2007). However, on the other hand, when pharmaceuticals have high Log

K_{ow} (usually log K_{ow}>2.8), the opposite effect is obtained, being these compounds likely to be adsorbed on membrane surfaces (FERNÁNDEZ *et al*., 2014, YOON *et al*., 2007). This result agrees with those obtained in an experimental work developed by Fernández *et al*. (2014) which assessed the interactions between PhACs and a UF membrane. This study showed a high membrane retention for Carbamazepine (70%), Gemfibrozil (51%), and Metoprolol (39%). In contrast, although several other compounds including Diclofenac, Ibuprofen, and Naproxen also have relatively high Log Kow values (Table 2), both the retention and adsorption caused by the membrane were almost negligible. This is presumably due to the hydrophobicity of these compounds that may reduce once they are deprotonated, similar results were obtained by Yoon *et al*. (2007).

For these reasons, MF and UF processes is mostly employed as pretreatment process to remove colloids and natural organic matter (NOM) (SNYDER *et al*., 2007). According to Garcia-Ivars *et al*. (2017), who assessed the performance of ceramic UF membrane on the treatment of WWTP secondary effluent in order to remove PhACs, have found that during the filtration experiments, it is formed a foulant layer by adsorbed organic and inorganic compounds onto the ceramic UF membrane which might act as a second barrier for separation and increase the efficiency of the process. This fouling layer formed on the membrane surface is characterized by its hydrophobicity and negatively charged particles on the surface. This reduces both the porosity and pore size of the ceramic membrane mainly because both complete and intermediate pore blocking occurred during the first stages of the filtration (CHON *et al*., 2013). As a result, the rejection of some PhACs are improved compared to those obtained for cleaner membranes (GARCIA-IVARS *et al*., 2017).

Also, applying UF membrane to the treatment of rich organic compounds effluents can be even more improved assuming that PhACs can get associated to organic macromolecules in the effluent which may led to form effluent organic matter compounds complexes that could be the result of hydrogen bonding and electrostatic attraction between the polar moieties of PhAC molecules and the phenolic or carboxylic groups of the humic-like substances. These complexes are rejected by sieving effect or charge repulsion between them and the membrane surface (GARCIA-IVARS *et al*., 2017). Still, PhACs polarity and hydrophobicity as well as the membrane nominal pore size (retention values were found to be higher for membrane with smaller MWCO (GARCIA-IVARS *et al*., 2017) play a major role in the in PhACs rejection.

Table 2 - Concentrations and removal (%) of selected pharmaceuticals when applying UF technology

PhAC Classes	PhACs	Membrane type	Sample type	Raw sample (ng/L)	Treated Sample (ng/L)	Overall removal (%)	Observation	Reference
Antiinflammatory drug	Ibuprofen	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	39	36	7.7	-	Snyder et al., 2007
		Three seven-channel ceramic UF membranes (INSIDE CéRAMTM, supplied by TAMI Industries, France) with a nominal pore size of 1, 5 and 8 kDa	Spiked WWTP secondary effluent samples – Spain	1000	NA	~ 60, 35, 25	1, 5 and 8 Kda, respectively, pH7	Garcia-Ivars et al., 2017
	Diclofenac	Hollow-fiber polyvinylidene fluoride (PVDF) UF membrane (Cleanfil-P75R, Kolon Membrane Corporation, Korea), nominal pore size of 0.1 μm	Secondary effluents – Korea	126.5	69.7	44.9	-	Chon et al., 2013
		Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	38	37	2.6	-	Snyder et al., 2007
		Three seven-channel ceramic UF membranes (INSIDE CéRAMTM, supplied by TAMI Industries, France) with a nominal pore size of 1, 5 and 8 kDa	Spiked WWTP secondary effluent samples – Spain	300	NA	~ 60, 37, 27	1, 5 and 8 Kda, respectively, pH7	Garcia-Ivars et al., 2017
	Naproxen	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	24	21	12.5	-	Snyder et al., 2007
		Three seven-channel ceramic UF membranes (INSIDE CéRAMTM, supplied by TAMI Industries, France) with a nominal pore size of 1, 5 and 8 kDa	Spiked WWTP secondary effluent samples – Spain	300	NA	~55, 36, 24	1, 5 and 8 Kda, respectively, pH7	Garcia-Ivars et al., 2017
Analgesic	Acetaminophen	Three seven-channel ceramic UF membranes (INSIDE CéRAMTM, supplied by TAMI Industries, France) with a nominal pore size of 1, 5 and 8 kDa	Spiked WWTP secondary effluent samples – Spain	1000	NA	~44, 30, 23	1, 5 and 8 Kda, respectively, pH7	Garcia-Ivars et al., 2017
		Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	18	17	5.6	-	Snyder et al., 2007
Antibiotic	Sulfamethoxazole	Three seven-channel ceramic UF membranes (INSIDE CéRAMTM, supplied by TAMI Industries, France) with a nominal pore size of 1, 5 and 8 kDa	Spiked WWTP secondary effluent samples – Spain	1000	NA	~45, 38, 13	1, 5 and 8 Kda, respectively, pH7	Garcia-Ivars et al., 2017
		Hollow-fiber polyvinylidene fluoride (PVDF) UF membrane (Cleanfil-P75R, Kolon Membrane Corporation, Korea), nominal pore size of 0.1 μm	Secondary effluents – Korea	155.5	109	29.9	-	Chon et al., 2013
		Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	66	63	4.5	-	Snyder et al., 2007
	Erythromycin	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	289	245	15.2	-	Snyder et al., 2007

	Trimethoprim	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	138	113	18.1	-	Snyder et al., 2007
		Three seven-channel ceramic UF membranes (INSIDE CéRAMTM, supplied by TAMI Industries, France) with a nominal pore size of 1, 5 and 8 kDa	Spiked WWTP secondary effluent samples – Spain	300	NA	~33, 29, 15	1, 5 and 8 KDa, respectively, pH7	Garcia-Ivars et al., 2017
b-Blockers	Atenolol	Hollow-fiber polyvinylidene fluoride (PVDF) UF membrane (Cleanfil-P75R, Kolon Membrane Corporation, Korea), nominal pore size of 0.1 μm	Secondary effluents – Korea	206.6	194.4	5.9	-	Chon et al., 2013
Psychiatric	Carbamazepine	Hollow-fiber polyvinylidene fluoride (PVDF) UF membrane (Cleanfil-P75R, Kolon Membrane Corporation, Korea), nominal pore size of 0.1 μm	Secondary effluents – Korea	105.5	97	8.1	-	Chon et al., 2013
		Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	191	161	15.7	-	Snyder et al., 2007
	Dilantin	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	130	98	24.6	-	Snyder et al., 2007
		Hollow-fiber polyvinylidene fluoride (PVDF) UF membrane (Cleanfil-P75R, Kolon Membrane Corporation, Korea), nominal pore size of 0.1 μm	Secondary effluents – Korea	60.4	60.4	0.0	-	Chon et al., 2013
	Fluoxetine	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	45	14	68.9	-	Snyder et al., 2007
	Diazepam	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	58	9	84.5	-	Snyder et al., 2007
		Three seven-channel ceramic UF membranes (INSIDE CéRAMTM, supplied by TAMI Industries, France) with a nominal pore size of 1, 5 and 8 kDa	Spiked WWTP secondary effluent samples – Spain	300	NA	~55, 53, 35	1, 5 and 8 Kda, respectively, pH7	Garcia-Ivars et al., 2017
Hormones	Estrone	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	98	9	90.8	-	Snyder et al., 2007
	Estriol	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	87	<1	~100	-	Snyder et al., 2007
	Ethinyl estradiol	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	87	<1	~100	-	Snyder et al., 2007
	Progesterone	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	87	<1	~100	-	Snyder et al., 2007
	Testosterone	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	81	23	71.6	-	Snyder et al., 2007
Lipid regulator and metabolite	Gemfibrozil	Zenon ZeeWeedTM 1000 (ZW1000) UF pilot system, nominal membrane pore size 0.02μm	Secondary wastewater effluent	82	89	-8.5	-	Snyder et al., 2007

NA – Not available

2.2.2. Membrane bioreactors (MBRs)

Membrane bioreactors comprise the association of aerobic, anoxic or anaerobic biological treatment processes and a low-pressure membrane, such as MF or UF, although the number of bioreactors that integrate the biological process to forward osmosis and membrane distillation processes is increasing. The membrane acts as a physical hindrance to contain microorganisms, replacing the secondary settling tank, reducing the sludge production and increasing the global efficiency of the two separated processes in the removal of micro-pollutant, producing a permeate with negligible presence of suspended solids. This is the only MSP which is able to degrade and not concentrate the compounds. According to Tiwari *et al*. (2017), the application of MBR technology in hospital wastewater treatment has become a common practice in the previous decades.

The integration of the membrane to the biological reactor propitiates the increase in the sludge retention time (SRT) implicating in the rise of the efficiency in removing PhACs. It reflects in the better conditions for the growth of specialized microbial community efficient in micropollutant biodegradation which lead to the higher removal rate of these compounds (TIWARI *et al*., 2017).

According to Dawas-Massalha *et al*. (2014) high nitrifying activity increases the degradation of pharmaceutical residues, which is enhanced by MBRs by providing a higher SRT. As the nitrification rate increases, the pH of the MBR system tends to decrease. In this way, it was verified that, for the pH of 6, the degradation of ibuprofen reached 90%; when evaluating ketoprofen, a degradation of up to 70% in MBR was observed when the pH reached values below 5 (TADKAEW *et al*., 2010). De Gusseme *et al*. (2009) reported 99% removal of 17β-ethinylestradiol in nitrifier enriched biomass of MBR. Snyder et al. (2007), when studying the role of MSP in treating raw, primary, secondary and tertiary effluent, demonstrated that when applying MBR in order to treat primary effluent, concentrations of caffeine, acetaminophen, sulfamethoxazole, carbamazepine, and gemfibrozil decreased with removal efficiencies varying between 99.1% (sulfamethoxazole) and 99.9% (acetaminophen).

Radjenovic *et al*. (2009) found no elimination of gemfibrozil by the conventional activated sludge treatment, whereas the MBR was able to eliminate 30-40% of this compound. Once more, it was observed higher removal efficiencies by the MBR technology (81%) than by the conventional activated sludge (75%) of sulfamethoxazole. Kimura *et al*. (2005) when comparing the efficiency of MBR and the conventional activated sludge, concluded that MBR

system showed higher removal of ketoprofen and naproxen whereas, it was not observed any significant difference in removal efficiency of clofibric acid, ibuprofen, diclofenac and mefenamic acid in CAS and MBR. The persistence and low removal of PhACs in the effluent of both treatment systems could be due to the presence of the aromatic ring or chlorine group in their structure. MBR system is remarkably more efficient according to table 3 when compared to conventional activated sludge treatment (TIWARI *et al*., 2017) for the removal of persistent micro-pollutant in a such a small concentration, especially for those compounds that are not readily degradable due to the possibility of growth of more specialized biomass in degrading those compounds.

As already stated, SRT is one of the most important parameters influencing the removal of PhACs in biological treatment systems, which includes MBR. From table 3 it is possible to note that it significantly affects the removal rates of diclofenac, ketoprofen, gemfibrozil, trimethoprim, and erythromycin. Many studies have been carried out assessing the influence of SRT on the efficiency rate of removal of PhACs, for instance, Bernhard *et al*. (2006) noted that by increasing the SRT from 20 days to 62 days, the removal rate of diclofenac improved from 8% to 59%. Also, Kimura *et al*. proved that the MBR with longer SRT of 65 days had better performance than the MBR with a shorter SRT of 15 days so that the removal rates of ketoprofen and diclofenac improved from 82 to 98% and from 50 to 82%, respectively (KIMURA *et al.*, 2005). Corroborating with these results, Maeng *et al*. found that when SRT was increased from 20 to 80 days, the removal rates of gemfibrozil and ketoprofen improved from 41 to 88% and from 64 to 90%, respectively (MAENG *et al*., 2013). One of the most important characteristics associated with MBR treatment is the possibility of slow growth of nitrifying microorganisms within a reactor with biomass already established, as well as a community more specific in degrading a certain type of pollutant, and also the retention capacity of hydrophobic compounds. These characteristics make MBR a powerful technique for treating domestic effluents (HUANG AND LEE, 2015).

Many studies (RADJENOVIC *et al*., 2009; BERNHARD *et al*., 2006; JOSS *et al*., 2004) observed that with high SRT, MBR process had a better removal of polar compounds such as diclofenac, sulfophenyl carboxylate and mecoprop as well as hormones like estrogen. The degradation efficiency of pharmaceuticals compounds in MBR is more pronounced than the efficiency of CAS for like diclofenac, metoprolol and clofibric acid was 87.4%, 58.7% and 71.8%, respectively, in MBR, whereas in CAS process only 50% for diclofenac and 27% for clofibric acid (RADJENOVIC *et al.*, 2009).

However, a few studies have shown that increasing SRT had no significant impact on the increase of removal of some PhACs, such as, ibuprofen, bezafibrate, naproxen, carbamazepine, and sulfamethoxazole (LI *et al*., 2015) For example, Tambosi *et al*. observed that by increasing the SRT from 15 to 30 days, the degradation rate of naproxen remained in the range of 85–90% (TAMBOSI *et al*., 2010). Similar behaviour was observed for sulfamethoxazole and its metabolites, while SRT changed from 16 to 81 days (GÖBEL *et al*., 2007). Also, carbamazepine was shown to be resistant to biodegradation regardless of increasing SRT (MAENG *et al*., 2013).

Another important parameter is the hydraulic retention time (HRT), which is related to the useful volume of the reactor and, consequently, has an impact directly proportional to capital and operating costs. However, some studies indicate that HRT has no significant effect on the removal of PhACs. Reif *et al*. (2008) evaluated the removal of ibuprofen, naproxen and erythromycin and noted that the increase in HRT did not affect the rate of removal of these compounds as well as the MBR permeate quality. In addition, from the reading of Table 3, comparing the results of different researchers, HRT had no effect on the removal of acetaminophen, bezafibrate, ofloxacin, gemfibrozil and metronidazole. However, the reduction of HRT may increase membrane fouling (HEMMATI *et al*., 2012).

pH is an important parameter in the degradation of PhACs, since reducing the pH can increase the hydrophobicity of the ionizable compounds and subsequently improve their adsorption capacity to the sludge particles. This implies in a time available for biodegradation is increased and consequently the rates of removal. However, this behaviour should be applied to ionizable compounds, with no change in the rate of removal of non-ionizable compounds at pH variation expected. Tadkaew *et al*. (2010) did not observe a significant increase in the removal of ionizable diclofenac, ibuprofen, sulfamethoxazole and carbamazepine that are non-ionizable compounds (TADKAEW *et al*., 2010). In the study by Tadkaew *et al*. (2010), which evaluated the ketoprofen compound that is ionizable, it observed a higher removal rate at pH = 9 and pH = 5 than pH = 7. Similar, there are reports that there is sorption of hydrophilic antibiotics in the sludge, which is expected to occur (CIRJA *et al*., 2008). Kim *et al*. (2011) investigated the removal of pharmaceutical products in MBR and reported that sorption processes was the major mechanism of antibiotics removal, such as tetracycline, norfloxacin, ciprofloxacin, while azithromycin and sulfamethoxazole were removed by degradation (Table 33).

For the temperature, it is expected that with its increase also occur the increase in the biodegration of the compounds by the increase in the metabolic activity in addition to influence the mechanism of sorption, since these compounds are expected to be stable to a wide facade of temperature variation. Hai *et al*. (2011) studied the effect of temperature variation on the removal of micropollutants and noted that the removal of most of the hydrophobic compounds was stable in the temperature range of 10-35°C, but the removal of less hydrophobic micropollutants (log D<3.2) was significantly influenced by the temperature variation below and above 20°C.

As above listed, physicochemical properties such as solubility, volatility, photo-degradation and biodegradability of PhACs pollutants associated to the WWTP operational parameters, like SRT, Hydraulic retention time (HRT), pH and temperature, play a crucial role in controlling the fate and removal efficiency of target pollutants in the wastewater. Pharmaceutical pollutant with high sorption potential has higher removal rate than the compounds with low sorption potential, thus MBRs can effectively eliminate hydrophobic and readily biodegradable compounds and they are less effective in removal of hydrophilic and biologically persistent materials (CIRJA *et al.*, 2008; NGUYEN *et al*., 2013).

PhACs typically, either because of their complex structure characteristics or toxic effects, render the wide variety of microorganisms (bacteria and fungi) applied in conventional sewage treatment systems not efficiently sufficient in the degradation of some PhACs (LLORET *et al*. 2010). For example, carbamazepine and diclofenac removal rates are 13.8% and 15%, respectively (CLARA *et al*., 2005; NGUYEN *et al*., 2013b). In this way, some studies are already being done in order to find new groups of microorganisms that are able to efficiently oxidize these compounds.

White rot fungi and their unique extracellular enzymes, termed lignin peroxidase, manganese peroxidase and laccase, are known to play an important role in the ecosystem by the degradation of lignin. Some studies have evaluated the application of these enzymes to the elimination of PhACs, such as diclofenac, naproxen and ketoprofen by these fungi (TRAN *et al*., 2010, URREA et al., 2009; ZHANG; GEIBEN, 2012). Nguyen *et al*. (2013b) investigated the efficiency of a mixed culture of bacteria and fungi of white rot in the removal of organic contaminants in the MBR system and noted that this system can achieve a better removal than a system containing only fungi or bacteria. Removal rates were increased from 15% to 50% for diclofenac and from 65% to 94% for ketoprofen (NGUYEN *et al*., 2013b). Yang *et al*. (2013)

investigated a fungal MBR inoculated with white rot fungus, *Trametes versicolor*, and operated in non-sterile conditions. More than 55% removal of diclofenac was achieved (YANG *et al*., 2013). Zhang *et al*. (2012) analysed the removal of PhACs under non-sterile conditions using *T. versicolor* and reported the high removal rate (60-80%) for carbamazepine, unobserved results in MBR operated with bacteria. It has been observed that sufficient nutrient supply is crucial for effective removal (ZHANG; GEIBEN, 2012). Still applying the fungus *T. versicolor*, Jelic *et al*. (50 mg/L), the removal rate is 61%, while at a higher concentration (9 mg/L), the removal rate may reach 94% (JELIC *et al*. 2015). Hata *et al*. found that repeated treatments of carbamazepine with laccase in the presence of the redox mediator 1-hydroxybenzotriazole (HBT) may increase the rate of removal from 22% to 60% (HATA *et al*., 2010). In addition, Murugesan et al. confirmed that the presence of HBT may increase the rate of Triclosan removal from 56% to 90% (MURUGESAN *et al*., 2010).

It is possible to notice that the MBR systems do not present regular results regarding the removal of PhACs. This behaviour may be associated with structural complexity of PhACs and also their side effects under different species of microorganisms. From Table 33, it is possible to state that MBRs remove acetaminophen, ibuprofen, ketoprofen, gemfibrozil, bezafibrate and naproxen efficiently (>90%), while carbamazepine and diclofenac removal rates are low (<40%). For other compounds, removal rates are in the mid-range (40-70%) or sometimes there is insufficient data for judgment.

Table 3 - Concentrations and removal (%) of selected pharmaceuticals when applying MBR technology

PhAC Classes	PhACs	System configuration	Raw water (ng/L)	Treated water (ng/L)	Overall removal (%)	Observation	Reference
Antiinflammatory drug	Ibuprofen	Aerobic MBR, using a membrane supplied by US Filter with a nominal pore size of 0.08 μm. HRT 2-6h	27	43	-59.26	Primary effluent	Snyder et al., 2007
		A submerged aerobic MBR prototype is equipped with three membrane plates, each having a surface of 0.1m^2 and a mesh with width of 0.4 mm and consisting of chlorinated polyethylene. HRT 10h; SRT 400d	6725±1071	92±65	99.00	Primary effluent	Bernhard et al., 2006
		Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	27100	NM	99.2±1.8	Primary effluent	Radjenovic et al. (2009)
	Diclofenac	Aerobic MBR, using a membrane supplied by US Filter with a nominal pore size of 0.08 μm. HRT 2-6h	16	<10	~90	Primary effluent	Snyder et al., 2007
		Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	1320	NM	65.8±13.1	Primary effluent	Radjenovic et al. (2009)
		A submerged aerobic MBR prototype is equipped with three membrane plates, each having a surface of 0.1m^2 and a mesh with width of 0.4 mm and consisting of chlorinated polyethylene. HRT 10h; SRT 400d	2083±279	875±170	58.00	Primary effluent	Bernhard et al., 2006
	Ketoprofen	Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	1080	NM	43.9±27.7	Primary effluent	Radjenovic et al. (2009)
	Naproxen	Aerobic MBR, using a membrane supplied by US Filter with a nominal pore size of 0.08 μm. HRT 2-6h	70	<10	~99	Primary effluent	Snyder et al., 2007
		Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	463	NM	90.7±3.2	Primary effluent	Radjenovic et al. (2009)
Anti-histamines	Ranitidine	Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	347	NM	44.2±29.6	Primary effluent	Radjenovic et al. (2009)
	Loratidine	Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	28	NM	<10	Primary effluent	Radjenovic et al. (2009)

		Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	9900	NM	99.8±0.2	Primary effluent	Radjenovic et al. (2009)
Antibiotic	Sulfamethoxazole	Aerobic MBR, using a membrane supplied by US Filter with a nominal pore size of 0.08 μm. HRT 2-6h	23	<10	~99	Primary effluent	Snyder et al., 2007
		Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	93	NM	80.8±12.2	Primary effluent	Radjenovic et al. (2009)
	Ofloxacin	Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	10500	NM	95.2±2.8	Primary effluent	Radjenovic et al. (2009)
	Erythromycin	Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	820	NM	43±51.5	Primary effluent	Radjenovic et al. (2009)
		Aerobic MBR, using a membrane supplied by US Filter with a nominal pore size of 0.08 μm. HRT 2-6h	800	34	95.75	Primary effluent	Snyder et al., 2007
	Trimethoprim	Aerobic MBR, using a membrane supplied by US Filter with a nominal pore size of 0.08 μm. HRT 2-6h	42	<10	~99	Primary effluent	Snyder et al., 2007
		Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	204	NM	66.7±20.6	Primary effluent	Radjenovic et al. (2009)
b-Blockers	Atenolol	Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	2000	NM	76.7±12.6	Primary effluent	Radjenovic et al. (2009)
Psychiatric	Carbamazepine	Aerobic MBR, using a membrane supplied by US Filter with a nominal pore size of 0.08 μm. HRT 2-6h	281	<10	~99.99	Primary effluent	Snyder et al., 2007
		Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	156	NM	<10	Primary effluent	Radjenovic et al. (2009)
		A submerged aerobic MBR prototype is equipped with three membrane plates, each having a surface of 0.1m^2 and a mesh with width of 0.4 mm and consisting of chlorinated polyethylene. HRT 10h; SRT 400d	1287±113	1119±170	13	Primary effluent	Bernhard et al., 2006
	Fluoxetine	Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	573	NM	98±1.9	Primary effluent	Radjenovic et al. (2009)

		Aerobic MBR, using a membrane supplied by US Filter with a nominal pore size of 0.08 μm. HRT 2-6h	44	<10	~99	Primary effluent	Snyder et al., 2007
Hormones	Estrone	Aerobic MBR with 3 membranes ran in parallel: microfiltration plate membrane module of type Kubota A50 (0.4 μm nominal pore size), an ultrafiltration hollow-fiber module of type Mitsubishi Aqua-RM (0.1 μm nominal pore size), and an ultrafiltration hollow-fiber module of type Zenon ZeeWeed 500-C (0.04 μm nominal pore size). SRT 30d	25 ±5	2.4±0.5	96±1	Primary effluent	Joss et al., 2004
	Ethinyl estradiol	Aerobic MBR with 3 membranes ran in parallel: microfiltration plate membrane module of type Kubota A50 (0.4 μm nominal pore size), an ultrafiltration hollow-fiber module of type Mitsubishi Aqua-RM (0.1 μm nominal pore size), and an ultrafiltration hollow-fiber module of type Zenon ZeeWeed 500-C (0.04 μm nominal pore size). SRT 30d	1.6±0.3	<0.5	>75	Primary effluent	Joss et al., 2004
Lipid regulator and metabolite	Gemfibrozil	Aerobic MBR, using a membrane supplied by US Filter with a nominal pore size of 0.08 μm. HRT 2-6h	74	<10	~99	Primary effluent	Snyder et al., 2007
		Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	3080	NM	42.2±36.7	Primary effluent	Radjenovic et al. (2009)
	Bezafibrate	Aerobic MBR, with hollow-fibre (HF) ultra-filtration (UF) membranes (nominal porosity 0.05 μm) purchased from Koch Membrane Systems. HRT 15h; SRT>60d	14900	NM	90.3±10.1	Primary effluent	Radjenovic et al. (2009)

2.2.3. Nanofiltration (NF) and Reverse osmosis (RO)

Nanofiltration (NF) and reverse osmosis (RO) processes, have been demonstrating promising results on the rejection of PhACs and other emerging micropollutants (YANGALI-QUINTANILLA *et al*., 2010; SADMANI *et al*., 2014). Unlike the reverse osmosis processes, NF, in addition to having a greater permeate flux and being able to work at lower pressures, does not promote the complete removal of ions, being a preferable process to RO in cases where there is no such need, since it is expected of showing effective removal organic pollutants (BRUGGEN *et al*., 2008), demonstrating promising results on rejection of PhACs and EDCs, since the majority of the PhACs have a molecular weight within 150–500 Da and the molecular weight cut-off (MWCO) for most commercial NF membranes ranges from about 100 to 2000 Da (WANG *et al*., 2014). Thus, these compounds are expected to be widely retained by physical sieving if their molecular weights are larger than the membrane MWCO.

In order to study the ability of RO membranes to retain PhACs, Kimura *et al*. (2004) showed that membranes composed of polyamide showed better rejection than cellulose acetate membranes (Table 5). The results indicate that electrostatic exclusion is the predominant phenomenon in these membranes and because of this, rejection of negatively charged pharmaceutical compounds was effective and exceeded 95% by RO membranes (KIMURA *et al*., 2003; XU *et al*., 2005). Khan *et al*. (2004) also found that the treatment with RO was the most successful in the removal of test compounds. Ozaki and Li (2002) investigated the rejection of several products, among them PhACs by NF and RO polyamide membranes, and showed that the rejection of organic compounds by ultra-low pressure RO (ULPRO) increased linearly with molecular weight and molecular weight of the compound evaluated.

A number of studies (XU *et al*., 2005; KIMURA *et al*., 2003; YANGALI-QUINTANILLA *et al*., 2009) have shown that the rejection of PhACs by the NF process is governed by several mechanisms such as steric effect, electrostatic repulsion, hydrophobic interactions, partitioning and diffusion which are highly dependent on the physico-chemical properties of the feed solution (ions concentration, pH, molecular weight (MW), molecular geometry, charge, hydrophobicity/hydrophilicity), and membrane properties such as molecular weight cut-off (MWCO), surface charge, morphology, porosity, and hydrophobicity.

Several types of NF membranes have already been studied and tested in the application for rejection of a large number of PhACs (Table 44). However, in general, the conclusion is that NF is not always as effective a process for the removal of all evaluated PhACs, as one might

suppose. The study carried out by Yoon *et al*. (2007), who used an NF membrane with a nominal MWCO of 200 Da, the rejection ratios for 52 endocrine disrupting compounds, among them several PhACs both synthetic solution and real surface water, ranged from 0% to more than 90%. Radjenović *et al*. (2008) applied an NF membrane with a nominal MWCO of 200 Da in a full-scale potable water treatment plant. In this experiment, in turn, showed high rejections (greater than 95%) of 9 of 12 pharmaceutical products, but slight rejection of acetaminophen, gemfibrozil and mefenamic acid, of which only about 50% was rejected, which was attributed to its hydrophilic behaviour and/or low MW. Generally, low rejection is mainly encountered when NF membranes with relatively large MWCO are applied, which are not effective in the removal of low molecular weight PhACs. NF was found to be effective in the removal of carbamazepine which is considered to be a human active indicator (NGHIEM *et* al., 2007). A dependence on filtration time and the rejection ratio of PhACs by NF to uncharged compounds was noted (KIMURA *et al*., 2003, STEINLE-DARLING *et al*., 2010). This strongly suggests that the mechanism of adsorption of these compounds on the membrane surface directly affects the performance of the rejection. Membranes with less polar characteristics (indicated by low dipole moment) and solutions with more hydrophobic compounds (indicated by high octanol-water partition coefficients) generally present preferentially adsorption (OZAKI *et al*., 2008). Adsorption generally impairs the performance of PhACs rejection after the NF membrane adsorption sites are exhausted (WANG *et al*., 2015).

The hydrophobicity of PhACs is one of the major factors influencing the performance of NF membranes. The hydrophobic compounds initially have tendencies to be adsorbed onto the membrane surface layer and into the pores and diffused into their matrix (TAHERAN *et al*., 2016). The higher hydrophobicity of compound the greater is its ability to be adsorbed on the membrane surface, especially when the compounds are electrostatically neutral (GEANIYU *et al*., 2015). The initial adsorption of the PhACs on the membrane causes a high initial rejection of the compound; as the adsorption occurs, free active sites are occupied, the membrane tends to change its charge which affects the transport of solutes to the permeate reducing its rejection capacity compared to hydrophilic compounds of the same size (HU *et al*., 2007; VERLIEFDE *et al*., 2007a). After electrostatic equilibrium, the next mechanisms that prevail in the rejection of PhACs are size exclusion and charge repulsion (YOON et al., 2007). However, in observing these mechanisms, it is possible that these are overestimated, since most of the studies were conducted for a short period of time (<24 h) in addition to using small sample volumes (<10 L) (CHANG *et al*., 2003, COMERTON *et al*., 2007, KIMURA *et al*., 2003). The hydrophilic

compounds, otherwise, remain dissolved in the aqueous phase and, consequently, their effective diameter may be larger (TAHERAN *et al*., 2016). Thus, when the size exclusion mechanism prevails, the hydrophilic compound can be rejected more effectively than the hydrophobic ones (BRAEKEN *et al.*, 2005).

The effect of hydrophobicity was most seeming to be more prominent for NF membranes having larger pores than those with smaller pores since the larger pores facilitate passage of the PhACs to the adsorption sites in the skin layer, backing layer and pores of the membrane. However, according to studies carried out by Yoon *et al*., (2007) the phenomenon of adsorption on the NF membrane is more prominent than the UF membrane. Verliefde *et al*., (2009), in turn, concluded that, in the case of the negatively charged NF membrane, the rejection of positively charged neutral-charged PhACs is reduced with increased hydrophobicity, since these compounds have higher tendencies to adsorbed onto the membrane surface. However, it was concluded that there was no clear relationship between the hydrophobicity of negatively charged PhACs and their rejection due to the repulsion of the charge that prevented the solutes from approaching the membrane surface (VERLIEFDE *et al*., 2009).

The ionic state of PhACs will depend on the pH solution and on acidic properties of solutes. Thus, changes in feedwater pH will significantly affect the PhACs rejection by NF/RO membranes by changing their ionic state of the PhACs. Another variable which plays an important role in determining the ionic state of the compound is the value of the dissociation constant (pKa). If the pKa value of the solute is below the investigated pH range, the solute will be negatively charged, otherwise the solute will be positively charged or a neutral and positively charged solute mixture. Vergili (2013) applied a nanofiltration membrane (FM NP010) in cross-flow filtration equipment for the removal of three PhACs (carbamazepine, diclofenac and ibuprofen) of samples from a drinking water treatment plant using surface water. This study showed that the overall rejection was approximately 31-39% for ionic diclofenac and ibuprofen and 55-61% for neutral carbamazepine. The low to moderate rejection values observed for the PhACs were most likely due to small molecular sizes (i.e., MW << MWCO).

Typically, the surface of most NF and RO membranes are negatively charged when in contact with solutions of neutral pH due to deprotonation of their functional groups (TAHERAN *et al*., 2016). Therefore, the charge of the PhAC molecules, as a consequence, and possible electrostatic interaction with the surface of the membrane can contribute significantly to its

removal. In the case of compounds having positive charges, attractive forces between the solutes and the surface of the negatively charged membrane will prevail, causing an increase in the solute concentration near the membrane surface and, therefore, results in lower rejections because it induces greater passage of the pollutants from the membrane. Otherwise, when the compounds are negatively charged, repulsive forces are predominant between the solutes and the surface of the membrane which have similar charges. This implies the reduction of the solute concentration on the membrane surface and, therefore, generates an increase in the rejection of the PhACs (KIMURA *et al*., 2003b; KIMURA *et al*., 2004; RADJENOVIC *et al*., 2008). Even neutral molecules, which have a high dipole moment, tend to align with membrane pores, due to electrostatic interactions with the membrane charge and, therefore, permeate more easily through the membrane (BRUGGEN; VANDECASTEELE, 2003; NGHIEM *et al*., 2005, YOON *et al*., 2006).

Some studies have been carried out to verify the effect of the electrostatic interactions between the membrane and the compound. Nghiem *et al*. (2005, 2006), for example, found this effect on NF membrane considered to be negatively charged loose when subjected to solution with pH values above 5. It was observed that the retention of ionizable PhACs, such as ibuprofen and sulfamethoxazole, increased because with the increase in the pH value of the solution as a result of the pKa value caused a change in the compound charge from neutral to negative. However, when evaluating non-ionizable PhACs, such as carbamazepine, they were found to be relatively independent of solution chemistry (NGHIEM *et al*., 2005, 2006). Although in the study conducted by Verliefde *et al*. (2007) investigated the removal of PhACs using a system of negatively charged NF with small (10%) and higher recovery rates (80%). It was concluded that the exclusion due to the size of the particle (that is, the phenomena of sieving) was the main mechanism for the rejection of the neutral solute; however larger and smaller rejections of negatively or positively arrayed solutes were attributed to phenomena of repulsion and electrostatic attractions, respectively. It was also concluded that when the system is operated at a low recovery rate (10%), high removal efficiencies (> 95%) are achieved for all evaluated PhACs. However, these efficiencies decreased when analysing a higher recovery (80%), phenomena that can be attributed to the increase in the mean concentration of PhACs in the feed solution as a result of internal recycling of the concentrate (CHELLAM; TAYLOR, 2001; VERLIEFDE *et al*., 2007). Bellona *et al*. (2010) evaluated the effect of surface charges of the NF membrane on the rejection of acidic solutes and observed that the presence of calcium in feed water can reduce the surface charge of the membrane due to adsorption of Ca in the active

layer of the membrane, but the rejection of negatively charged solutes was lower only in membranes whose MWCO is higher than the molecular weight of the solutes (HEBERER, 2002). Its conclusion contrasts with the results obtained by Comerton *et al*. (2008) which observed a reduction in gemfibrozil removal rate (MW = 250 Da) and unchanged removal rate for acetaminophen (MW = 151 Da) using an NF membrane (MWCO = 200 Da) and a RO membrane after the addition of divalent cations in the feed solution, however, no significant changes was observed for RO rejections (HEBERER, 2002). In addition, Dolar *et al*. studied the effect of the influent matrix on rejection of PhACs across the NF and RO membrane using four different water sources, namely Milli-Q® water, synthetic water and drug solution, tap water and actual pharmaceutical wastewater and noted that the PhACs rejection was higher in the synthetic solution and tap water than in Milli-Q water due to the adsorption of ions into the membrane pores that strengthened the size exclusion effect (DOLAR *et al*., 2011).

The process of retention of solutes by the membrane due to the complexity of phenomena that occur on its surface should not be considered as a simple filtration process. The sieving phenomenon is not the only one to affect the transport and the convection of solutes through membranes. Other phenomena such as liquid absorption at the membrane solute interface and transport within the membrane can significantly influence the removal efficiency of compounds (AGENSON *et al*., 2003). In turn, liquid absorption and preferential transport are influenced by other parameters, such as charge repulsion and hydrophobic interaction. Generally, the size exclusion phenomenon plays an important role in the rejection of neutral and non-hydrated solutes besides being able to present high rejections (ie> 85%) for compounds with MW greater than MWCO of NF/RO membranes. Radjenovic *et al*. (2008) evaluated the rejection of several PhACs by real-scale NF/RO membranes in a real drinking water treatment plant. It was concluded that, since the MW of acetaminophen was lower than the MWCO of the NF and RO membranes used and also did not present in its ionic state at neutral pH, its rejection rate varied 44.8-73%, not elevated. However, when observing diclofenac which has higher MW and negatively charged at neutral pH had the highest rejection rate. However, the low rejection rate of gemfibrozil despite high MW and the presence of charge repulsion effect was unexpected (RADJENOVIC *et al*., 2008). Quintanilla *et al*. (2009) concluded that the rejection of hydrophilic neutral solutes may correlate linearly with the physical characteristics of the compound, such as its molar volume and molecular length, however no correlation was observed between its rejections and equivalent width (QUINTANILLA *et al*., 2009). In turn, Agenson *et al*. (2003) observed a better correlation

between rejection and molecular width. Pronk *et al*. (2006) and Rehbun *et al*. (1998) assigned the highest removal rate of some PhACs to their complexation with oxalic acid, uric acid, amino acids and humic acid which led to an increase in their size giving rise to the possibility of sieving effect (PRONK *et al*. 2006; REBHUN *et al*., 1998). Kim *et al*. (2008) applied methacrylic acid, ethylenediamine and succinic acid to modify the surface of the commercial NF membrane and found that methacrylic acid can increase hydrophilicity, steric hindrance and negative surface charge of the membrane and, therefore, it is possible to increase the rejection of the ibuprofen and salicylic acid (by approximately 1%). However, application of ethylenediamine reduced the surface charge and had a negative effect on rejection of charged PhACs (KIM *et al*., 2008).

Nghiem *et al*. (2008) verified the effect of scaling in RO and NF membranes using synthetic solutions with hydrophobic and hydrophilic impurities in the rejection of triclosan and concluded that when applied to hydrophilic colloidal silica, no change in permeate flow or rejection of triclosan was observed. However, hydrophobic impurities, such as alginate, significantly reduce flow and increase triclosan rejection (NGHIEM; COLEMAN, 2008).

When applying NF or RO process in treating natural water or also treated effluent, the natural organic matter (NOM) in natural matrices may influence the rejection of organic compounds traces by two main mechanisms: fouling (or interactions between the membrane surface and the feed solution compounds) or interactions between solute molecules (solute-solute interactions) (SADMANI *et al*., 2014).

Membrane fouling caused by the organic matter present in the effluent (EfOM) results in a decrease in permeate flux throughout the filtration operation and can either increase or decrease solute rejection, depending on the interaction between the membrane and the fouling layer (ionic neutral, hydrophobic and hydrophilic) compared to clean membranes (AZAIS *et al*., 2014). This phenomenon occurs by modifying the surface characteristics of the membrane, which also changes the adsorption phenomenon of organic compounds in the fouling layer (HAJIBABANIA *et al*., 2011). Same trends were found by Nghiem et al. (2010). Bellona *et al.* (2010) found rejections by NF when assessing the membrane NF 270, (considered a loose membrane) process were markedly lower of non-ionic PhACs (acetaminophen, carbamazepine, etc.) when previously fouled with EfOM. This result was attributed to an increase in hydrophobicity and a decrease in surface charge, being linked to the cake-enhanced polarization concentration (CECP) phenomena (BELLONA *et al*., 2010). However, when

analysing the membrane NF90 (considered a tight membrane) the rejection of the same studied PhACs was found to be relatively unaffected by EfOM, where it was observed a decrease in hydrophobicity and an increase in surface charge (BELLONA *et al*., 2010).

This is a phenomenon that is considered as the diffusion barrier of which the solute located on the surface of the membrane may suffer upon returning to the feed solution due to the presence of a porous cake layer (NG; ELIMELECH, 2004). This can be responsible of the increase of organic compounds concentration and therefore promoting an alteration of membrane surface charge and, by consequence, its rejection. Agenson and Urase (2007), reconfirming the previous results, have suggested that the adsorption and diffusion of compounds having larger MW, which present high rejections by the virgin membranes, through RO and NF membranes fouled by leachate, facilitating the transport of high MW contaminant. On the contrary, Zazouli *et al*. (2009) observed an increasing rejection for PhACs with higher molecular weight, while compounds with smaller MW and with moderate polarity (such as acetaminophen) were found to be less rejected due to the polymeric fouling layer applying alginate as a model compound. Hajibabania *et al*. (2011) found that the rejections of the hydrophilic non-ionic and ionic solute are negatively impacted when membranes are fouled with humic acids and even more with alginates. The rejection of hydrophobic compounds was found to be not influenced by the type of studied foulants. Thus, in addition to the type of solutes and soils, the MWCO of the membranes or the pore size of the membrane determines whether the scale will have a beneficial or negative influence on the rejection of PhACs either through the pore restriction or CECP (BELLONA *et al*., 2010; NGHIEM *et al.*, 2007).

As many of these studies illustrate, it is clear that membrane fouling has the potential to affect rejection mechanisms of organic solutes as a result of modified electrostatic, steric and hydrophobic/hydrophilic solute–membrane interactions (AZAIS *et al*., 2014). Though, reported results are difficult to generalize since the characteristics of the feed solutions, and, therefore, the composite nature of foulants and particular interactions with each membrane type leads to a diversity of scenarios in terms of PhACS rejection. Understanding the fouling effect requires a comprehensive characterization of the contaminated membrane and the physicochemical properties of the selected PhACs (AZAIS *et al*., 2014).

According to the study conducted by Azais *et al*. (2014), the rejection of neutral PhACs by the virgin and pre-fouled membrane, in the case of the NF-90 membrane was attributed to steric hindrance, which explains a nearly constant rejection yield for all the compounds, whatever the

surface state of the membrane or the type of PhACs (shape and geometry), and then was little influenced by the fouling. The rejection by pre-fouled NF-270 membrane was lower in comparison to the virgin membrane, probably due to the establishment of CECP that facilitated the transport of small MW nonionic organic compounds. In addition, the NF-270 membrane is strongly influenced by the chemical structure of the PhACs. Also, it was observed that the geometry and charge of the compound also plays an important role. In this same study, Azais *et al*. (2014) has also shown that solute-solute interactions in the tertiary effluent matrix significantly increased the rejection of PhACs, especially when loose NF was used, for which the association of PhACs with organic macromolecule was the reason for this better rejection due to steric hindrance.

The second mechanism involved in drug rejection when involving a matrix composed of organic matter (OM) is through the binding of compounds. Several studies (SADINMANI *et al*., 2014) suggest that the mechanism that promotes greater rejection is the formation of compound-OM complexes. This is attributed to the increase in molecule size and a negative charge if compared to the compound alone. It has been observed that the presence of OM (whether natural or from a synthetic solution) increases the removal of hormone (estrogens) (SCHAFER *et al*., 2010) and PhACs (KIMURA *et al*., 2009) through solute-solute interactions.

The formation of OM-compounds complexes due to the adsorption of PhACs into organic macromolecules may depend on the types of solutes and macromolecules involved in the process and on their binding capability (HAJIBABANIA *et al*., 2011). In addition, the calcium concentration present in the solution can influence both membrane fouling, reducing permeate flow, and PhAC retention when applied NF. When the feed solution is rich in divalent cations, there may be competition between these elements and PhACs by active adsorption sites in organic matter to form complexes with OM, resulting in lower rejections of PhACs (SADINMANI *et al*., 2014). In particular, when calcium is abundant in the solution, studies have reported that the carboxylic groups of humic substances and polysaccharides are neutralized, which promotes denser fouling (SEIDEL; ELIMELECH 2002). However, when it exceeds a critical calcium concentration, the complexation of these elements with OM may also occur in the solution (bulk complexation), leading to aggregate formation and lower organic fouling (MO *et al*., 2011). Reznik *et al*. studied the seasonal effects on the rejection of carbamazepine and found that the rejection of RO membranes was not affected by seasonal change but the rejection of carbamazepine by NF membrane decreased from 92% in summer to 50% in winter. They concluded that reducing the temperature can affect metabolic rate which

consequently affects organic matter degradation and their interaction with solutes (REZNIK *et al*., 2011).

The type of fouling, the ionic state and pre-treatment used in the sample strongly affects the cleaning period of the membrane, the chemicals to be applied and, consequently, the cost of cleaning (TAHERAN *et al*., 2016). In general, the membranes are cleaned when a 10-15% drop in the permeate flux is observed, a 10-15% increase in solute concentration in the permeate or a 15-20% drop in pressure in a vessel of pressure. As a general rule, the usual cleaning frequency rotates around once every four times a year and in terms of cost, this operation should revolve around 5 to 20% of the operating costs (ARNAL *et al*., 2011). In one case study, the total RO membrane cleaning costs, including labor, chemicals and loss of production, were calculated in Orange County Water District's groundwater replenishment system. According to data provided, for a total capacity of 265,000 m^3/day operated with a recovery rate of 85%, the total cost of cleaning was US $ 15,929, which should be multiplied by the cleaning number per year (OWENS; PATEL, 2010).

Table 4 - Concentrations and removal (%) of selected pharmaceuticals when applying RO technology

PhAC Classes	PhACs	Membrane type	Overall removal (%)	Feed characteristics	Reference
Antiinflammatory drug	Ibuprofen	TFC-HR	96	Synthetic feed - DI	Xu et al., 2005
		TFC-HR	99	Synthetic feed - EfOM	Xu et al., 2005
		Koch	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Koch - prefouled	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Saehan	<MQL	Tertiary effluent	Snyder et al., 2007
		XLE	100	Synthetic feed - Humic Acid	Lin, 2017
		XLE	99	Synthetic feed - Silica	Lin, 2017
		XLE	100	Synthetic feed - Humic Acid + Silica	Lin, 2017
		XLE	95	Synthetic feed - Humic Acid + Sodium Alginate	Lin, 2017
		Spiral-wound LCF1-4040	96.9	Secondary effluent treated with UF	Urtiaga et al., 2013
	Naproxen	Flat sheet UTC 60	95	Synthetic feed - pH 7	Ozaki et al., 2008
		Flat sheet UTC 70U	97	Synthetic feed - pH 7	Ozaki et al., 2008
		Spiral-wound LCF1-4040	98.3	Secondary effluent treated with UF	Urtiaga et al., 2013
		Koch	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Koch - prefouled	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Saehan	<MQL	Tertiary effluent	Snyder et al., 2007
		TFC-HR	98	Synthetic feed - DI	Xu et al., 2005
		TFC-HR	99	Synthetic feed - EfOM	Xu et al., 2005
	Diclofenac	Full scale BW30LE-440	100	Groundwater	Radjenovic et al., 2008
		Flat sheet UTC 60	95	Synthetic feed - pH 7	Ozaki et al., 2008
		Flat sheet UTC 70U	97	Synthetic feed - pH 7	Ozaki et al., 2008
		TFC-HR	95	Synthetic feed - DI	Xu et al., 2005
		TFC-HR	99	Synthetic feed - EfOM	Xu et al., 2005
		RO-XLE	95	Synthetic feed - DI	Kimura et al., 2003
		Koch	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Koch - prefouled	<MQL	Saline groundwater - Spiked	Snyder et al., 2007

		Saehan	<MQL	Tertiary effluent	Snyder et al., 2007
		XLE	95	Synthetic feed	Xie et al., 2012
		Spiral-wound RE8040-FL	99	UF permeate feed with secondary effluent	Chon et al., 2013
	Ketoprofen	Full scale BW30LE-440	>99	Groundwater	Radjenovic et al., 2008
		Flat sheet UTC 60	95	Synthetic feed - pH 7	Ozaki et al., 2008
		Flat sheet UTC 70U	97	Synthetic feed - pH 7	Ozaki et al., 2008
		TFC-HR	98	Synthetic feed - DI	Xu et al., 2005
		TFC-HR	99	Synthetic feed - EfOM	Xu et al., 2005
	Mefenamic acid	Full scale BW30LE-440	>99	Groundwater	Radjenovic et al., 2008
Analgesic	Acetaminophen	X20	82.1	Raw Lake Ontario water	Comerton et al., 2008
		X20	99.7	MBR effluent	Comerton et al., 2008
		Full scale BW30LE-440	>99	Groundwater	Radjenovic et al., 2008
	Propyphenazone	Full scale BW30LE-440	>99	Groundwater	Radjenovic et al., 2008
Antibiotic	Trimethoprim	Koch	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Koch - prefouled	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Saehan	<MQL	Tertiary effluent	Snyder et al., 2007
	Sulfamethoxazale	Full scale BW30LE-440	>99	Groundwater	Radjenovic et al., 2008
		Saehan	98.7	Tertiary effluent	Snyder et al., 2007
		XLE	100	Synthetic feed - Humic Acid	Lin, 2017
		XLE	100	Synthetic feed - Silica	Lin, 2017
		XLE	100	Synthetic feed - Humic Acid + Silica	Lin, 2017
		XLE	90	Synthetic feed - Humic Acid + Sodium Alginate	Lin, 2017
		XLE	70	Synthetic feed - DI	Kimura et al., 2004
		SC-3100	82	Synthetic feed - DI	Kimura et al., 2004
		X20	94.1	Raw Lake Ontario water	Comerton et al., 2008
		X20	98.8	MBR effluent	Comerton et al., 2008
		Spiral-wound RE8040-FL	99	UF permeate feed with secondary effluent	Chon et al., 2013
	Sulfadiazine	XLE	9	Synthetic feed - Humic Acid	Lin, 2017
		XLE	95	Synthetic feed - Silica	Lin, 2017

		XLE	100	Synthetic feed - Humic Acid + Silica	Lin, 2017
		XLE	99	Synthetic feed - Humic Acid + Sodium Alginate	Lin, 2017
	Sulfamethazine	XLE	98	Synthetic feed - Humic Acid	Lin, 2017
		XLE	99	Synthetic feed - Silica	Lin, 2017
		XLE	100	Synthetic feed - Humic Acid + Silica	Lin, 2017
		XLE	90	Synthetic feed - Humic Acid + Sodium Alginate	Lin, 2017
		X20	87.9	Raw Lake Ontario water	Comerton et al., 2008
		X20	97.9	MBR effluent	Comerton et al., 2008
	Oflaxacin	Spiral-wound LCF1-4040	95.4	Secondary effluent treated with UF	Urtiaga et al., 2013
b-Blockers	Atenolol	Spiral-wound RE8040-FL	85	UF permeate feed with secondary effluent	Chon et al., 2013
		Spiral-wound LCF1-4040	99.5	Secondary effluent treated with UF	Urtiaga et al., 2013
	Metoprolol	Full scale BW30LE-440	76.1	Groundwater	Radjenovic et al., 2008
	Sotolol	Full scale BW30LE-440	>99	Groundwater	Radjenovic et al., 2008
Psychiatric	Carbamazepine	Flat sheet UTC 60	70	Synthetic feed - pH 7	Ozaki et al., 2008
		Flat sheet UTC 70U	92	Synthetic feed - pH 7	Ozaki et al., 2008
		Spiral-wound RE8040-FL	99	UF permeate feed with secondary effluent	Chon et al., 2013
		XLE	91	Synthetic feed - DI	Kimura et al., 2004
		SC-3100	85	Synthetic feed - DI	Kimura et al., 2004
		Full scale BW30LE-440	98.5	Groundwater	Radjenovic et al., 2008
		X20	91	Raw Lake Ontario water	Comerton et al., 2008
		X20	97	MBR effluent	Comerton et al., 2008
		XLE	99	Synthetic feed - Humic Acid	Lin, 2017
		XLE	98	Synthetic feed - Silica	Lin, 2017
		XLE	100	Synthetic feed - Humic Acid + Silica	Lin, 2017
		XLE	89	Synthetic feed - Humic Acid + Sodium Alginate	Lin, 2017
	Fluoxetine	Koch	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Koch - prefouled	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Saehan	<MQL	Tertiary effluent	Snyder et al., 2007
	Dilatin	Koch	<MQL	Saline groundwater - Spiked	Snyder et al., 2007

		Koch - prefouled	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Saehan	<MQL	Tertiary effluent	Snyder et al., 2007
		Spiral-wound RE8040-FL	90	UF permeate feed with secondary effluent	Chon et al., 2013
	Primidone	TFC-HR	91	Synthetic feed - DI	Xu et al., 2005
		TFC-HR	92	Synthetic feed - EfOM	Xu et al., 2005
		XLE	87	Synthetic feed - DI	Kimura et al., 2004
		SC-3100	85	Synthetic feed - DI	Kimura et al., 2004
		RO-XLE	84	Synthetic feed - DI	Kimura et al., 2003
	Erythromycin	Saehan	<MQL	Tertiary effluent	Snyder et al., 2007
	17-a-estradiol	XLE	83	Synthetic feed - DI	Kimura et al., 2004
		SC-3100	29	Synthetic feed - DI	Kimura et al., 2004
		Flat sheet UTC 60	55	Synthetic feed - pH 7	Ozaki et al., 2008
		Koch	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Koch - prefouled	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
Hormones		X20	98	Raw Lake Ontario water	Comerton et al., 2008
		X20	96.8	MBR effluent	Comerton et al., 2008
	Enthynylestradiol	X20	96.6	Raw Lake Ontario water	Comerton et al., 2008
		X20	96.8	MBR effluent	Comerton et al., 2008
		Koch - prefouled	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Koch	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
	Bezafibrate	Spiral-wound LCF1-4040	100	Secondary effluent treated with UF	Urtiaga et al., 2013
	Gemfibrozil	Full scale BW30LE-440	>99	Groundwater	Radjenovic et al., 2008
		TFC-HR	90	Synthetic feed - DI	Xu et al., 2005
		TFC-HR	100	Synthetic feed - EfOM	Xu et al., 2005
		Koch	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Koch - prefouled	<MQL	Saline groundwater - Spiked	Snyder et al., 2007
		Saehan	<MQL	Tertiary effluent	Snyder et al., 2007
		X20	97.7	Raw Lake Ontario water	Comerton et al., 2008
		X20	98.5	MBR effluent	Comerton et al., 2008

		Spiral-wound LCF1-4040	98.8	Secondary effluent treated with UF	Urtiaga et al., 2013
		Flat sheet UTC 60	95	Synthetic feed - pH 7	Ozaki et al., 2008
		Flat sheet UTC 70U	97	Synthetic feed - pH 7	Ozaki et al., 2008
	Glibenclamide	Full scale BW30LE-440	>99	Groundwater	Radjenovic et al., 2008

Table 5 - Concentrations and removal (%) of selected pharmaceuticals when applying NF technology

PhAC Classes	PhACs	Membrane type	Overall removal (%)	Feed characteristics	Reference
Antiinflammatory drug	Ibuprofen	Flat sheet NF 270	73	Synthetic feed - DI	Hajibabania et al., 2011
		Flat sheet NF 270	58	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	30	Synthetic feed - Alginate	Hajibabania et al., 2011
		Flat sheet NF 90	99	Synthetic feed - Humic acid	Nghiem et al., 2010
		Flat sheet NF 270	98	Synthetic feed - Humic acid	Nghiem et al., 2010
		Flat sheet NF 90	99	Synthetic feed - DI	Nghiem et al., 2010
		Flat sheet NF 270	89	Synthetic feed - DI	Nghiem et al., 2010
		NF 90	96	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	97	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	89	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	89	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		ESNA	45	Spiked surface water	Yoon et al., 2007
	Naproxen	Flat sheet NF 270	70	Synthetic feed - DI	Hajibabania et al., 2011
		Flat sheet NF 270	45	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	25	Synthetic feed - Alginate	Hajibabania et al., 2011
		NF 90	95	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	95	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	91	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	92	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NE70	73.6	Synthetic feed - DI (spiked with cations)	Sadmani et al., 2014
		NE70	86.7	Raw Lake Ontario sample	Sadmani et al., 2014
		NE70	78.4	UF-pretreated Lake Ontario Sample	Sadmani et al., 2014
		NE70	86.9	FIEX[a]-Lake Ontario water	Sadmani et al., 2014
		ESNA	10	Spiked surface water	Yoon et al., 2007
	Diclofenac	Full scale NF90-400	100	Groundwater	Radjenovic et al., 2008

		NE70	91.9	Synthetic feed - DI (spiked with cations)	Sadmani et al., 2014
		NE70	91.8	Raw Lake Ontario sample	Sadmani et al., 2014
		NE70	89	UF-pretreated Lake Ontario Sample	Sadmani et al., 2014
		NE70	80.9	FIEX[a]-Lake Ontario water	Sadmani et al., 2014
		ESNA	45	Spiked surface water	Yoon et al., 2007
		Flat sheet NF 270	82	Synthetic feed - DI	Hajibabania et al., 2011
		Flat sheet NF 270	78	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	50	Synthetic feed - Alginate	Hajibabania et al., 2011
	Ketoprofen	NF 90	95	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	95	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	91	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	92	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NE70	87.1	Synthetic feed - DI (spiked with cations)	Sadmani et al., 2014
		NE70	90.9	Raw Lake Ontario sample	Sadmani et al., 2014
		NE70	89.5	UF-pretreated Lake Ontario Sample	Sadmani et al., 2014
		NE70	88.7	FIEX[a]-Lake Ontario water	Sadmani et al., 2014
		Full scale NF90-400	>99	Groundwater	Radjenovic et al., 2008
		Flat sheet NF 270	70	Synthetic feed - DI	Hajibabania et al., 2011
		Flat sheet NF 270	60	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	38	Synthetic feed - Alginate	Hajibabania et al., 2011
	Phenazone	NF 90	91	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	95	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	73	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	79	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
	Fenoprofen	NF 90	94	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	95	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	91	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	91	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
	Indomethacin	TFC Kock SR2	82	Synthetic feed - NaCl 10mM; No alginate	Zazouli et al., 2009

		TFC Kock SR2	85	Synthetic feed - NaCl 10mM; 25 mg/L alginate	Zazouli et al., 2009
		TFC Kock SR2	95	Synthetic feed - NaCl 10mM; 50 mg/L alginate	Zazouli et al., 2009
	Mefenamic acid	Full scale NF90-400	>99	Groundwater	Radjenovic et al., 2008
Analgesic	Paracetamol	Flat sheet NF 270	5	Synthetic feed - DI	Hajibabania et al., 2011
		Flat sheet NF 270	5	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	1	Synthetic feed - Alginate	Hajibabania et al., 2011
	Propyphenazone	Full scale NF90-400	98.6	Groundwater	Radjenovic et al., 2008
	Acetaminophen	Full scale NF90-400	>99	Groundwater	Radjenovic et al., 2008
		Flat sheet NF 90	90	Secondary Effluent	Azas et al., 2014
		Flat sheet NF 270	30	Secondary Effluent	Azas et al., 2015
		Flat sheet NF 90 - Prefouled	88	Secondary Effluent	Azas et al., 2016
		Flat sheet NF 270 - Prefouled	20	Secondary Effluent	Azas et al., 2017
		NF 90	75	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	78	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	22	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	24	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NE70	27.2	Synthetic feed - DI (spiked with cations)	Sadmani et al., 2014
		NE70	37.9	Raw Lake Ontario sample	Sadmani et al., 2014
		NE70	38.6	UF-pretreated Lake Ontario Sample	Sadmani et al., 2014
		NE70	29.9	FIEX[a]-Lake Ontario water	Sadmani et al., 2014
		TFC Kock SR2	34	Synthetic feed - NaCl 10mM; No alginate	Zazouli et al., 2009
		TFC Kock SR2	32	Synthetic feed - NaCl 10mM; 25 mg/L alginate	Zazouli et al., 2009
		TFC Kock SR2	30	Synthetic feed - NaCl 10mM; 50 mg/L alginate	Zazouli et al., 2009
		ESNA	30	Spiked surface water	Yoon et al., 2007
	Phenacetine	NF 90	72	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	71	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	42	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	40	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
Antibiotic	Trimethoprim	Flat sheet NF 270	90	Synthetic feed - DI	Hajibabania et al., 2011

		Flat sheet NF 270	50	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	30	Synthetic feed - Alginate	Hajibabania et al., 2011
		Flat sheet NF 270	88	Synthetic feed - DI	Steinle-Darling et al., 2010
		ESNA	65	Spiked surface water	Yoon et al., 2007
	Erytromycin	ESNA	60	Spiked surface water	Yoon et al., 2007
	Amoxicillin	TFC Kock SR2	65	Synthetic feed - NaCl 10mM; No alginate	Zazouli et al., 2009
		TFC Kock SR2	64	Synthetic feed - NaCl 10mM; 25 mg/L alginate	Zazouli et al., 2009
		TFC Kock SR2	62	Synthetic feed - NaCl 10mM; 50 mg/L alginate	Zazouli et al., 2009
	Sulfamethoxazale	Full scale NF90-400	>99	Groundwater	Radjenovic et al., 2008
		NE70	87.1	Synthetic feed - DI (spiked with cations)	Sadmani et al., 2014
		NE70	92.9	Raw Lake Ontario sample	Sadmani et al., 2014
		NE70	90.8	UF-pretreated Lake Ontario Sample	Sadmani et al., 2014
		NE70	85.1	FIEX[a]-Lake Ontario water	Sadmani et al., 2014
		ESNA	40	Spiked surface water	Yoon et al., 2007
		NF 90	96	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	95	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	84	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	84	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		Flat sheet NF 270	50	Synthetic feed - DI	Hajibabania et al., 2011
		Flat sheet NF 270	20	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	5	Synthetic feed - Alginate	Hajibabania et al., 2011
		Flat sheet NF 90	99	Synthetic feed - Humic acid	Nghiem et al., 2010
		Flat sheet NF 270	95	Synthetic feed - Humic acid	Nghiem et al., 2010
		Flat sheet NF 90	98	Synthetic feed - DI	Nghiem et al., 2010
		Flat sheet NF 270	90	Synthetic feed - DI	Nghiem et al., 2010
		Flat sheet NF 270	87	Synthetic feed - DI	Steinle-Darling et al., 2010
	Sulfamethizole	NE70	83.1	Synthetic feed - DI (spiked with cations)	Sadmani et al., 2014
		NE70	90.9	Raw Lake Ontario sample	Sadmani et al., 2014
		NE70	84.2	UF-pretreated Lake Ontario Sample	Sadmani et al., 2014

		NE70	87.4	FIEX[a]-Lake Ontario water	Sadmani et al., 2014
	Cephalexin	TFC Kock SR2	~100	Synthetic feed - NaCl 10mM; No alginate	Zazouli et al., 2009
		TFC Kock SR2	~100	Synthetic feed - NaCl 10mM; 25 mg/L alginate	Zazouli et al., 2009
		TFC Kock SR2	~100	Synthetic feed - NaCl 10mM; 50 mg/L alginate	Zazouli et al., 2009
	Tetracycline	TFC Kock SR2	89	Synthetic feed - NaCl 10mM; No alginate	Zazouli et al., 2009
		TFC Kock SR2	94	Synthetic feed - NaCl 10mM; 25 mg/L alginate	Zazouli et al., 2009
		TFC Kock SR2	97	Synthetic feed - NaCl 10mM; 50 mg/L alginate	Zazouli et al., 2009
b-Blockers	Atenolol	Flat sheet NF 90	90	Secondary Effluent	Azais et al., 2014
		Flat sheet NF 270	62	Secondary Effluent	Azais et al., 2015
		Flat sheet NF 90 - Prefouled	90	Secondary Effluent	Azais et al., 2016
		Flat sheet NF 270 - Prefouled	50	Secondary Effluent	Azais et al., 2017
	Metoprolol	Full scale NF90-400	>99	Groundwater	Radjenovic et al., 2008
	Sotolol	Full scale NF90-400	>99	Groundwater	Radjenovic et al., 2008
Cardiac	Hydrochlorothiazide	Full scale NF90-400	91.5	Groundwater	Radjenovic et al., 2008
Psychiatric	Carbamazepine	Flat sheet NF 90	95	Secondary Effluent	Azais et al., 2014
		Flat sheet NF 270	89	Secondary Effluent	Azais et al., 2015
		Flat sheet NF 90 - Prefouled	94	Secondary Effluent	Azais et al., 2016
		Flat sheet NF 270 - Prefouled	65	Secondary Effluent	Azais et al., 2017
		Flat sheet NF 90	95	Synthetic feed - Humic acid	Nghiem et al., 2010
		Flat sheet NF 270	80	Synthetic feed - Humic acid	Nghiem et al., 2010
		Flat sheet NF 90	95	Synthetic feed - DI	Nghiem et al., 2010
		Flat sheet NF 270	70	Synthetic feed - DI	Nghiem et al., 2010
		NF 90	90	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	92	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	80	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	85	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NE70	59.8	Synthetic feed - DI (spiked with cations)	Sadmani et al., 2014
		NE70	69.6	Raw Lake Ontario sample	Sadmani et al., 2014

		NE70	70.1	UF-pretreated Lake Ontario Sample	Sadmani et al., 2014
		NE70	60.8	FIEX[a]-Lake Ontario water	Sadmani et al., 2014
		ESNA	55	Spiked surface water	Yoon et al., 2007
		Full scale NF90-400	98.8	Groundwater	Radjenovic et al., 2008
	Primidone	Flat sheet NF 270	60	Synthetic feed - DI	Hajibabania et al., 2011
		Flat sheet NF 270	15	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	10	Synthetic feed - Alginate	Hajibabania et al., 2011
	Clozapine	Flat sheet NF 270	99	Synthetic feed - DI	Hajibabania et al., 2011
		Flat sheet NF 270	99	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	99	Synthetic feed - Alginate	Hajibabania et al., 2011
	Risperidone	Flat sheet NF 270	99	Synthetic feed - DI	Hajibabania et al., 2011
		Flat sheet NF 270	99	Synthetic feed - Humic acid	Hajibabania et al., 2011
		Flat sheet NF 270	99	Synthetic feed - Alginate	Hajibabania et al., 2011
	Dilantin	ESNA	45	Spiked surface water	Yoon et al., 2007
		Flat sheet NF 270	89	Synthetic feed - DI	Steinle-Darling et al., 2010
	Fluoxetine	Flat sheet NF 270	91	Synthetic feed - DI	Steinle-Darling et al., 2010
	Diazepam	ESNA	55	Spiked surface water	Yoon et al., 2007
	Meprobamate	ESNA	50	Spiked surface water	Yoon et al., 2007
Hormones	Estradiol	ESNA	40	Spiked surface water	Yoon et al., 2007
		NE70	67.9	Synthetic feed - DI (spiked with cations)	Sadmani et al., 2014
		NE70	74.5	Raw Lake Ontario sample	Sadmani et al., 2014
		NE70	89.2	UF-pretreated Lake Ontario Sample	Sadmani et al., 2014
		NE70	62.4	FIEX[a]-Lake Ontario water	Sadmani et al., 2014 b
		NF 90	96	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	97	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	80	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	90	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
	Ethynylestradiol	NF 90	90	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	94	Synthetic feed - DI	Yangali-Quintanilla et al., 2010

		NF 200	89	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	91	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NE70	82.8	FIEX[a]-Lake Ontario water	Sadmani et al., 2014 b
		ESNA	60	Spiked surface water	Yoon et al., 2007
	Testoterone	ESNA	65	Spiked surface water	Yoon et al., 2007
	Progesterone	ESNA	70	Spiked surface water	Yoon et al., 2007
Lipid regulator and metabolite	Gemfibrozil	ESNA	50	Spiked surface water	Yoon et al., 2007
		NF 90	96	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 90 - Prefouled	96	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200	90	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NF 200 - Prefouled	92	Synthetic feed - DI	Yangali-Quintanilla et al., 2010
		NE70	95.4	Synthetic feed - DI (spiked with cations)	Sadmani et al., 2014
		NE70	94.6	Raw Lake Ontario sample	Sadmani et al., 2014
		NE70	96.2	UF-pretreated Lake Ontario Sample	Sadmani et al., 2014
		NE70	94.3	FIEX[a]-Lake Ontario water	Sadmani et al., 2014
		Full scale NF90-400	89.3	Groundwater	Radjenovic et al., 2008
	Glibenclamide	Full scale NF90-400	>99	Groundwater	Radjenovic et al., 2008

[a]FIEX - fluidized anionic ion exchange

2.2.4. Membrane distillation

Membrane distillation (MD) is a low temperature distillation process that operates transporting water in vapour phase through a microporous and hydrophobic membrane on the distillate (product) side. This process has a theoretical 100% retention of non-volatile components. Due to the temperature difference between the feed and distillate side, only the most volatile compound (typically water) vaporizes passing through the pore openings at the feed-membrane interface, and then condenses at the distillate-membrane interface. Direct contact membrane distillation (DCMD) is considered the most widely studied MD system configuration due to its simple operation (CURCIO AND DRIOLI, 2007). In DCMD, the feed solution is maintained at a higher temperature than the distillate; thus, creating a difference in vapor pressure between the feed and the distillate. The membrane separates the liquid phase from the feed and distillation streams but allows the water vapor to flow freely through its dry microporous which is maintained dry due to the membrane's hydrophobicity, thus it prevents wetting of the pores by the liquid or distilled feed solution in normal operational conditions.

Since mass transfer can only occur in the gaseous phase, it is possible to achieve complete rejection of all non-volatile solutes such as inorganic salts and pathogenic microorganisms. In addition, MD is less susceptible to fouling, due to the absence of the need to apply a hydraulic pressure to the process execution (ALKHUDHIRI *et al*., 2013). Even when the fouling development is observed, it occurs in a less compacted and easily removed layer (ALKHUDHIRI *et al*., 2013). As a result, until the present date, much of the effort in MD research has focused on desalination applications (CURCIO; DRIOLI, 2007; CATH *et al*., 2004).

As MD works under low temperature, it is possible to use renewable energy as solar or any other low quality as a source of energy (CURCIO; DRIOLI, 2007; MERICQ *et al*., 2011). Given the advantages of high separation efficiency, low propensity to scale and potentially low energy consumption (when low heat quality is readily available), the MD process can be applied to a wide variety of applications besides brackish water desalination and sea water. It was observed several studies that explored the application of MD for food processing, such as recovery of whey protein in dairy processing (HAUSMANN *et al*., 2013), recovery of polyphenolic antioxidants from olive oil wastewater (EL-ABBASSI *et al*., 2012) and orange juice concentration (ALVES *et al*., 2006), separation of fermentation broth (GRYTA *et al*., 2013) as well as treatment of wastewater from the textile and petrochemical industries

(KHAING *et al.*, 2010), and municipal reuse of water (MERICQ *et al*., 2011; CATH *et al*., 2005). However only a few studies are focused on evaluating the application of MD for the removal of PhACs (WIJEKOON *et al.*, 2014; HAN *et al.*, 2017).

WIJEKOON *et al*. (2014) verified the feasibility of applying the membrane distillation (MD) process aiming at the removal of trace organic compounds (TrOCs), including active pharmaceutical compounds, during the treatment of water and wastewater. First of all, it was not observed any difference in the performance of the MD process with respect to the water flux and conductivity rejection when either the synthetic solution or MBR effluent was used as the feed. A total of 29 compounds were evaluated, including 11 PhACs, which occur ubiquitously in municipal wastewater. The results reported in the study suggest that the main mechanism of rejection, fate and transport of the compounds during the MD processes are governed by their intrinsic characteristics, being more expressive the volatility and, to a lesser extent, by hydrophobicity. All PhACs with pK_H> 9 (which can be classified as non-volatile) were well removed by the MD, ie they were concentrated in the feed solution. Otherwise, PhACs with pK_H <9, such as for example triclosan (pK_H 6.18), losses were observed either by adsorption or evaporation. The results indicate that the rejection of compounds with pK_H <9 can be governed by the interaction between their hydrophobicity and volatility (WIJEKOON *et al.*, 2014).

Further, the transport of the compounds during the MD process were also investigated. Hydrophilic compounds with negligible volatility were concentrated in the feed, while hydrophobic compounds with moderate volatility were substantially lost by evaporation or adsorption (WIJEKOON *et al.*, 2014).

When the MD process was integrated with a thermophilic membrane bioreactor (MBR), high removal (> 95%) of all compounds investigated in this study was observed despite their various physicochemical properties (ie, hydrophobicity, persistence and volatility). The results suggest that MD could be a promising post-treatment to be used in conjunction with thermophilic MBR for micropollutant removal (WIJEKOON *et al.*, 2014).

Han *et al.* 2017 evaluated the application of MD for the rejection of ibuprofen in the presence of NOM and inorganic salts for a synthetic solution of water which simulates surface water and well water. Again, no flux reduction was observed throughout the test with humic acid concentrations up to 160 mg/L, NaCl, 20 mM and $CaCl_2$ in concentrations of up to 11 mM.

Approximately 90% of ibuprofen rejection was also observed for both DI water and the synthetic solution in the pH range of 2.6-11. The results indicate that the presence of humic acid or the deposition of humic acid on the surface of the membrane has negligible effect on the rejection of ibuprofen, in contrast to other processes of membrane separation which apply pressure as a driving force, where rejection of contaminants can vary significantly with respect to scale. As the observed detection of ibuprofen, which is also non-volatile, in the permeate is similar to that observed from the passage of humic acids to the permeate suggesting a possible hydrophobic interaction with the membrane. Han *et al*. (2017) also states in the study that there is still the feasibility of implementing MD at reasonable flows (eg below critical flow) for long-term continuous operation for treatment of surface or recovered wastewater.

In spite of the presence of different components in real feeds, bench scale experiments tend to focus mainly on a target contaminant such as boron (HOU *et al.*, 2010), arsenic (PAL *et al*., 2010; CRISCUOLI *et al*., 2013) and organic trace compounds (WIJEKOON *et al.*, 2014), forgetting the influence of inorganic salts and natural organic matter (NOM) inevitably present in natural waters, therefore, these results make it impossible to fully understand the rejection of organic micropollutants according to the characteristics of the feed.

In particular, some studies point to the occurrence of membrane fouling by NOM in MD, which becomes a critical issue that still requires considerable research effort mainly in the understanding of this mechanism (NAIDU *et* al., 2014; TIJING *et al*., 2015). In fact, other studies indicate that the decline in the permeate flux caused by humic acids is insignificant due to the ionic concentration of sodium chloride (NaCl) and calcium chloride ($CaCl_2$) (KHAYET *et al*., 2004). The opposite is observed by Srisurichan *et al.* (2005) which found a significant decline in flux (up to 40%) due to calcium ion-induced humic acid scaling (referred to as Ca_2^+ carboxylate complexation), which was shown to be pH dependent (SRISURICHAN *et al*., 2005). These divergent conclusions on the effect of fouling due to humic acid and the impact on the permeate flux of the MD process imply that the study of organic contaminant rejection should be given in parallel with that of membrane fouling and/or wetting of pores by NOM. Many studies have already been published on the impact of fouling on the rejection of contaminants in relation to the NF, FO and ED processes, which for MD a further research is still necessary. Studies focusing on the effect of NOM and organic salts concentration on the MD membrane scale as well as on the rejection processes of the micropollutants, especially the

PhACs, are necessary in view of the differentiated motive power and mechanism of transport for MD.

2.3. Treatment options for membrane concentrate rich in PhACs

Besides from the MBR, MSP is only meant to promote a separation generating a concentrate rich in the target pollutant, and, in general, this concentrate is still in need of treatment in order to breakdown the retained molecules. The final disposal of the concentrate generated in the filtration process is a serious problem in wastewater treatment/reclamation plants employing MSP (BRUGGEN *et al*., 2005).

Advanced oxidation processes (AOPs) have been studied due to their capability of breaking down the organic matter and therefore, eliminating the PhAC. Also, since APOs are more efficient when applied to higher concentrations, the utilization of these processes to the concentrate is more effective (GEANIYU *et al*., 2015). The smaller volumes to be treated is also important due to the reduction of the cost associated to the chemicals used.

Abdelmelek *et al*. (2011) assessed the application of ozonation on the treatment of RO concentrate and the results indicated that AOP can effectively remove PhACs from the RO retentate reaching removal rates of 94, 95, 98 and 94 % for gemfibrozil, naproxen, erythromycin, and Atenolol, respectively. Benner *et al*., (2008) also used ozonation in order to treat RO concentrate. Experiments showed that an ozone concentration of only 5 mg/L resulted in a quantitative removal of propranolol in 0.8 s and 10 mg O3/L oxidized 70% of metoprolol in only 1.2 s.

The combination of MSP and Fenton's process is considered to be more efficient on the removal of PhACs than photo-Fenton alone (GEANIYU *et al*., 2015). Miralles-Cuevas et al. (2013), for instance, assessed the efficiency of combined NF and photo-Fenton and photo-Fenton alone as a tertiary treatment for removal of some PhACs from water. It was demonstrated that the combined NF and photo-Fenton treatment used less reagent (hydrogen peroxide) per contaminants mass because of elevated contaminants concentration, reduced the photo-Fenton treatment time as well as the water volume treated. Thus, this arrangement was found to be a promising approach for wastewater containing extremely low concentrations of microcontaminants.

Photocatalysis is tipically applied as post treatment stage for the MSP retentate. And most studies investigated the removal of organics in the concentrate stream to allow proper disposal in the environment (GANIYU *et al*., 2015). Westerhoff *et al*. (2009) investigated the feasibility of applying UV/TiO_2 photocatalysis and UV/TiO_2 photocatalysis followed by simple biological system (sand filter) as post-treatment stages for oxidation of organics present in reverse osmosis concentrate from wastewater reuse facilities. UV/TiO_2 treatment achieved up to 95% DOC removal at 10.4 kWh m^{-3} UV doses, which was nearly independent of both catalyst dose between 1 and 5 g L^{-1} and addition of H_2O_2.

Despite the general removal of specific effects by OAPs, there is a concern about the unspecific toxicity of the mostly unknown transformation products, which rises up possible problems with the application of OAPs and the consequences to human health as well as the wild life. Also, the cost associated to most of these processes is high, due to the necessity of application of reagents, as well as the generation of a sludge which still needs treatment and proper destination.

2.4. Future prospects

Regarding the MBR systems, it is possible to affirm that there are still gaps in the knowledge, requiring future studies in the deepening and clarification of these questions, which can be mentioned the types sorts mechanisms of the PhACs in the sludges, how occurs the degradation in phase solid and mainly the effects of the PhACs on the microbial activity existing in the MBR, that consequently affect the fouling and the rejection of compounds by the membrane. In addition, there is a need for continued studies to identify microorganisms that are resistant to PhACs and that favour the removal of pharmaceutical products in MBR in addition to their degradation mechanisms. In addition, it is necessary to migrate from the benchtop experiments to the full-scale application in order to verify the actual performance of the system in terms of removal of PhACs, since bench scale MBRs are not likely to predict the performance of MBRs on a large scale (TAHERAN *et al*., 2016).

Although NF and RO are very understood processes and proved to have good and reliable performances on the removal of PhACs, close attention has to be paid to their concentrate, specially the possible toxicity associated to the applied process used in order to break down the target pollutants. MBR can be studied an alternative in order to promote the biodegradation of the NF/RO concentrates, reducing the PhACs contents in the water as well as risk associated

with the formation of toxic bioproducts. In addition, an economic assessment is still necessary to analyse the feasibility of the conjugation of all the processes cited above.

MD is technology which is still in need of many improvements, for instance, breakthroughs in material development and membrane fabrication have been made for MD membranes, however, development of membranes made from low cost materials with good thermal stability and high hydrophobicity are still needed and in order to reduce prices, coupling MD with renewable energy like solar energy are also required to improve the possibility of application of this technology towards large-scale application (WANG; CHUNG 2015). Still, MD process is a very promising technology in order to be applied to in the treatment of water and wastewater and pursuit of high-purity permeate, however it is in need of much more efforts in order to understand its mechanisms.

2.5. Conclusion

Pharmaceutically active compounds are a real threat all around the world. Conventional water and wastewater treatment are not efficient in removing these kinds of micropollutants organics ending up in the realise of these compounds in the environment. The short and long-time effects of these compounds on the wild life and public health are not fully understood or predicted, especially the effect of a PhACs mix.

Membrane separation processes is a very promising technology to be applied in order to prevent public health and environmental problems caused by the release of PhACs in the environment since they are able to produce a high quality permeate without increasing its toxicity due to the lack of adding chemicals. Also, it can be scalable, and applied to a broad range of contaminants. However, it concentrates the contaminants, reducing the efficiency throughout the test and needing further treatment for the concentrate.

Nanofiltration and reverse osmosis are mainly applied for water treatment due to their high propensity of fouling. Their rejection mechanisms and how the interactions between PhACs and NOM or inorganic salts are well understood. However, there still some controversial results when NF is concerned, although it is consensual that tighter NF membranes are more efficient than looser membranes, reaching >99% of efficiency, but the tighter the membrane, the greater is the flux decline.

Membrane distillation is a relatively new technology especially because of its robustness in dealing with a broad spectrum of pollutants, however only a few studied are focused on the application of MD in removing PhACs from water and wastewater and few are known about the rejection mechanisms and the interaction between PhACs, NOM, inorganic salts and membrane. Studies are needed in order to cover these gaps to open access to the application of this technology in full scale. Also, MD, when using low-cost renewable energy, its cost can be comparable to NF technology, turning MD much more preferable to be apply in long term run due to the much smaller flux decline.

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3. ASSESSING POTENTIAL OF NANOFILTRATION, REVERSE OSMOSIS AND MEMBRANE DISTILLATION DRINKING WATER TREATMENT FOR PHARMACEUTICALLY ACTIVE COMPOUNDS (PhACs) REMOVAL

3.1. Introduction

More than 200 pharmaceutically active compounds (PhACs) have been detected in varying concentrations (ng/L to μg/L) in surface, ground water, and sewage and have been recognized as potential environmental threats (PETRIE *et* al., 2015; TAHERAN *et al*., 2016; CAMACHO-MUNOZ *et al*., 2014). PhACs have been attracting global attention due to increase in their production, usage, continuous discharge to the environment as well as potential ecological effects (SADMANI *et al*., 2014). Additionally, their actual effects and interactions with the environment are still not well-known and understood.

A large spectrum of pollutants from industrial and domestic effluents as well as farming activities arrive to conventional wastewater treatment plants (WWTPs). These facilities are designed to remove organic matter and nutrients in the order of g/L to mg/L and, thus, the complete removal of PhACs by a conventional WWTP is challenging due to several factors such as low volatility, hydrophobicity, complex structures, and extremely low concentrations (KEEN *et al*., 2012). Consequently, PhACs are discharged into waterbodies as they are not completely eliminated during the treatment processes (YOON *et al.*, 2010).

Previous studies have reported the adverse effects of PhACs, such as human/wildlife reproduction disorders and the appearance of antibiotic resistant bacteria, on non-target organisms after their release into the environment (MARTI *et al*., 2014; YOKOTA *et al*., 2015). Additionally, it is known that releasing estrogenic pharmaceuticals into water bodies can interfere with sex differentiation, thereby, reducing or increasing fertility (SPINA *et al*., 2013). The physicochemical properties of PhACs favor their persistence in the environment, propensity for bioaccumulation in living organisms, and capability to be transformed into products after natural oxidative processes (VERLICCHI *et al*., 2012). Therefore, environmental risk assessment should be conducted in this regard.

Moreover, it has been reported that some PhACs persist through treatment processes at drinking water treatment plants (DWTPs) due to their small size and polarity which makes them highly water soluble, mobile, and extremely difficult to remove by conventional treatments (GABARRON *et al*., 2016, VERLIEFDE *et al.,* 2009). Thus, PhACs are likely to be detrimental to humans as they can return to the human body through water cycle and food chain (AMON, 2011). Therefore, considering the possibility of inadvertent exposure to PhACs via drinking water, it is important to assess their consequent risks to human health.

Considering the limitations associated with conventional treatment processes, the need to achieve removal of PhACs has led to alternative technologies such as membrane separation processes (MSPs) (GRACIA-IVARS *et al*, 2017; SADMANI *et al*., 2014; NGUYEN *et al*., 2013; PARK *et al*., 2017; HUBNER *et al*., 2015). MSPs, such as membrane distillation (MD), reverse osmosis (RO), and nanofiltration (NF), have been successfully applied, either as a single process or as a combination of different membrane techniques, at pilot and full-scale installations in domestic or industrial wastewater reclamation to achieve a high quality permeate by efficiently removing a large spectrum of pollutants, microorganisms, salts, organic micropollutants, proteins, sugars, and inorganic ions.

NF and RO processes have demonstrated promising results for treatment of PhACs and other emerging micropollutants (YANGALI-QUINTANILLA *et al*., 2010; SADMANI *et al*., 2014). Despite incomplete removal of ions, NF presents a greater permeate flux and is able to work at lower pressures. It is expected to show effective removal of organic pollutants (BRUGGEN *et al*., 2008), especially PhACs since a majority of them have molecular weights within 150–500 Da and the molecular weight cut-off (MWCO) for most commercial NF membranes ranges from about 100 to 2000 Da (WANG *et al*., 2014). Previous studies have indicated that steric hindrance effects by these membranes are the predominant phenomenon for rejection of PhACs (COUTO *et al*., 2018). The electrostatic effect is also significant in rejection of charged pharmaceutical compounds which explains the high rejection of negatively charged PhACs by loose NF (KONG *et* al., 2016) and RO membranes (exceeding 95%) (XU *et al*., 2016). In addition, almost all PhACs can physically and/or chemically interact with the membrane material leading to their adsorption onto the membrane and potentially impacting their rejection (VERLIEFDE *et al*., 2009).

Studies point that electrostatic exclusion is the predominant phenomenon in the rejection process of these membranes and, therefore, effective rejections of negative pharmaceutical compounds were observed, exceeding 95% by RO membranes (KIMURA *et al*., 2003; XU *et al*., 2005; NGHIEM *et al*., 2003).

MD is a low temperature distillation process that operates by transporting water in vapor phase through a microporous and hydrophobic membrane to the distillate side. Theoretically, this process shows 100% retention of non-volatile components. Due to the temperature difference between the feed and distillate sides, only the most volatile compounds (typically water) vaporize to pass through the pore openings at the feed-membrane interface and subsequently, condense at the distillate-membrane interface. Direct contact membrane distillation is considered the most widely studied MD system configuration due to its simple operation (CURCIO AND DRIOLI, 2005). MD is less susceptible to membrane incrustation than pressure membrane processes since the latter are subject to hydraulic pressure. Moreover, even when a fouling layer is formed on the membrane surface, it is expected to be less compact and can be easily removed (ALKHUDHIRI *et al*., 2013). Wijekoon *et al.* (2014) studied the application of MD for removing PhACs during water and wastewater treatment. The results suggested that the rejection and fate of PhACs during MD were governed by their volatility and hydrophobicity. All PhACs with $pK_H > 9$ were completely removed.

Several studies (GRACIA-IVARS *et al*., 2017; SADMANI *et al*., 2014; NGUYEN *et al*., 2013; PARK *et al*., 2017; HUBNER *et al*., 2015) have evaluated and compared the application of NF and RO. However, only a few studies (HAN et al. 2017; ALKHUDHIRI et al., 2013) have focused on the application of MD in removing PhACs from water and wastewater. Moreover, most studies have been carried out using synthetic or spiked solutions. Therefore, studies that focus on the application of MSPs to real water matrixes while dealing with real concentrations (in the order of ng/L to μg/L) and their complex matrices are still needed. This allows for improvement of the treatment efficiency by reducing membrane fouling and energy requirements. Additionally, it helps understand the rejection mechanisms and interactions between the membrane and the PhACs to help establish the most effective operational systems to produce safe potable water. Therefore, the aim of this study was to compare NF, RO, and MD technologies in terms of their technical and economic performances with regard to the removal of PhACs from a real water matrix.

3.2. Materials and methods

3.2.1. Study area and sample collection

The present study was conducted with water samples collected from Doce River located at Governador Valadares in Minas Gerais, Brazil. The sampling point was one which supplies to the DWTP of Governador Valadares city (18º51'47.83" (latitude) and 41º56'47.02" (longitude)). The water sample was collected according to the technical specifications of the Standard Methods for the Examination of Water and Wastewater (2012) for monitoring of surface water and wastewater. Additionally, the water in Doce River was monitored over a one-year period from April 2016 to April 2017, according to chapter 4, and its main characteristics are shown on Table 6. During this monitoring, five pharmaceutical compounds were quantified in different samples (N = 5): betamethasone (295 ± 165 ng/L; quantification frequency (QF) = 4), fluconazole (356 ± 266 ng/L; QF = 3), phenylbutazone (132 ng/L; QF = 1), prednisone (233 ng/L; QF= 2), and metformin (36 ng/L; QF = 1).

Table 6 - Characteristics of water collected from Doce River and the legal limits according to the Brazilian legislation for drinking water (2011)

Parameter	Average ± SD	Legal limit	Parameter	Average ± SD	Legal limit
pH	7.1 ± 0.1	6.0–9.5	Turbidity (NTU)	22.6 ±19.2	1
Conductivity (µS/cm)	127.9 ± 27.9	-	NH_4^+ (mg/L)	< 1.25	-
Apparent color (mg Pt-Co/L)	131.4 ± 53.1	15	Ca^{2+} (mg/L)	4.3 ± 0.9	-
Real color (mg Pt-Co/L)	41.2 ± 39.1	-	Mg^{2+} (mg/L)	1.6 ± 0.4	500*
TS[a] (mg/L)	98.0 ± 60.4	-	Na^+ (mg/L)	2.9 ± 0.9	200
TSS[b] (mg/L)	20.4 ± 6.5	-	K^+ (mg/kg)	2.4 ± 0.4	-
TOC[c] (mg/L)	1.6 ± 0.8	-	Fe^{3+} (mg/kg)	0.6 ± 0.5	0.3
TN[d] (mg/L)	0.8 ± 0.2	-	Al^{3+} (mg/kg)	0.4 ± 0.3	0.2
Alkalinity (mg CaCO3/L)	17.4 ± 10.1	-	As^+ (ppb)	5.2 ± 2.6	0.01
Total Coliforms (NMP/100mL[1b])	> 2419.2	absence in 100 mL	Pb^{2+} (ppb)	3.4 ± 1.7	0.01

E. coli (NMP/100mL[1b])	> 5700	absence in 100 mL	Si (mg/kg)	6.6 ±	1.8 -

[a] Total solids; [b] Total suspended solids; [c] Total organic carbon; [d] total nitrogen; *The Administrative Ordinance 2914 defines the maximum permitted value of 500 mg/L for hardness (sum of the concentrations of Mg and Ca).

3.2.2. Selected compounds, sample preparation, and instrumental analysis

A total of 28 PhACs were selected based on the list of pharmaceuticals distributed by the Brazilian health system (Sistema Único de Saúde - SUS) to represent the Brazilian consumption pattern as well as the various classes of micropollutants. The physicochemical properties, including molecular weight, geometry, hydrophobicity/hydrophilicity, polarity, and charge, of the selected PhACs are shown in Appendix 2. The analytical standards of the selected PhACs were obtained from Sigma-Aldrich (Steinheim, Germany). HPLC-grade formic acid and solvents were purchased from Dikma (USA). Ultrapure water (18.2 $M\Omega cm^{-1}$) was produced by a Milli-Q unit (Millipore, USA).

PhACs were analyzed using HPLC (DGU/20A3 Prominence, Shimadzu, Japan) coupled to a micrOTOF-QII mass spectrometer (Bruker) with an electrospray ionization source (ESI). The uncertainty of estimation was 1% according to the validation method of the analysis protocol. Recoveries were between 86% and 100% but were compensated by the calibration, which is processed the same way as the samples. Water samples were previously filtered using a 0.45 µm hydrophilic PVDF filter. Analytes were isolated from water samples (1 L) in two steps, firstly without pH adjustment (pH 7), and then with pH adjustment to 2 by adding 0.002 mol/L H_2SO_4 solution, using a polymeric C18/18% cartridge (500 mg/6 mL – Applied Separations) preconditioned with 5 mL methanol and 5 mL ultra-pure water, and then eluted with methanol using an Aspec Gilson GX-271 Liquid Handler. Separation was achieved on a Shim-pack XR-ODS C18 column (2.0 mm; 50 mm and 2.0 µm; Shimadzu, Japan) with a mixture of 0.1% formic acid water and methanol as the mobile phase. The flow rate and injection volume were 0.1 mL/min and 10 µL, respectively. The mobile phase gradient followed an isocratic method using 95% of methanol for 15 min

3.2.3. Experimental set-up

The NF test was carried out with the DK NF membrane and the RO test was carried out with the BW30 membrane. Membrane characteristics are shown on Table 7.

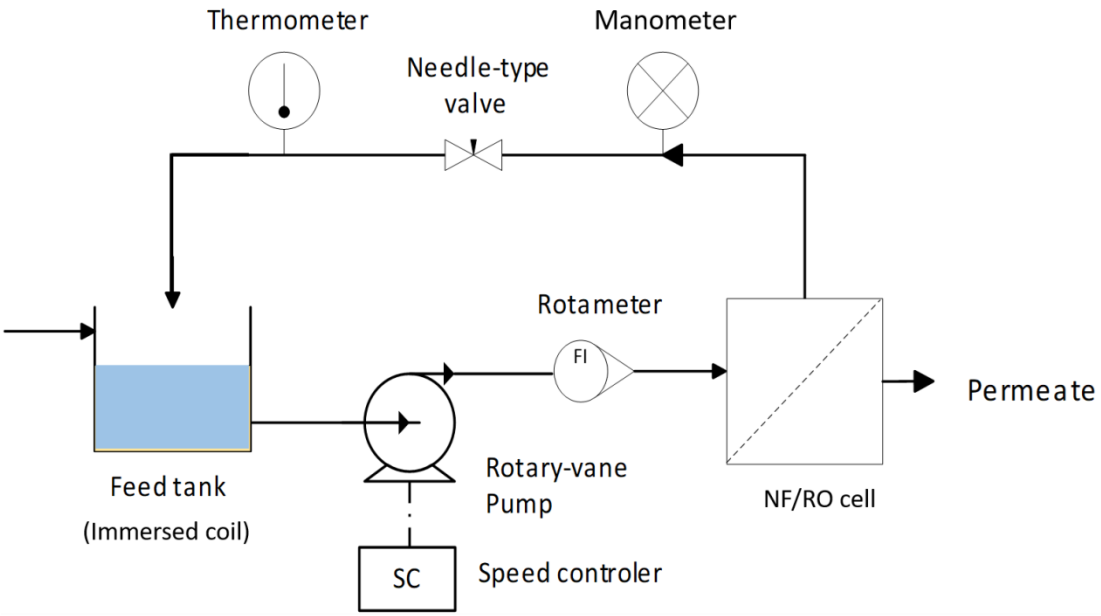
Table 7 - NF and RO membranes characteristics

Product	**Manufacturer specification**				**Properties**				
	Manufacturer	Membrane chemistry	MWCO (Da)	Salt rejection	Maximum temperature (ºC)	Pore size (mm)	Surface roughness (Ra, nm)	Zeta-potential (mV)	Contact angle (°)
BW30	DOW/Filmtec	Polyamide RO	N/A	99.5% NaCl[a]	45	N/A	68.3[c]	-10.1 (pH = 9.0)[c]	76 ± 7[f]
DK	GE Osmonics	Piperazine NF	150–300	98% $MgSO_4$[b]	50	0.76[c]	16.4[c]	-18.5 (pH = 9)[c]	40.6 ± 5.2[c]

N/A: not available; test conditions specified by the respective manufacturers: [a]2,000 ppm NaCl, 25°C, 15% recovery at 15.5 bar; [b]2,000 ppm $MgSO_4$, 25°C, 15% recovery at 7.6 bar; 25°C, 15% recovery at 4.8 bar; [c]Tang et al. (2009); [d]Yin et al. (2013); [e]Widjaya et al. (2012); [f]Pontié et al. (2008)

Figure 2 shows a schematic of the laboratory-scale NF/RO system. The NF/RO unit had a maximum operating pressure of 20 bar which was provided by a rotary vane pump equipped with a speed controller and a maximum flow of 530 L/h. A needle-type valve was used to adjust the feed flow rate and the trans-membrane pressure (TMP). The pressure was measured by a manometer. NF and RO were conducted in a stainless-steel membrane cell with a diameter of 9 cm and filtration area of 63.6 cm^2. The flat-sheet commercial membranes were cut to fit the membrane cell and a feed spacer of 28 mils (25.4 µm) was placed over the membrane to promote flow distribution. The feed temperature was maintained at 20 ± 5ºC by an immersed coil.

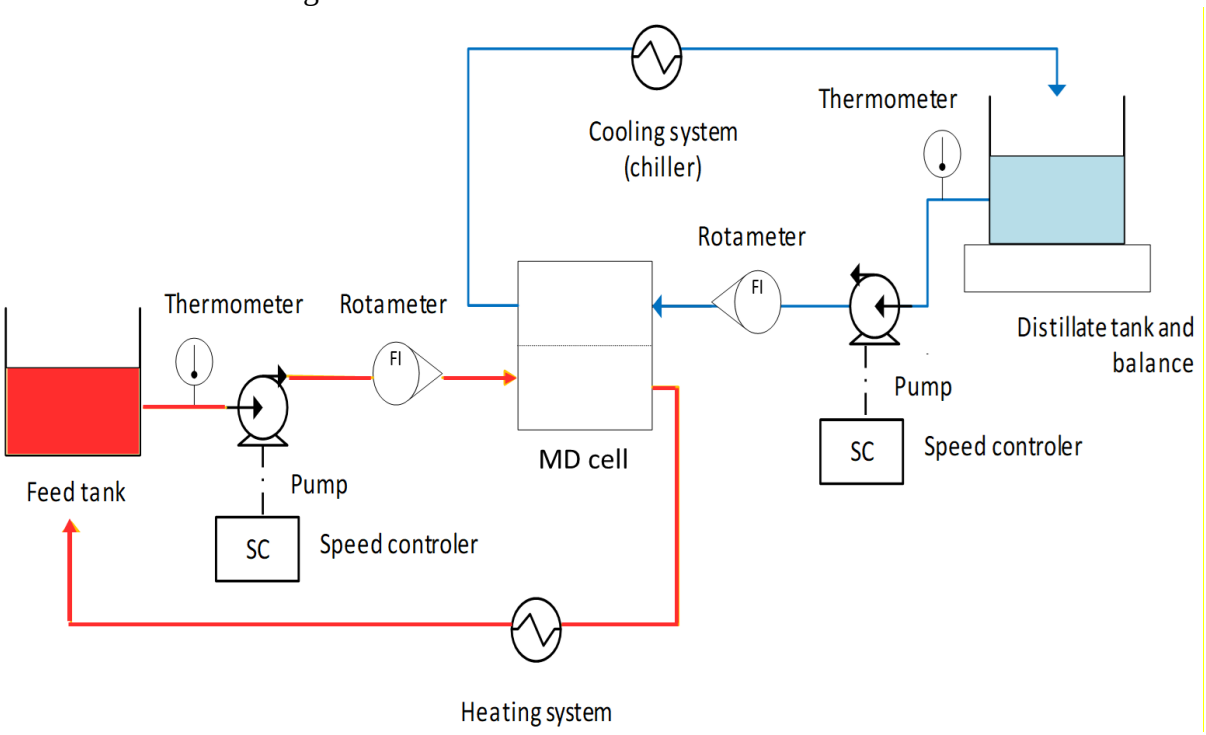
Figure 2 - A schematic of the NF/RO bench scale unit



MD tests were conducted using a flat hydrophobic microporous polytetrafloroethylene membrane (Sterlitech). According to the manufacturer, the average pore size and porosity of the MD membrane were 0.22 µm and 70%, respectively. The membrane cell was made of acrylic glass and a flow channel was engraved in each of the two acrylic glass blocks that made up the feed and permeate the semi cells. The feed solution was circulated from a glass reservoir to the membrane cell and then returned to the feed reservoir (Figure 3). Feed temperature was maintained by a hot plate. The temperature of the distillate was regulated using a chiller (AquaCooler, Australia) equipped with a stainless-steel heat exchanging coil immersed directly in the distillate reservoir. The distillate reservoir was placed directly on an analytical balance (Mettler Toledo, Switzerland) and the flux was calculated by mass increase observed over time.

At the end of each experiment, the solution volume was measured again and the total volume loss was found to be less than 15%.

Figure 3 - A schematic of the MD bench scale unit



3.2.4. Experimental procedure

The following procedure was adopted for the NF and RO tests: (i) de-ionized water filtration under three different TMPs (10, 8, and 6 bar) until a constant flux was obtained at each pressure; (ii) water sample filtration under 10 bar at a concentrated flow rate of 3.2 L min^{-1} and a temperature of 25°C up to 70% recovery rate (which took 12 and 18 hours for NF and RO respectively); (iii) washing the fouled membrane module with flowing de-ionized water for 2 minutes at a concentrated flow rate of 1.2 L min^{-1} to remove the foulants that were loosely deposited on the membrane surface; (iv) de-ionized water filtration under 10 bar for 20 minutes; (v) chemical cleaning of membrane (acid citric 2% followed by NaOH 0.4% m/m); (vi) de-ionized water filtration under three different TMPs (10, 8, and 6 bar) until a constant flux was obtained at each pressure. The flux rate was measured every 10 minutes throughout the test and permeate samples were collected every permeate recovery rate of 10%.

With regard to the MD experiments, the following procedure was adopted: (i) de-ionized water recirculation under three different temperature (50, 60 and 70ºC) until a constant permeate flux

was obtained at each temperature; (ii) water sample recirculation under feed and distillate temperatures of 60 and 25 °C, respectively, and cross-flow velocity of feed and distillate circulation of 11.4 cm/s. The initial feed volume was 2 L, and 1L of Milli-Q water was used as the initial distillate.; (iii) washing the fouled membrane module with flowing de-ionized water for 2 minutes at a circulation of 11.4 cm/s to remove the foulants that were loosely deposited on the membrane surface; (iv) de-ionized water recirculation under 60ºC for 20 minutes and distillate side under 25ºC; (v) chemical cleaning of membrane (acid citric 2% followed by NaOH 0.4% m/m); (vi) de-ionized water recirculation under three different temperature (50, 60 and 70ºC) until a constant permeate flux was obtained at each temperature. The flux rate was measured every 30 minutes throughout the test. The experiment was concluded once the water recovery had reached 70%, at which stage the feed and distillate samples were collected for the PhACs analysis. The concentrations of PhACs in the distillate were corrected for dilution by accounting for the initial volume of Milli-Q water in the distillate. The duration of each MD experiment was approximately 13 h.

3.2.5. Analytical Methods

Color (2120 C) and TSS (total suspended solids) (2540 B E) were analyzed in accordance with the recommendations of the Standard Methods for the Examination of Water and Wastewater [30]. pH was measured according to the method 4500 H B using a digital calibrated pH-meter. TOC was analyzed using the TOC (total organic carbon) Shimadzu TOC-V CNP. Conductivity was determined following the method 2510 B with a calibrated conductivity meter (Hach 44600). The concentrations of Cl^-, SO_4^{2-}, PO_4^{3-}, F^-, NO_3^-, and NO_2^- were measured by ion chromatography (ICS-1000 ion chromatograph equipped with the Dionex AS-22 column and ICS 12a). The concentrations of metals K^+, Mg^{2+}, Ca^{2+}, and Na^+ were quantified by atomic absorption spectrometry (Atomic Absorption Spectrophotometer - GBC - AVANTA).

3.2.6. Environmental and human health risk assessment

The potential environmental risks of PhACs were evaluated based on the hazard quotient (HQ) values. HQ values were calculated for acute and chronic effects by dividing the measured environmental concentration with the predicted no effect concentration (PNEC), which was

determined by dividing the mean effect or lethal concentration (EC50 or LC50) and the non-observed effect concentration by safety factors, whose typical values, as reported in literature, are 1000 and 10, respectively (WHO, 2011). For HQ calculation, the lowest PNEC values were considered to obtain the worst-case scenario. The mixture toxicity was estimated by using the classical concentration addition model to calculate mixture hazard quotients (MHQ). The risk was classified into the following categories: high risk (MHQ > 1), medium risk (0.1 ≤ MHQ ≤ 1), low risk (0.01 ≤ MHQ < 0.1), and negligible risk (MHQ < 0.01) (EC, 1996).

To assess the impact on public health, the margin of exposure was calculated by comparing the concentration of each PhAC in treated water samples to its concentration below which the probability of adverse effects as a result of long-term (lifetime) exposure are negligible. Tolerable daily intake (TDI), which was derived from the non-observed adverse effect level (NOAEL) and a safety factor of 100, was used to estimate the safe exposure levels (WHO, 2011). TDI values for each PhAC were selected from literature or derived from NOAEL (DWI, 2007).

3.2.7. Calculations

The volumetric permeate fluxes (L m^{-2} h^{-1}) for NF (J_{NF}) and RO (J_{RO}) were calculated using Eq. (1), as follows:

$$J_{NF} = J_{RO} = \frac{\Delta V_P}{A_m \times \Delta t} \quad (1)$$

where A_m is the effective membrane area; ΔV_p is the permeate volume collected; and Δt is the collection time. Flux normalization at 25 °C was accomplished by means of a correction factor related to the fluid viscosity according to Eq. (2):

$$J(25°C) = \frac{\Delta V_P}{A_m \times \Delta t} \cdot \frac{\mu(T)}{\mu(25°C)} \quad (2)$$

where $J(25°C)$ is the normalized permeate flux at 25 °C; $\mu(T)$ is the water viscosity at the process temperature; and $\mu(25\ °C)$ is the water viscosity at 25 °C. The permeate recovery ratio (RR_{NF} and RR_{RO}) can be defined by Eq. (3):

$$RR_{NF} = RR_{RO} = \frac{V_p}{V_f} . 100 \quad (3)$$

where V_p corresponds to the accumulated volume of permeate and V_f to the initial volume of the feed.

For the MD system, the permeate flux ($J_{P(MD)}$) was calculated according to Eq. (4):

$$J_{P(MD)} = \frac{m_{di} - m_{df}}{A_m . (t_i - t_f)} \quad (4)$$

Where m_{di} and m_{df} correspond to the mass (kg) of the initial and final distillate, respectively. A_m is the area of the membrane (m^2) and t_i and t_f correspond to the initial and final times, respectively.

The recovery rate (RR_{MD}) is calculated by Eq. (5):

$$RR_{MD} = \frac{m_{df} - m_{di}}{m_{fi}} . 100 \quad (5)$$

Where m_{fi} corresponds to the mass (kg) of the initial feed. The observed rejection was calculated using Eq. (6), as follows:

$$Rejection(\%) = \frac{C_f - C_p}{C_f} \times 100 \quad (6)$$

where C_f and C_p represent the solute content in the feed and permeate streams, respectively. PhACs losses during the MD experiments were calculated by considering the mass balance of each analyzed compound in the feed, concentrate, and distillate, as given in Eq. (7).

$$C_F x V_F = (C_D x V_D) + (C_C x V_C) + total\ loss \quad (7)$$

where C_F, C_D, and C_C are concentrations in the feed, distillate, and concentrate, respectively. Similarly, V_F, V_D, and V_C are the feed, distillate, and concentrate volumes, respectively.

According to the simplified resistance-in-series model, the total filtration resistance could be divided into membrane resistance (R_M) and fouling resistance (R_f). R_M was determined from Eq. (8):

$$R_M = \frac{1}{K \cdot \mu(25°C)} \tag{8}$$

where *K* is the membrane water permeability for each test. It was obtained from the ratio of normalized permeate flux of pure water (J_w) and applied pressures (ΔP) at 10.0, 8.0, and 6.0 bar linearization. R_f was calculated based on the normalized effluent permeate flux (J_{sd}) obtained near the end of each experiment (Eq. 9). This resistance includes concentration polarization (CP), components adsorption on the membrane surface, and scaling.

$$R_f = \frac{\Delta P - \Delta\pi}{\mu(25°C) \cdot J_{sd}} - R_M \tag{9}$$

where ($\Delta P - \Delta\pi$) is the process effective pressure, i.e., applied pressure minus osmotic pressure. The osmotic pressure difference was calculated using van't Hoff equation (Eq. 10):

$$\Delta\pi = \sum_{i=0}^{n} \left(C_c - C_p\right) \cdot R \cdot T \tag{10}$$

where R is the universal gas constant; T is the permeation temperature in Kelvin; and the sum of the difference of the molar concentration of the main dissolved species that are present in the concentrate (C_c) and permeate (C_p) at each recuperation rate (RR).

R_f is a combination of reversible fouling (R_{fr}) and irreversible fouling layer (R_{fir}) (CHEN *et al*., 2015). R_{fr} results mostly due to deposition of a cake layer on the membrane surface which can be removed through physical cleaning such as water washing; thus, it can be controlled by adjusting the feed flow conditions. R_{fir} occurs due to adsorption onto membrane surface and into its pores and can be removed by chemical cleaning.

For the MD resistance calculations, i.e., membrane resistance (R_m), feed boundary layer

resistance (R_{fb}) and permeate boundary layer resistance (R_{pb}), Eq. (11) to (13) were used (SRISURICHAN *et al*., 2006).

$$R_m = \frac{P_1 - P_2}{J_{p(MD)}} \tag{11}$$

$$R_{fb} = \frac{P_f - P_1}{J_{p(MD)}} \tag{12}$$

$$R_{pb} = \frac{P_2 - P_p}{J_{p(MD)}} \tag{13}$$

where P_1 and P_2 represent the vapor pressure at feed and permeate membrane surfaces, respectively; and P_f and P_p represent the vapor pressure at the bulk feed and permeate, respectively. Pressures were calculated according to Eq. (14) and temperatures at the membrane surface were estimated according to Eq. (15) and (16) (SRISURICHAN *et al*., 2006).

$$P = exp\left(23.238 - \frac{3841}{T - 45}\right) \tag{14}$$

$$T_{w,f} = \frac{h_m\left(T_p + \left({h_f}/{h_p}\right)T_f\right) + h_f T_f - J_{p(MD)}\Delta H_v}{h_m + h_f(1 + \frac{h_m}{h_p})} \tag{15}$$

$$T_{w,p} = \frac{h_m\left(T_f + \left({h_p}/{h_f}\right)T_p\right) + h_p T_p - J_{p(MD)}\Delta H_v}{h_m + h_p(1 + \frac{h_m}{h_f})} \tag{16}$$

Where $T_{w,f}$, $T_{w,p}$, T_f, and T_p represent the temperatures at interface and bulk for feed and permeate, respectively; h_m, h_p, and h_f stand for the convective heat transfer coefficient of the membrane, permeate, and feed, respectively; and ΔH_v is the vaporization heat.

The total flux decline (FD) for all three processes was calculated as follows:

$$FD = \frac{(J_w - J_{sd})}{J_w} \tag{17}$$

Flux decline can be attributed to CP and fouling (F); thus, the flux decline due to CP was obtained using Eq. (18):

$$CP = \frac{(J_{pc} - J_{sd})}{J_w} \quad (18)$$

where J_{pc} is the volumetric water flux of the physically cleaned membrane after effluent filtration. The flux decline due to fouling was obtained using Eq. (19):

$$F = \frac{(J_w - J_{pc})}{J_w} \quad (19)$$

The specific energy consumption (SEC) for NF and RO was calculated from Eq. (20) and (21) (ZHU *et al*., 2009):

$$SEC = \frac{W_{pump}}{Q_P} \quad (20)$$

$$W_{Pump} = \Delta p \times Q_F \quad (21)$$

where W_{pump} is the pump work rate (kWh/s); Δ_P is the difference between the feed pressure at the entrance of the membrane and the pressure of raw water, which is assumed to be equal to the atmospheric pressure (N/m²); and Q_F and Q_P are the feed and permeate flow rates (m³/s), respectively. The permeate product water recovery for NF processes (Y) can be defined using Eq. (22), as follows:

$$Y = \frac{Q_P}{Q_F} \quad (22)$$

By combining Eq. (20), (21), and (22), the SEC equation can be rewritten as follows:

$$SEC = \frac{\Delta P}{Y} \quad (23)$$

Energy consumptions for the MD system are estimated both for heat/cooling energy and for circulation of the streams. The specific thermal energy consumption, or STEC (kWh/m^3), was calculated according to Qtaishat and Banat (2013):

$$STEC = \frac{m_f . c_f . (T_{f,in} - T_{f,out})}{J_{sd}} \quad (24)$$

Where m_f is the feed flow rate; c_f is the specific heat of the feed (4.18 kJ kg^{-1}K^{-1}); T_f is the temperature of the feed in ($T_{f,in}$) and out ($T_{f,out}$) of the module. The temperature difference represents the thermal energy entering the MD process via the hot feed cycle.

Electric energy (E_E) for streams circulation can be calculated by Eq. (25):

$$E_E = \frac{m_f . \Delta P}{\eta} \quad (25)$$

where m_f is the feed flow rate; ΔP is the pressure experienced by the membrane; and η is the efficiency of the pump which was considered equal to 0.95. ΔP was considered 0.00175 bar for the MD system (experimental data).

3.2.8. Statistic Evaluation

Due to the small quantity of data (i.e. seven data points per NF test), a non-parametric statistical test was used. Kruskal Wallis' test was used to check for significant differences between the evaluated parameters, and then non-parametric multiple comparisons were investigated among the groups (α = 5%). STATISTICA 8.0 software was used for all statistical analyses.

3.2.9. Preliminary Investment and Cost Estimate

A preliminary economic evaluation was conducted to estimate the capital and operational expenses (CapEx and OpEx) to treat Doce River water by NF, RO, and MD. The variables considered were costs of membrane unit, membrane replacement, chemical cleaning agents, energy consumption, and system maintenance.

For NF and RO, the membrane unit capital cost was based on a price provided by a major supplier of commercial membranes in Brazil (8,750.00 USD/m^3.h of effluent). For MD, the membrane unit capital cost was considered to be 7,680.00 U$/$m^3$.h (SCHWANTES *et al*., 2018). It assumed one filtration stage and volumetric flows equal to the designed systems capacity (Q_{des}) of 0.04 m^3/s. To estimate the capital cost per cubic meter of effluent, the capital cost was annualized by means of the amortization factor, as presented in Eq. (26) (SETHI; WIESNER, 2000).

$$A/P = \frac{i_c \cdot (1 + i_c)^{DL}}{(1 + i_c)^{DL} - 1} \tag{26}$$

where (A/P) is the amortization factor; i_c is the investment rate (14% in 2018 for Brazil); and DL is the design life of the plant. The membrane systems design life was considered to be 15 years. The capital cost per cubic meter was obtained from Eq. (27):

$$C_{cap/m^3} = \frac{C_{cap} \cdot A/P}{Q_{des}} \tag{27}$$

where C_{cap/m^3} is the capital cost per cubic meter of effluent, C_{cap} is the system capital cost, and Q_{des} is the capacity of the designed system.

Membrane replacement costs considered an average membrane lifespan of 5 years. The permeate recovery rate was set at a value greater than one that provided PhAC concentrations below the method quantification limit (MQL) for each assessed treatment. NF, RO, and MD membrane costs were provided by a large commercial membrane supplier as 50, 40, and 60 US$/$m^2$, respectively.

The energy cost estimate comprised the assessed systems feed pump requirement and the

thermal energy for heating the MD feed solution. A once-through operation process was considered, and the power requirement was estimated from Eq. 20 to 25. The energy tariff paid by the water production company in Brazil is 0.04 US$/kWh (at an exchange rate of R$1 = US$0.25). The costs of chemicals for membrane cleaning and maintenance costs were estimated at 2 and 5% (per year) of the initial investment cost, respectively (SHEN *et al*., 2014).

3.3. Results and discussion

3.3.1. Occurrence of PhACs in the surface water

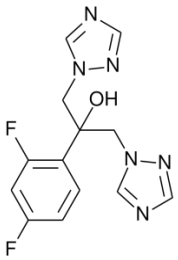
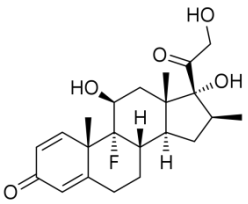
Betamethasone (anti-inflammatory) and fluconazole (antifungal), among the 28 assessed PhACs evaluated, were quantified in the water sample collected for this specific study (Table 8).

Table 8 - Concentration and limit detection (LD) of the 28 assessed PhACs

PhACs	Concentration (ng/L)	LD (ng/L)	PhACs	Concentration (ng/L)	LD (ng/L)
Atenolol	<LD	10.2	Scopolamine	<LD	2.4
Fluconazole	**573.8**	**2.4**	Prednisone	<LD	7.2
Trimethoprim	<LD	10.6	**Betamethasone**	**165.1**	**2.4**
Clarithromycin	<LD	6.5	Phenazone	<LD	3.3
Erythromycin	<LD	6.6	Phenylbutazone	<LD	2.4
Amoxicillin	<LD	1.6	Fenofibrate	<LD	7.6
Ampicillin	<LD	1.3	Cimetidine	<LD	8.9
Atorvastatin	<LD	12.8	Omeprazole	<LD	17.8
Caffeine	<LD	22.9	Paroxetine	<LD	20.0
Danofloxacin	<LD	0.9	Loratadine	<LD	13.6
Enoxacin	<LD	10.0	Ranitidine	<LD	8.0
Enrofloxacin	<LD	0.5	Ibuprofen	<LD	8.0
Metformin	<LD	0.3	Ketoprofen	<LD	8.0
Norfloxacin	<LD	1.0	Genfizobril	<LD	8.0

These PhACs were the most recurrent during monitoring performed in a previous study and their occurrence and concentrations were subject to seasonality (SANTOS *et al*., 2018). November marks the beginning of the rainy season in Brazil which propitiates increased fungal populations and may explain the higher fluconazole concentration. Table 9 shows the physical-chemical properties and toxicity indicators of betamethasone and fluconazole in the water sample.

Table 9 - Physical-chemical properties, toxicity indicators, and measured concentrations (ng/L) of betamethasone and fluconazole in the water sample collected from Doce River

Pharmaceutical compound	**Fluconazole**	**Betamethasone**
Therapeutic class	Antifungal	Corticosteroid
Chemical group	Antifungal	Analgesics and anti-inflammatories
Molecular formula	$C_{13}H_{12}F_2N_6O$	$C_{22}H_{29}FO_5$
Structural formula[a]		
Molecular weight (g/mol)	306.1	393.2
Log K_{ow}[a]	0.40	1.94
Dissociation constant[a]	pKa = 12.71	pKa = 12.42
Charge at pH 7	Neutral	Neutral
Molar volume (cm^3/mol) [a]	205	296
Polarizability[a]	26.92	39.70

Molecular radius (Å)[a]	5.49	6.16
KH (atm-m^3/mole)[d]	7.11 x 10^{-09}	7.36 x 10^{-11}
Vapor pressure (mmHg)[d]	1.02 x 10^{-06}	3.49 x 10^{-10}
Acute PNEC (mg/L)	0.100	0.032
Chronic PNEC (mg/L)	0.306	1.000
TDI (mg/kg.d)	0.0500	0.0625
Concentration (ng/L)	573.8	165.1

[a]Drugbank, (2018); [b]EPA, (2018); logK_{ow} is the octanol–water partition coefficient; KH is the Henry law constant; pka is the acidity constant; TDI is the tolerable daily intake

Fluconazole concentrations were found to be significantly higher than the ones found in rivers in Spain (28.5 ng/L), China (22.8 ng/L), and Korea (46.2 ng/L) (CASADO *et al*., 2014; HUANG *et al*., 2013; KIM *et al*., 2009). Betamethasone concentration was also higher than those found in the US and Germany (BATT *et al*., 2015; VESTEL *et al*., 2016). According to Vestel *et al*. (2016), the Pharmaceutical Assessment and Transport Evaluation model estimated betamethasone concentrations to be < 0.6 ng/L in 95% of all U.S. surface waters and in Germany, the concentrations were found to be between 0.07 and 2.8 ng/L (WEIZEL *et al*., 2018). The highest concentration observed in the Doce River may be related to untreated sewage discharge. The city – Governador Valadares - does not count with wastewater treatment coverage, thus, the sewage is released *in natura* in the river. Regardless, both fluconazole and betamethasone pose negligible environmental risks (HQ < 0.01). Considering the mixture, Doce river water poses low toxicological risk, as the MHQ found owing to these two PhACs was 0.011 for acute toxicity and 0.002 for chronic toxicity. Regarding human health risk, the MOE obtained was 2125, indicating low probability of risk.

3.3.2. Membrane performance: fouling propensity

As expected, RO membrane resistance is much higher than NF membranes (Table 10) owing to the dense polymeric structure of the former. This directly impacts the performance of the evaluated membranes. NF has a high initial flux and the final flux is about 70% greater than RO; moreover, NF presented a much lower flux decline (Table 10). Fouling presented a greater contribution than the CP phenomenon to flux decline in both membranes analyzed. The membrane fouling is related to deposition and/or pore blocking by natural organic matter since the water salts concentration is low. Moreover, the membrane fouling was much more evident in the RO system confirmed by the resistance-in-serie models results (Table 10). Thus, fouling formation seems to be directly related to membrane characteristics such as pore size, hydrophobicity, and surface charge.

The greater pore diameter associated with lesser surface roughness, lower hydrophobicity, and higher negative zeta potential of the NF membrane (Table 7) could subsequently lead to lower fouling potential compared to RO membrane (Table 10). The high surface roughness of a membrane could render this membrane more susceptible to fouling because foulant particles could accumulate in the valleys on the membrane surface due to higher local flux over valley regions (TU *et al*., 2011). According to Schäfer et al. (2011), a more negative membrane zeta potential could lead to a higher salt rejection due to an enhanced electrostatic interaction between the negatively charged membrane surface and charged solutes.

MD presented constant permeate flux during the monitoring time and did not show any tendency or indication of critical fouling, however, it is about 60% and 37% smaller than NF and RO processes, respectively. It should be noted that the range of initial fluxes were the same as the one observed by Han et al. (2017) (17 kg/m^2h) for the same temperature gradients (T_f-T_p = 40ºC). MD is known for a low propensity to fouling in comparison to other filtration processes that have pressure as the driving force (DRIOLI *et al*., 2015). In the MD process, the additional foulant layer can also increase the heat transfer resistance (HAN *et al*., 2017). MD performance with regard to both flux and water quality highlights this technology to be a viable process for surface water treatment.

Table 10 - Water and permeate fluxes and flux decline due to water filtration in Doce River (20°C; natural pH; at a flow rate of 3.2 L/m; and 10 bar)

Membrane	J_i[a] (L/m².h)	J_f[b] (L/m².h)	J_{rf}[c] (L/m².h)	J_{irf}[d] (L/m².h)	Flux decline type (%)			SEC (kWh.m³.m²)	Membrane Resistance (m^{-1} x10^{12})	Fouling Resistance (m^{-1} x10^{12})
					Total	Fouling	CP[e]			
NF	50.00	47.71	48.63	49.10	4.58	2.74	1.84	0.32	72	2
RO	41.50	27.47	30.52	40.00	33.79	26.46	7.33	1.12	88	63
MD	17.14	17.14	17.14	17.14	-	-	-	41.63	24	0

[a]Initial effluent permeate flux; [b]Final effluent permeate flux; [c]Water permeate flux after physical cleaning; [d]Water permeate flux after chemical cleaning; [e]Concentration polarization

The SEC relates the permeate flux with the required energy. This factor is directly associated with operational costs. Since NF membrane has a less salient hydraulic resistance, it is possible to observe a smaller energy requirement (SEC=0.32 kWh.m³.m²); for RO the value found was 1.12 kWh.m³.m², owing to the higher resistance imposed by the denser membrane. Regarding the MD process, two types of energy demands should be considered: pump and heating requirements. The former is the lowest (0.02 kWh.m³.m²), however, the heating requirement is significantly higher (41.61 kWh.m³.m²).

3.3.3. Rejection of PhACs and toxicological risk reduction

The capability of rejection of PhACs by NF and RO membranes decreases as the permeate recovery rate (RR) increases (Table 11). The higher the RR, the higher the compound accumulation in the feed solution which results in lower rejections because it induces greater passage of pollutants through the membrane (TAHERAN *et al*., 2016). The first PhAC occurrence in the permeate happened at 40% and 60% permeate recovery rates for NF and RO, respectively. MD showed a rejection > 99% for both fluconazole and betamethasone for up to 70% RR.

Table 11 - Betamethasone and fluconazole permeate concentrations and removal percentages for NF, RO and MD processes according to the permeate recovery rate

RR (%)	Betamethasone			Fluconazole		
	MD	RO	NF	MD	RO	NF
10	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)
20	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)
30	< MQL (> 99)	< MQL (> 99)	<MQL (> 99)	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)
40	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)	< MQL (> 99)	**9.360 (98)**
50	< MQL (> 99)	< MQL (> 99)	**8.85 (95)**	< MQL (> 99)	< MQL (> 99)	**17.25 (97)**
60	< MQL (> 99)	**21.03 (87)**	**8.88 (95)**	< MQL (> 99)	< MQL (> 99)	**76.68 (87)**
70	< MQL (> 99)	**31.54 (81)**	**41.14 (75)**	< MQL (> 99)	< MQL (> 99)	**118.5 (79)**

MQL = Method quantification limit

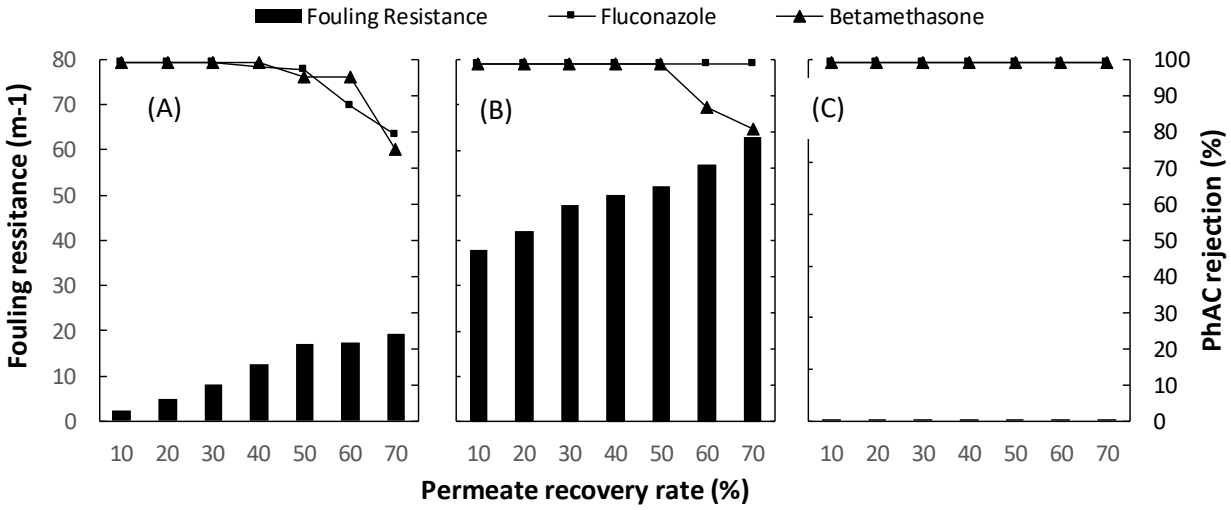
Betamethasone and fluconazole have similar molecular weights, charges, and molecular radiuses; however, they have a distinguishing hydrophobicity character. Considering that the molecular radiuses for both PhACs are greater than the membrane pore radius, the main rejection mechanism involved in both NF and RO appears to be size exclusion. The loss of the PhAC rejection capacity of NF and RO membranes for higher permeate recovery rate values suggest that other mechanisms also affect PhACs rejection.

Since both PhACs are neutral compounds under the experimental conditions, the electrostatic repulsion mechanism did not contribute to their rejection. According to Bellona *et al*. (2004), the hydrophobic interaction between the PhAC and the membrane is an important rejection factor and the existing interactions between non-ionic solutes and membranes may influence rejection of PhACs.

Since fluconazole are more hydrophilic than betamethasone ($\log K_{ow}$ values are 0.40 and 1.94, respectively), in water solutions fluconazole is solvated and, consequently, its effective diameter becomes larger (LICONA *et al*., 2018). Therefore, they can be rejected more effectively by steric effects (BRAEKEN *et al*., 2005) (Figure 10), increasing the membrane efficiency.

As indicated in Figure 4, the rejection of betamethasone and fluconazole declined throughout the test, especially when assessing the NF performance. The assessed compounds are accumulated on the membrane surface due to size exclusion and could eventually diffuse through the membrane polymer matrix towards the permeate side throughout the test (LICONA *et al*., 2018).

Figure 4 - Betamethasone and fluconazole removal and NF (A), RO (B) and MD (C) resistances as a function of RR



Moreover, the selected PhACs exhibit the additional separation mechanism of adsorption when organic matter is mainly hydrophobic or has strong hydrogen-bonding characteristics, which makes it readily adsorbed on the fouled membranes surface (LICONA *et al*., 2018).

To analyze the effects of hydrogen bonding potential (HFP) on adsorption, the HFP was defined as (ZHAO *et al*., 2017):

$$HFP = (N_D + N_A)/M_W \quad (28)$$

where N_D and N_A were numbers of H-bonding donors and acceptors, respectively, and M_w was the molecular weight of the compound. Since the PhAC doses in this experiment were at trace levels, the influence of H-bonding sites on the membrane were not considered.

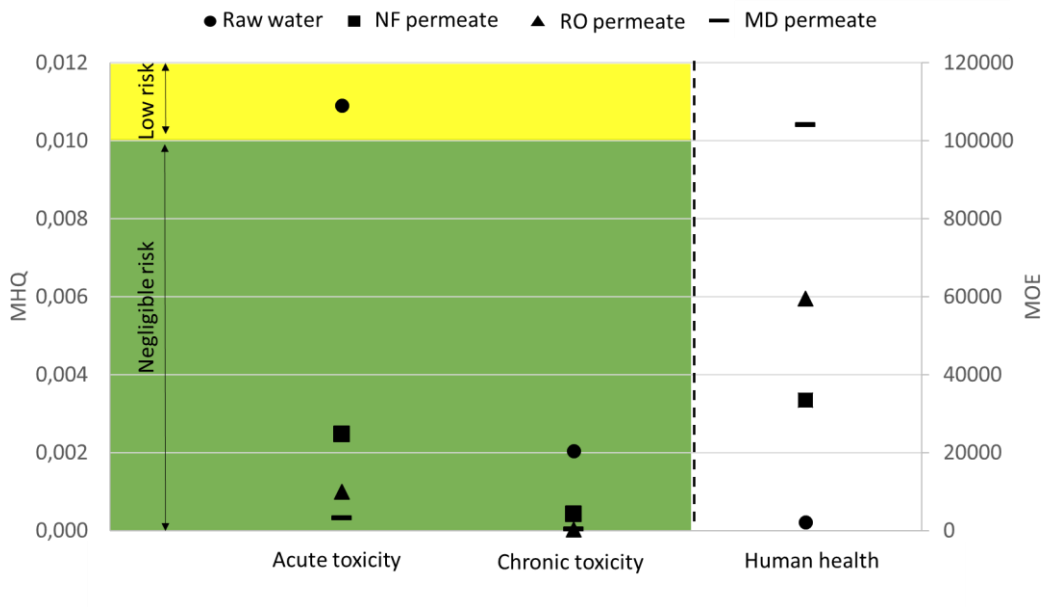
The two PhACs were classified as a higher group with the HFP > 0.02 (ZHAO *et al*., 2017), which indicates that the solute of this group had greater adsorption extent. Adsorption can result

from hydrophobic interactions and the formation of hydrogen bonds between the PhACs and other materials in the sample matrix with the membrane materials (LIANG *et al*., 2009). The RO membrane rejected the PhACs at a much higher rate of up to 50% indicating that adsorption plays an important role in PhACs rejection. The effects of molecular hydrophobicity and HFP on PhAC rejection by the NF membrane were vague in comparison to RO. This might be attributed to characteristics of the membrane. BW30 is denser than the DK with a much smaller MWCO and, thus, has a greater rejection not only for organic compounds but also for inorganic compounds including monovalent ions, However, upon long-term filtration, a membrane's adsorptive sites become exhausted and the adsorbed solutes eventually desorb to the permeate side of the membrane, decreasing its efficiency as observed on Figure 10.

MD process showed a rejection > 99% for both fluconazole and betamethasone for a 70% RR. These higher rejection results were expected since MD rejection processes are mainly governed by volatility and, to a lesser extent, by hydrophobia. Both PhACs presented kH values much lower than 10^{-3} mol/m^3.Pa and, therefore, were classified as non-volatile compounds. Since the MD membrane only enables permeation of volatile compounds, the PhACs were concentrated in the feed solution. Similar results were also observed by Wijekoon *et al.* (2014).

High PhACs removal by the MD leads to a high toxicological risk reduction. As betamethasone and fluconazole concentrations in the permeate obtained were below the MQL, the water can be considered free of toxicological risk occurrence, both for the environment and for human health. The same is true for NF and RO processes at low permeate recovery rates. Even when these processes reach a 70% recovery rate, the toxicological risks of the permeates obtained are negligible. Figure 5 shows the environmental and human health risk reduction by NF, RO, and MD processes.

Figure 5 - Environmental and human health risk reduction by NF, RO, and MD processes at 70% RR (MHQ = mixture hazard quotient; MOE = margin of exposure)



It is important to state that the concentrates of the three investigated processes are still in need of further treatment to degrade the PhACs retained. However, the MSP reduce the volume to be treated, contributing to the reduction of costs, and increase contaminants concentration, facilitating their removal by chemical processes. Despite the higher concentration, all three concentrates pose low acute environmental risk (HQ equal to 0.017, 0.020 and 0.023 for NF, RO and MD, respectively) and do not pose chronic risk. Their MOE are all above 1000, so they do not represent a risk for human health either.

Although no environmental risk was observed in the concentrate, this stream still needs treatment to permanently degrade organic compounds. For this, several advanced oxidation processes (AOPs) have been applied as post-treatment stage to complement membrane filtration, especially for the treatment of the retentate streams before discharging into environment (GEANIYU *et al*., 2015). The higher PhACs concentration in the concentrates stream provides an enabling condition for enhancing the efficiency of these processes, since most AOPs are highly efficient at elevated pollutants concentration (GEANIYU *et al*., 2015).

3.3.4. Membrane desalting ability

In this study, no significant difference in TOC content was observed for the three MSPs. With regard to electrical conductivity, no statistical difference was observed in the MD and RO

permeates (*p* value = 0.05) (Table 12); however, a slightly higher quality of MD permeate was noted. These results can be associated to the different permeation mechanisms. The applied pressure contributes to a greater flow of solute on the membrane surface and, therefore, in a concentration polarization that, in turn, contributes to the greater transport of solute through the membrane.

However, in the MD process, the temperature difference is the driving force and it is not sufficient to reach the volatile point of ions and organic matter; therefore, only water is expected to pass through the membrane. These results agree with Han *et al*. (2017) and Meng *et al*. (2014). However, the passage of organic matter through the membrane is possibly associated with its amphiphilicity: the hydrophobic part interacts with the membrane matrix, whereas the hydrophilic part can bond to the water molecules (via hydrogen bonds) to diffuse through the membrane (MEANG *et al*., 2014).

It is observed that all of the three processes were able to completely remove the color and turbidity, agreeing with the Brazilian legislation for drinking water (Table 6), as well as the standards recommended by the World Health Organization (WHO, 2017) (Table 12).

According to the Brazilian legislation for drinking water, the water should contain at least 30 mg/L of the calcium, magnesium, potassium and sodium salts, however, it should be noted from Table 12 that all three processes permeate don't have minimum requirement of salts for distribution, therefore, it is possible to add the cited salts of food grade in the permeate to reach the minimum required concentration for drinking water distribution.

Overall, all the three assessed processes were able to meet all of the Brazilian legal limits for drinking water, when organic matter, solids, turbidity and color are concerned. Also, it is important to highlight that the non-addition of chemicals during the water treatment process reduces the possible risks associated to byproducts formation.

Table 12 - Characteristics of raw sample, NF, RO, and MD permeates and removal efficiency (values in parentheses)

Parameter	Raw water	Nanofiltration		Reverse Osmosis		Membrane distillation		WHO Limits[a]
pH	7.09 ± 0.03	6.9 ± 0.2	-	6.6 ± 0.3	-	6.52 ± 0.2	-	6.5-8.5
Conductivity (µS/cm)	127 ± 28	69 ± 0.9	(45 %)	12.7 ± 5.1	(90%)	11.9 ± 0.2	(92.6 %)	-
Turbidity (NTU)	22.6 ± 19.2	0.07 ± 0.01	(99.6 %)	< 0.005	(99.9 %)	< 0.005	(> 99.9 %)	0.5
TDS (mg/L)	20.40 ± 6.54	< 0.001	(> 99.9%)	< 0.001	(> 99.9 %)	< 0.001	(> 99.9 %)	600
Color (mg Pt-Co/L)	131 ± 53	< 5	(> 87.9%)	< 5	(> 87.9 %	< 5	(> 87.9 %)	15
TOC (mg/L)	1.59 ± 0.82	0.4	(74 %)	0.5	(68.5 %)	0.5	(68.5 %)	-
Ca (mg/L)	4.30 ± 0.9	< 2.5	(> 42 %)	< 2.5	(> 42 %)	< 2.5	(> 42 %)	100-300
Mg (mg/L)	1.59 ± 0.44	< 1.25	(> 33 %)	< 1.25	(> 33 %)	< 1.25	(> 33 %)	500
Na (mg/L)	2.93 ± 0.96	< 2.5	(> 37 %)	< 2.5	(> 37 %)	< 2.5	(> 37 %)	200
K (mg/kg)	2.45 ± 0.41	< 2.5	(> 10 %)	< 2.5	(> 10 %)	< 2.5	(> 10 %)	-

[a]*World health organization limits (2017)*

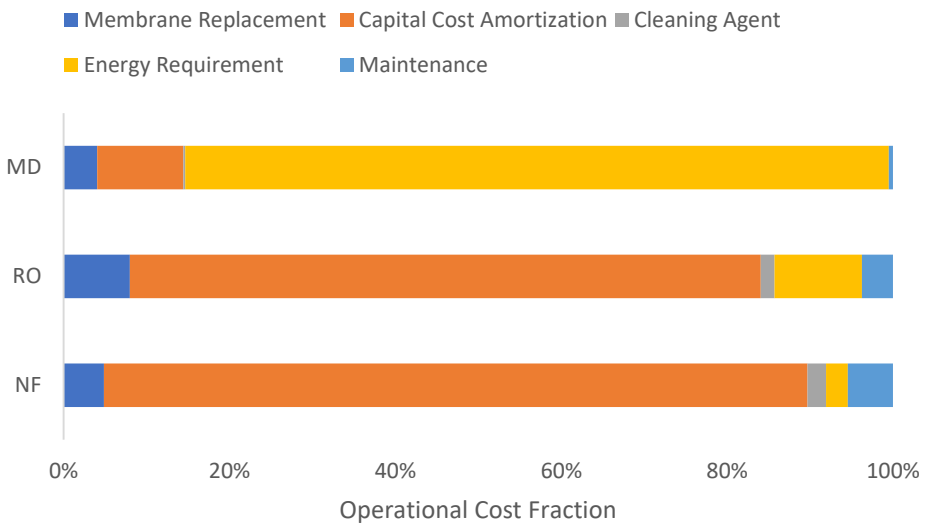
3.3.5. Preliminary cost evaluation

The cost-effectiveness of NF, RO, and MD processes for treating surface water was studied with regard to supply to a medium-sized city (Annual System Capacity = 500 m^3 d^{-1}). The permeate recovery rate for each process was selected considering the reduction of the PhAC concentration to values lower than the limit of detection being 30, 50 and 70% for NF, RO and MD respectively. Table 13 shows the characteristics of the NF, RO and MD system considered for the calculation as well as the Capex and OPEX for all systems. The Capex was strongly influenced by permeate recovery rate adopted, being the NF the most expensive process. The amortization cost adds considerable cost to the overall price of the drinking for NF and RO, while for MD, energy cost corresponds to 85% of overall drinking water price (Figure 6). It is noteworthy that the preliminary economic study did not consider the concentrate disposal cost, membrane and long-term performance costs, especially for membrane fouling and lifetime and permeate quality.

Table 13 - Cost estimation of the NF, RO, and MD systems for treatment of superficial water

	Description	**Values**			**Units**
		NF	RO	MD	
System Characteristics	Annual System Capacity	182,500	182,500	182,500	m^3/year
	Average Permeate Flux	0.047	0.027	0.0174	$m^3/h.m^2$
	Recovery Rate	30	50	70	%
	Required Membrane Area	443	772	1197	m^2
	Design Plant Life	15	15	15	years
	Membrane Lifespan	5	5	5	years
	Brazil Investment Rate	0.14	0.14	0.14	%
	Energy Price	0.04	0.04	0.04	US$/kWh
CapEx	Systems	607,638.89	364,583.33	228,571.43	US$
OpEx	Membrane Replacement	0.024	0.034	0.079	US$/$m^3$
	Capital Cost Amortization	0.42	0.325	0.204	US$/$m^3$
	Cleaning Agent	0.011	0.007	0.004	US$/$m^3$
	Energy Requirement	0.013	0.045	1.664	US$/$m^3$
	Maintenance	0.027	0.016	0.010	US$/$m^3$
	Total	**0.50**	**0.43**	**1.96**	**US$/$m^3$**

Figure 6 – Participation of the various components in the operation cost of NF, RO and MD



As indicated by the results of this study as well as previous studies, MD is much less susceptible to fouling than NF and RO. In addition, rejection of contaminants by MD was much higher than those of NF or RO and it remained constant throughout the test. However, the cost associated to this process is still not feasible. The operational cost found here is in the same as the one observed by Hitsov *et al* (2018) where values range between 2.1-5.4 €/m^3. However, the cost may be further reduced if low cost energy is used. The operational cost could reach 0.30 \$/m^3 if residual heat is used (HAN *et al*., 2017). Additionally, several studies have successfully used solar energy to minimize the use of thermal energy and electricity (ASHOOR *et al*., 2016). Moreover, MD membranes with better permeability need to be developed as well as a study to estimate the NF, RO and MD membrane lifetime.

3.4. Conclusion

NF, RO, and MD are efficient single step technologies for treatment of surface water to achieve drinking water quality and PhAC removal. The rejection of PhACs by NF and RO is mainly due to size exclusion and hydrophobic interactions, whereas MD rejection is mainly attributed to low volatility of PhACs. All evaluated processes lead to a high toxicological risk reduction. In addition to presenting the highest PhAC removal, MD did not present fouling tendency which was the principal cause of flux decline in RO and NF. The NF and RO membrane fouling

occurred due to deposition and/or pore blocking by natural organic matter since the water salts concentration is low.

Opex were estimated at 0.5, 0.43 and 1.93 US$/m3 for NF, RO and MD respectively. Although the MD process is more robust, the practical application is restricted by the high cost. Moreover, the costs for MD can be further reduced by utilizing low cost energy such as solar energy or residual heat. Future prospect for MD membrane relies on membrane permeability improvement. And, NF and RO are feasible alternative to remove PhACs from drinking water.

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4. EFFECT OF HUMIC ACID CONCENTRATION ON PHARMACEUTICALLY ACTIVE COMPOUNDS (PhACs) REJECTION BY DIRECT CONTACT MEMBRANE DISTILLATION (DCMD)

4.1. Introduction

Membrane distillation (MD) is a low-temperature distillation process that operates transporting water in the vapour phase through a microporous and hydrophobic membrane on the distillate (product) side. As a mass transfer can only occur in the gas phase, MD can offer a complete rejection of all non-volatile products such as inorganic salts and pathogenic microorganisms.

Due to the temperature difference between the feed and distillate side, only the most volatile compound (typically water) vaporizes passing through the pore openings at the feed-membrane interface and then condenses at the distillate-membrane interface. Direct contact membrane distillation (DCMD) is considered the most widely studied MD system configuration due to its simple operation (SWAMINATHAN *et* al., 2016; CURCIO; DRIOLI, 2005). In DCMD, the feed solution is maintained at a higher temperature than the distillate; thus, creating a difference in vapour pressure between the feed and the distillate.

As MD works under low temperature, it is possible to use renewable energy as solar or any other low quality as a source of energy (CURCIO; DRIOLI, 2005; MERICQ *et al*., 2011). Given the advantages of high separation efficiency, low propensity to scale and potentially low energy consumption (when low heat quality is readily available), the MD process can be applied to a wide variety of applications besides brackish water desalination and seawater. It was observed several studies that explored the application of MD for food processing, such as recovery of whey protein in dairy processing (HAUSMANN *et al*., 2013), recovery of polyphenolic antioxidants from olive oil wastewater (EL-ABBASSI *et al*., 2012) and orange juice concentration (ALVES *et al*., 2006), separation of fermentation broth (GRYTA *et al*., 2013) treatment of wastewater from the textile and petrochemical industries (KHAING *et al.*, 2010; JACOB *et al*., 2015; WU *et al*., 2018), municipal reuse of water (MERICQ *et al*., 2011; CATH *et al*., 2005) and even radioactive wastewater (JIA *et al*., 2018).

PhACs can be detected in the environment from ng/l to μg/l concentrations all around the world and they were recognized as potential environment threats (PETRIE *et al.*, 2015; TAHERAN *et al*., 2016; CAMACHO-MUNOZ *et al*., 2014). Due to their increase in production, usage and continuously discharged to the environment and their potential ecological effect, PhACs have been attracting global attention (SADMANI *et al*., 2014). MD may pose an important treatment route for the removal of these pollutants, however only a few studies are known to focus on the application of MD on the PhACs removal (HAN *et al*. 2017; WIJEKOON *et al.*, 2014; ALKHUDHIRI *et al*., 2013; COUTO *et al*., 2018a).

WIJEKOON *et al*. (2014) verified the feasibility of applying the membrane distillation (MD) process aiming at the removal of trace organic compounds (TrOCs), including PhACs, during the treatment of water and wastewater. Results suggested that the rejection of compounds with pK_H <9 can be governed by the interaction between their hydrophobicity and volatility (WIJEKOON *et al.*, 2014). Further, the transport of the compounds during the MD process was also investigated. Hydrophilic compounds with negligible volatility were concentrated in the feed, while hydrophobic compounds with moderate volatility were substantially lost by evaporation or adsorption (WIJEKOON *et al.*, 2014).

Unlike pressure-driven membrane processes, due to hydraulic pressure, MD is less susceptible to membrane fouling (ALKHUDHIRI *et al*., 2013). Even when a fouling layer forms on the membrane surface, it is expected to be less compact and can be easily removed (ALKHUDHIRI et al., 2013). However, fouling is still the major obstacle for membrane distillation, since it adds resistance to water permeation (thus diminishing water flux), increase heat transfer resistance and causes progressive membrane wetting (GRYTA *et al*., 2009).

In membrane distillation, fouling deposition decreases the membrane hydrophobicity, causing the membrane wetting. In this case, liquid starts to penetrate the membrane pores, reducing its selectivity and impairing its goals of separation (WARSINGER *et al*., 2015) which may reduce PhACs rejection since compounds are able to pass through the membrane along with the other and other contaminants. This phenomenon has been reported for several types of foulant agents (GUILLEN-BURRIEZA *et al*., 2014; GE *et al*., 2014; WANG; LIN, 2017), including silica and iron oxide (GRYTA, 2007; BUSH *et al*., 2018).

Besides, the existence of a fouling layer adds both thermal and hydraulic resistance to the system, thus, increasing the temperature polarization effect (CURCIO *et al*., 2010;

SRISURICHAN, *et al*., 2005; QIN *et al*., 2018). In particular, some studies point to the occurrence of membrane fouling by NOM in MD, which becomes a critical issue that still requires considerable research effort mainly in the understanding of this mechanism (NAIDU *et al*., 2014; TIJING *et al*., 2015).

According to Tan *et al*., (2015), biofouling and fouling owing to organic matter in MD are not well-understood. It is yet not known if the observed flux decline observed by several studies is, in fact, really explained by any additional resistance to heat transfer offered by the thin fouling layers (TAN *et al*., 2015). It has been speculated that the unexplained flux decline might well be due to an additional mass-transfer or hydraulic resistance in the fouling layer, although no definitive experimental studies have confirmed this. Goth *et al*., (2013) pointed that the small pores in a biofouling layer might cause a vapour-pressure depression, however, so far, no data are available in the literature to confirm definitively that vapour-pressure depression, in fact, can occur during MD fouling. Otherwise, Srisurichan *et al*. (2005) explained the flux decline due to their humic-acid fouling by incorporating a heat-transfer resistance owing to the fouling layer, this could have resulted from a vapour-pressure depression that they did not consider.

Some studies observed negligible permeate flux decline due to humic acid, regardless of the ionic concentration of sodium chloride (NaCl) and calcium chloride ($CaCl_2$) (KHAYET *et al*., 2004; HAN *et al*., 2017). However, in other cases, it was noted significant flux decline (up to 40%), which was associated with the fouling by humic acid induced by the calcium ions (referred to as Ca^{2+}-carboxyl complexation) (SRISURICHAN *et al*., 2005). These divergent conclusions on the effect of fouling due to humic acid and the impact on the permeate flux of the MD process imply that the study of organic contaminant rejection should be given in parallel with that of membrane fouling and/or wetting of pores by NOM, since it is common the presence of NOM in waters that are used for water supply. Many studies have already been published on the impact of fouling by NOM on the rejection of contaminants in relation to the NF, FO and ED processes, which for MD further research is still necessary. Studies focusing on the effect of NOM concentration on the MD membrane fouling as well as on the rejection processes of the micropollutants, especially the PhACs, are necessary, considering the differentiated driving force and mechanism of transport for MD. Thus, this study aims to assess the influence of organic matter on the rejection of PhACs by the MD.

4.2. Materials and methods

4.2.1. Feed solution, selected compounds and properties

It was selected 25 PhACs that showed previous potential of real occurrence in Brazilian water according to item 3, as well as different physicochemical properties (Table 14) including molecular weight, geometry, hydrophobicity/hydrophilicity, polarity, and charge which propitiates the assessment of the influence of these characteristics on DCMD rejection efficiency.

Table 14 - Selected PhACs and their physicochemical properties

PhACs	Structure	Molecular weight (g/mol)	Molar Volume (cm^3)	log Kow	Pka	KH (atm-m^3/mole)	Vapor pressure (mmHg)	Class	Limit Detection (ng/L)
Atenolol	**C14H22N2O3**	**266**	**237**	**–0.03**	**N.A.**	**4.35E-10**	**7.25E-09**	b-Blocker	10.2
Fluconazole	**C13H12F2N6O**	**306**	**205**	**0.40**	**11.01-2.64**	**7.12E-09**	**1.02E-06**	Antifungals	2.4
Trimethoprim	**C14H18N4O3**	**290**	**232**	**0.981**	**6.6-7.1**	**9.94E-08**	**5.69E-09**	Antibiotic	10.6
Clarithromycin	**C38H69NO13**	**748**	**632**	**1.70**	**8.99**	**1.01E-10**	**2.12E-11**	Antibiotic	6.5
Erythromycin	**C37H67NO13**	**734**	**607**	**3.06**	**8.90**	**1.28E-11**	**1.08E-10**	Antibiotic	6.6
Amoxicillin	**C16H19N3O5S**	**365**	**236**	**0.87**	**3.23**	**1.88E-11**	**1.43E-08**	Antibiotic	1.6
Ampicillin	**C16H19N3O4S**	**349**	**239**	**1.35**	**3.24**	**1.52E-11**	**5.36E-11**	Antibiotic	1.3
Atorvastatin	**C33H35FN2O5**	**558**	**452**	**5.04**	**4.33**	**1.08E-11**	**1.67E-10**	Lipid regulator and metabolite	12.8
Caffeine	**C8H10N4O2**	**194**	**133**	**-0.07**	**10.40**	**1.59E-06**	**1.22E-06**	Stimulant	22.9
Danofloxacin	**C19H20FN3O3**	**357**	**241**	**0.51**	**4.12**	**1.53E-09**	**1.53E-09**	Antibiotic	0.9
Enoxacin	**C15H17FN4O3**	**320**	**231**	**-0.23**	**5.50**	**7.63E-12**	**4.89E-10**	Antibiotic	10.0
Enrofloxacin	**C19H22FN3O3**	**359**	**259**	**0.80**	**5.15**	**7.18E-09**	**3.83E-08**	Antibiotic	0.5
Metformin	**C4H11N5**	**130**	**101**	**-1.37**	**12.40**	**3.46E-09**	**4.42E-01**	Lipid regulator and metabolite	0.3
Norfloxacin	**C16H18FN3O3**	**320**	**237**	**-0.30**	**5.77**	**1.00E-11**	**8.88E-10**	Antibiotic	1.0
Scopolamine	**C17H21NO4**	**303**	**231**	**0.98**	**7.75**	**4.86E-10**	**2.12E-08**	Anticholinergics	2.4
Prednisone	**C21H26O5**	**358**	**274**	**1.46**	**12.58**	**1.24E-09**	**7.40E-10**	Anti-inflammatory	7.2
Betamethasone	**C22H29FO5**	**392**	**296**	**1.94**	**12.42**	**7.36E-11**	**3.49E-10**	Anti-inflammatory	2.4
Phenazone	**C11H12N2O**	**188**	**163**	**0.38**	**1.40**	**2.66E-06**	**9.09E-04**	Anti-inflammatory	3.3
Phenylbutazone	**C19H20N2O2**	**308**	**263**	**3.16**	**4.50**	**6.22E-08**	**6.79E-06**	Anti-inflammatory	2.4
Fenofibrate	**C20H21ClO4**	**361**	**306**	**5.28**	**-4.90**	**4.11E-09**	**1.93E-07**	Lipid regulator and metabolite	7.6
Cimetidine	**C10H16N6S**	**252**	**198**	**0.40**	**6.80**	**6.43E-10**	**3.95E-07**	Pump inhibitor	8.9
Omeprazole	**C17H19N3O3S**	**345**	**252**	**2.23**	**9.29**	**3.62E-06**	**6.64E-08**	pump inhibitor	17.8
Paroxetine	**C19H20FNO3**	**329**	**272**	**3.60**	**9.77**	**4.64E-07**	**1.66E-05**	Psychiatric	20.0
Loratadine	**C22H23ClN2O2**	**383**	**304**	**5.20**	**4.33**	**1.60E-08**	**5.34E-09**	Antihistamine	13.6
Ranitidine	**C13H22N4O3S**	**314**	**265**	**0.27**	**8.08**	**7.29E-09**	**2.65E-08**	Antihistamine	8.0

[a]EPA, 2017; logKow octanol–water partition coefficient; KH Henry law constant; pka: acidity constant

Stock standard solutions of the individual pharmaceutical were made at a 1 $g.L^{-1}$ in methanol and stored at 4 ◦C in the dark.

To investigate the influence of organic matter on PhACs removal and on membrane distillation performance, it was used a synthetic solution composed by deionized water (DI), PhACs and humic acid sodium salt (HA, $C_9H_8Na_2O_4$). Humic acid is ever-present in natural water and it is a typical organic model foulant used widely (BAALOUSHA *et al*., 2006). PhACs were added to the synthetic sample in a concentration of 1 μg/L and HA in the concentrations of 20, 40, 60 and 80 mg/L

4.2.2. Experimental set-up and methods

Figure 3 shows the schematic of the laboratory-scale MD system. MD tests were conducted using a hydrophobic microporous polytetrafloroethylene (PTFE) membrane (Sterlitech). According to the manufacturer, the average pore size and porosity of the MD membrane were 0.22 μm and 70%, respectively. The membrane cell was made of acrylic glass (126.56 cm^2), and a flow channel was engraved in each of the two acrylic glass blocks that make up the feed and permeate semi cells. The feed solution was circulated from a glass reservoir to the membrane cell and then returned back to the feed reservoir. Feed temperature was maintained by a hot plate. The temperature of the distillate was regulated using a chiller (AquaCooler, Australia) equipped with a stainless-steel heat exchanging coil immersed directly in the distillate reservoir. The distillate reservoir was placed directly on an analytical balance (Mettler Toledo, Switzerland), and flux was calculated by the mass increase observed over time. At the end of each experiment, the solution volume was measured again and the total volume loss was found to be less than 15%.

4.2.3. Experimental procedure

In the MD experiments, the feed and distillate temperatures were 60 and 25 °C, respectively and the cross-flow velocity of the feed and distillate circulation flow was 11.4 cm/s. The initial feed volume was 1.5 L and 1L of Milli-Q water was used as the initial distillate. The experiment was concluded once the water recovery had reached 60% at which stage the feed and distillate samples were collected for PhACs analysis. The duration of each MD experiment was approximately 7 h. Thus, PhACs concentration in the distillate was corrected for dilution by considering the initial volume of Milli-Q water in the distillate.

4.2.4. Analytical Methods

It was carried out according to item 3.2.2 (sample preparation) and 3.2.5 (analytical methods).

4.2.5. Calculations

The volumetric permeate flux (*J*) in terms of litres per square meter per hour (Kg m^{-2} h^{-1}) for MD, was calculated using Eq. (2), as follows:

$$J = \frac{m_2 - m_1}{(t_2 - t_1) \times A_m} \quad (2)$$

Where J is the permeate flux; t_1 and t_2 are the time; $m_2 - m_1$ is the increase in the permeate mass between times t_1 and t_2; and A_m is the membrane area.

To estimate the expected flux, Eq. 3 was used (KHAYET *et al*., 2011).

$$J_{exp} = C\Delta p \quad (3)$$

In the previous equation, C is named membrane coefficient; J_{exp} is the mass flux across the membrane; and Δp is the vapour pressure difference between both interfaces. For the different liquid-gas phase equilibria states of water, its vapor pressure relates to temperature as shown in Eq. 4 (KHAYET *et al*., 2011).

$$P = EXP\left(23.238 - \frac{3841}{T - 45}\right) \quad (4)$$

The observed rejection was calculated using Eq. (5), as follows:

$$R(\%) = \frac{C_f - C_p}{C_f} \times 100, \quad (5)$$

where C_f and C_p represent the solute content on the feed and permeate streams, respectively.

Losses of PhACs during the MD experiments were calculated by considering the mass balance of each analysed compound in the feed, concentrate and distillate as given in Eq. 6.

$$C_F x V_F = (C_D x V_D) + (C_C x V_C) + total\ loss \quad (6)$$

In Equation 3, C_F, C_D and C_C are concentration in the feed, distillate and concentrate, respectively. Similarly, V_F, V_D and V_C are the volume of the feed, distillate and concentrate, respectively.

For the calculation of the resistances for MD, Equations 7 to 9 were used (SRISURICHAN et al., 2006).

$$R_{fb} = \frac{P_f - P_1}{J} \quad (7)$$

$$R_m = \frac{P_1 - P_2}{J} \quad (8)$$

$$R_{pb} = \frac{P_2 - P_p}{J} \quad (9)$$

In which R_{fb}, R_m, and R_{pb} stand for feed boundary layer, membrane, and permeate boundary layer resistances. In addition, P_1 and P_2 represent the vapor pressure at feed and permeate membrane surface, P_f, P_p the vapor pressure at the bulk feed and permeate, and J, the permeate flux. Pressures were calculated according to Eq. 10 and temperatures at the membrane surface were estimated according to Equations 11 and 12 (SRISURICHAN et al., 2006).

$$P = EXP\left(23.238 - \frac{3841}{T-45}\right) \quad (10)$$

$$T_{w,f} = \frac{h_m\left(T_p + \left({}^{h_f}/_{h_p}\right)T_f\right) + h_f T_f - J\Delta H_v}{h_m + h_f\left(1 + \frac{h_m}{h_p}\right)} \quad (11)$$

$$T_{w,p} = \frac{h_m\left(T_f + \left({}^{h_p}/_{h_f}\right)T_p\right) + h_p T_p - J\Delta H_v}{h_m + h_p\left(1 + \frac{h_m}{h_f}\right)} \quad (12)$$

Where $T_{w,f}$, $T_{w,p}$ T_f and T_p represent the temperatures at interface and bulk for feed and permeate, respectively; h_m, h_p, and h_f stand for the convective heat transfer coefficient of the membrane, permeate and feed; and ΔH_v is the vaporization heat.

The temperature polarization coefficient (TPC) was estimated by Eq. 13 (SRISURICHAN et al., 2006).

$$TPC = \frac{T_{w,f} - T_{w,p}}{T_f - T_p} \quad (13)$$

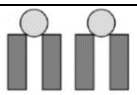
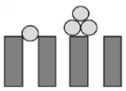
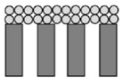
In addition, membrane thermal conductivity was calculated according to Eq. 14 (PHATTARANAWIK *et al*., 2003).

$$k_m = (1 - \emptyset)k_s + \emptyset k_f \quad (14)$$

Where $\emptyset$, k_s, and k_f stand for the membrane porosity, and the thermal conductivity of each of the individual solid and vapor phases, respectively.

As a mean to elucidate the fouling phenomenon, the Hermia model was used (YUAN *et al*., 2002). By adding the cake erosion model, Hermia's law can be adapted to cross-flow filtration mode, according to Tabela 15 (SRISURICHAN et al., 2006). In addition, the resistance to filtration, wetting time (the time it took for the conductivity to start rising) and wetting rate (the observed rise in conductivity over time) were also calculated.

Table 15 - Blocking filtration laws

Law	Schematics	Linearized equation	N
Complete blocking model		$-\ln\left(\frac{J_o}{J}\right) - 1 = Kt$	3
Standard blocking model		$\frac{J_o}{J} - 1 = Kt$	3/2
Intermediate blocking model		$\sqrt{\frac{J_o}{J}} - 1 = Kt$	1
Cake blocking model		$\left(\frac{J_o}{J}\right)^2 - 1 = Kt$	0

4.2.6. Statistic Evaluation

It was carried out according to item 3.2.8.

4.3. Results and discussion

4.3.1. Fouling propensity

As expected, the experiment carried out with no addition of HA didn't exhibit any flux decline (Figure 7), which was slightly increasing from 0 to 8% when the HA concentration increased from 0 to 80mg/L. A previous study showed that MD flux declines due to HA (concentration in the range of 20–100 mg/L) alone were less than 6% (SRISURICHAN *et al.*, 2005), which is in accordance with the finds of this study. The observed flux decline can be attributed, in all cases, to the membrane fouling ($R_{fouling}$ in Table 16) that added hydraulic resistance to the transfer of liquid water through the membrane and can cause a reduction in the vapor-pressure driving force owing to the small pores within the it. The mass of organic matter (quantified as TOC) and HA deposited on membrane surface was estimated by mass balance. The results indicated an increase in the organic matter/HA mass deposited on membrane surface when the feed HA concentration increased from 20 to 80 mg L^{-1} (Figure 7).

Figure 7 - Flux decay, acid humic and total organic carbon deposited on the membrane at different HA concentrations (Tf-Tp = 35°C, feed and permeate crossflow velocity = 11.4 cm s-1)

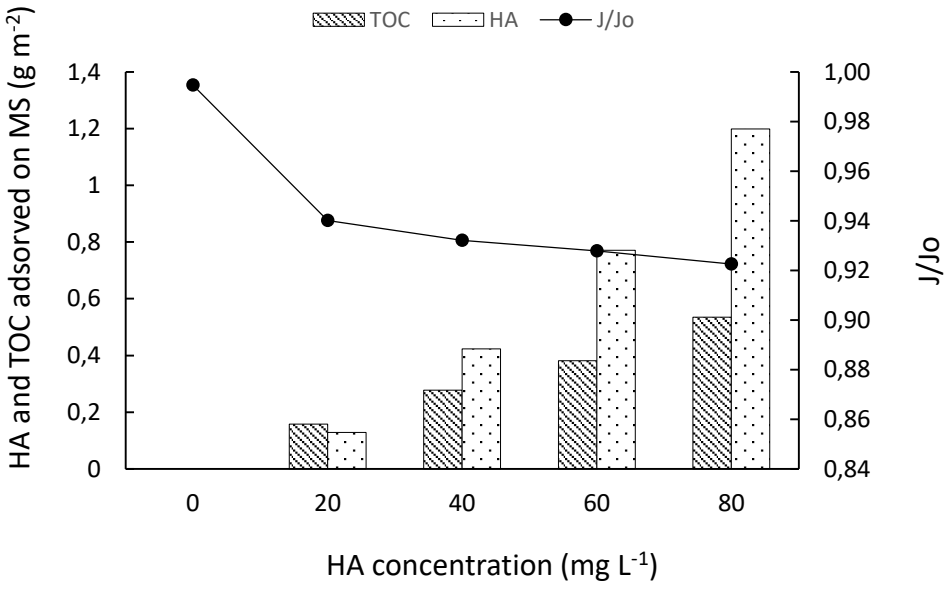


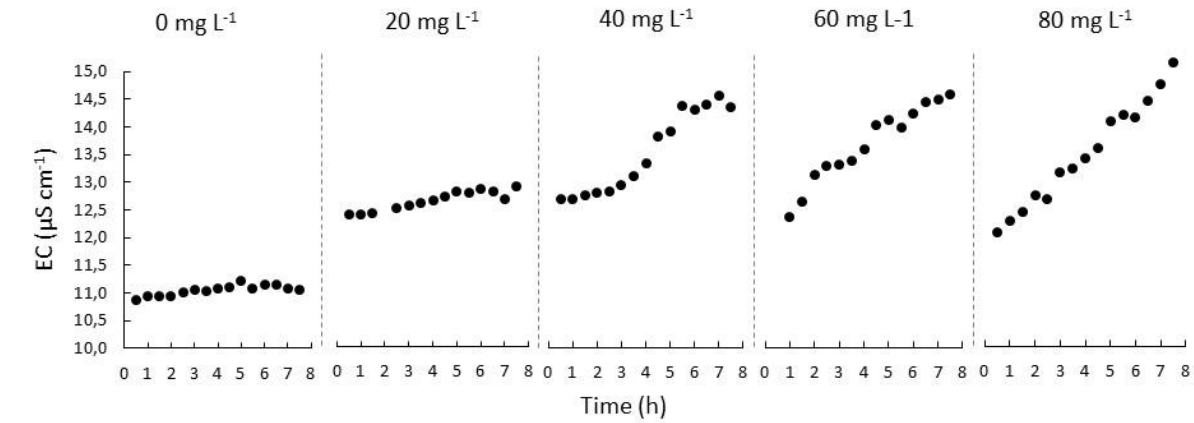
Table 16 - Water and permeate fluxes, flux decline, resistances and chemical cleaning efficiency due to water filtration in different HA concentrations

HA (mg/L)	Jo ($kg/m^2.h$)	J ($kg/m^2.h$)	Resistance*($Pa/Kg.m^2.h$)				Cleaning efficiency (%)
			R_{fb}	R_{pb}	R_m	$R_{fouling}$	
DI	12.03	11,96	584	255	557	0	100
20	12.06	11,34	615	264	554	59	100
40	12,06	11,24	616	263	554	71	100
60	12,03	11,16	618	262	557	85	100
80	12	11,07	619	262	555	100	100

DI = deionized water; *R_{fb} = Feed boundary resistance, R_{pb} = Permeate boundary resistance, R_m = Membrane resistance, $R_{fouling}$ = Fouling resistance

In membrane distillation processes, the additional foulant layer also increases the heat transfer resistance (HAN *et al*., 2017) reducing the vapour pressure at higher concentrations and increasing temperature polarization (Table 16), and, therefore, reduces the permeate flux. Notably, the feed boundary resistance was significantly lower for MD feed with no HA dose than for every HA dose studied at a p value of 0.05, however, the feed boundary resistance values were similar for the different dosage of HA studied. These results suggest that the flux decline observed as HA concentration increases could be related to the resistance to filtration imposed by the fouling resistance. The HA deposits form a loose layer on the membrane surface increasing the membrane hydrophilicity due to their hydroxyl and carboxylic functional groups (SRISURICHAN et al., 2005). In the present study, the membrane hydrophilicity has not been evaluated, but the increase in the pore wetting rate reinforces the occurrence of changes in the hydrophobic character of the membrane after fouling (Figure 8). It is reported that a thin layer of an amphiphilic fouling, caused by the presence of HA, can reduce the membrane contact angle and result in wetting (WARSINGER, 2015). When an amphiphilic molecule reaches a membrane surface, the hydrophobic membrane surface adsorbs the hydrophobic part while the hydrophilic part of the surfactant stays in the water phase (CHEW et al., 2017). Therefore, the hydrophobic surface is converted to a hydrophilic surface, resulting in a decreased contact angle and increased incidence of membrane wetting (REZAEI et al., 2018).

Figure 8 - Electrical conductivity (EC) profile, wetting time and wetting rate at four different feed HA concentration (Tf-Tp = 35°C, feed and permeate crossflow velocity = 11.4 cm s^{-1})



WT (h)	no	5	3	1	0.5
WR (µS cm^{-1} h^{-1})	no	0.08	0.27	0.32	0.41

WT = wetting Time;
WR = wetting rate.

In addition, Hermia's model was used to explain the fouling mechanism. Table 17 summarizes k, J_0 and R^2 values under all the HA assessed conditions. The higher values of R^2 correspond to a better fit of the model. It is observed that R^2 values at 20 and 40 mg/L (Table 17), the best fitting values have obtained for the standard blocking filtration and cake filtration. As expected, as the concentration is increased, cake filtration and cake formation play a major role to describe the fouling phenomenon, corroborating once more to the cause of flux decline due to deposition of HA on the membrane surface (Figure 7 and Table 16).

Table 17 - Hermia's model for the diferente HA concentrations test (k, J_0 and R^2 values)

HA (mg/L)	Model											
	Complete blocking filtration			Standard blocking filtration			Intermediate blocking filtration			Cake filtration		
	J_o	k (min^{-1})	R^2	J_o	k (min^{-1})	R^2	J_o	k (min^{-1})	R^2	J_o	k (min^{-1})	R^2
	(kg/m^2.h)			(kg/m^2.h)			(kg/m^2.h)			(kg/m^2.h)		
DI	11.88	1.22E-03	0.02	11.88	1.05E-04	0.02	11.88	1.79E-04	0.02	11.88	1.82E-05	0.02
20	12.05	9.78E-03	0.97	12.05	8.38E-04	**0.98**	12.05	1.43E-03	0.97	12.05	1.44E-04	**0.98**
40	12.01	9.90E-03	0.95	12.01	8.53E-04	**0.96**	12.01	1.45E-03	0.95	12.02	1.47E-04	**0.96**
60	11.96	9.68E-03	0.93	11.97	8.36E-04	**0.94**	11.96	1.42E-03	**0.94**	11.97	1.44E-04	**0.94**
80	11.90	1.18E-02	0.93	11.91	1.03E-03	0.93	11.91	1.74E-03	0.93	11.91	1.79E-04	**0.94**

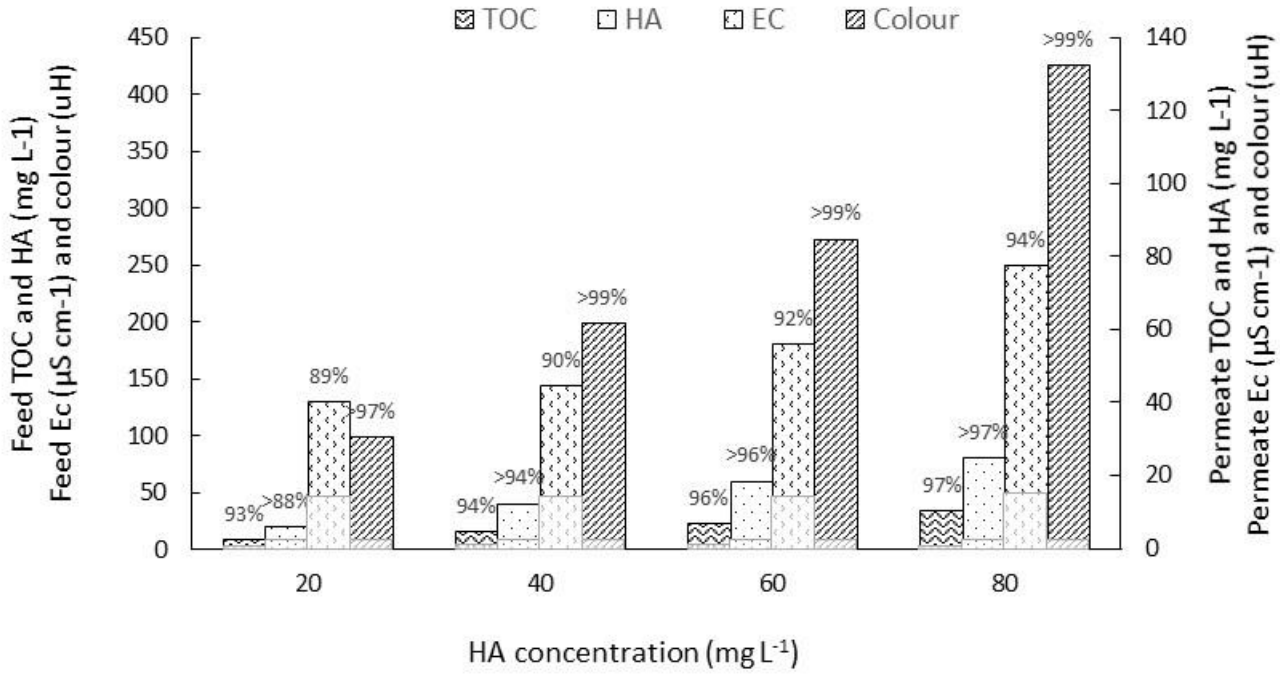
DI = deionized water.

The reversibility of the MD fouling development with different HA solutions was evaluated by cleaning the membrane. For all condition evaluated, 100% of permeate flux was recovered suggesting the reversibility of the fouling layer (Table 16), which indicates the greater sustainability of the process.

4.3.2. Distillate quality

Figure 9 presents the feed and distillate characterization in terms of TOC, EC and colour for the performed tests. HA was not detected on distillate. A high removal (>90%) for all the assessed parameters was attained, despite the differences in the feed. As expected, the feed conductivity increased as HA concentrations raised, however, the process was able to maintain the quality of the final distillate even with the membrane wetting, confirming the good performance of MD when ions are concerned (COUTO *et al*, 2018b). In the MD process, the temperature difference is the driving force and it is not sufficient to reach the volatile point of ions and organic matter; therefore, only water is able to pass through the membrane. These results agree with Han *et al*. (2017) and Meng *et al*. (2014).

Figure 9 - Permeates characterization for a recovery rate of 60% (fill in black corresponds to the values of the feed and fill in grey corresponds to the values of permeate. Label values correspond to removal efficiency)



DI = deionized water.

However, it is possible to note that there is a passage of organic matter through the membrane, even the HA was not detected in the distillation, indicating that the membrane cannot provide a 100% rejection of organic matter. The passage of HA across the membrane is probably associated with the amphiphilicity of the substance, such that while the hydrophobic part interacts with the membrane matrix, the hydrophilic part can bind to the water molecules (via hydrogen bonding) to diffuse through of the membrane (MENG et al., 2014). This agrees with an earlier study which also uses the same PVDF membrane applied in this work (MENG et al., 2014). It is possible to point out that the improvement in the transport of water through the membrane (discussed in the previous item) affected the rejection of HA in an insignificant way (Figure 9). Similar results were also found by Han *et al*. (2017), which found only 1% of HA in the distillate applying a PVDF membrane.

MD is well known for the lower propensity to scale compared to other filtration processes that have pressure as a driving force (e.g., microfiltration (MF), nanofiltration (NF) and reverse osmosis (RO)) (DRIOLI *et al*., 2015), which was confirmed by the results found here because it presented constant performance when evaluated flow decay along the tests in addition to the conductivity. These results provide evidence that MD is a robust process, supporting abrupt changes in feed composition thus becoming possibly a viable process for the treatment of surface water because it shows constant performance and a high quality permeate. Changes in flow and conductivity are insignificant under the conditions investigated with p value=0.05. As expected, the only difference was found for DI water which was below the other assessed conditions.

4.3.3. PhACs rejection

MD process showed a rejection ≥ 99% for the 25 assessed PhACs for a 60% recovery rate (Table 18), since 24 out of the 25 were below limit detection, similar results were found by Woldemariam *et al*. (2016). These higher rejection results were expected since MD rejection processes are mainly governed by volatility and, to a lesser extent, by hydrophobia (which can be obtained from log K_{ow}) (WOLDEMARIAM *et al*., 2016; WIJEKOON *et al*., 2014). For the PhACs presented kH values much lower than 10^{-3} mol/m^3.Pa (Table 14) and, therefore, were classified as non-volatile compounds. Since the MD membrane only enables the permeation of

volatile compounds, the PhACs were concentrated in the feed solution or adsorbed on the membrane surface. Similar results were also observed by Wijekoon et al. (2014) and by Couto *et al*. (2018b). When the performance of the DCMD tested is compared with related membrane-based technologies from literature, especially NF and RO, in most cases, only RO was found to have comparable removal performances (COUTO *et al*., 2018a).

Couto *et al*. (2018b) assessed the rejection of betamethasone and fluconazole using a real water matrix, and it was observed that the first PhAC occurrence in the permeate happened at 40% and 60% recuperation rate (RR) for NF and RO, respectively. Hajibabania et al (2011) applying an NF membrane found a rejection ranging from 20-78% using a synthetic feed composed by water and a mixture of PhACs, such as ibuprofen, naproxen, diclofenac, trimethoprim, sulfamethoxazale. Licona *et al.*, (2018), found rejections ranging from 88 to 99% for PhACs, such as acethaminophen, ibuprofen, caffeine, diclophenac and dipyrone, when applying RO membrane using ultrapure water. These results reinforce the robustness of the MD process. Even at high recovery rates (60%), most of the assessed PhACs are found below limit detection and the observed PhAC has rejection greater than 99%.

Table 18 - PhACs content in the MD distillate for a 60% of recovery rate

PhACs	HA concentration (mg/L)				
	DI	20	40	60	80
Atenolol	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Fluconazole	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Trimethoprim	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Clarithromycin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Erythromycin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Amoxicillin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Ampicillin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Atorvastatin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Caffeine	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Danofloxacin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Enoxacin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Enrofloxacin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Metformin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Norfloxacin	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Scopolamine	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Prednisone	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Betamethasone	**99.2**	**99.0**	**98.9**	**98.7**	**99.1**
Phenazone	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Phenylbutazone	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Fenofibrate	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)

Cimetidine	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Omeprazole	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Paroxetine	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Loratadine	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)
Ranitidine	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)	< MQL (>99)

The PhAC rejection was not impaired even with increasing HA concentration, and wetting of the membrane observed, except for betamethasone. Even observing a passage of organic matter through the membrane indicating that the membrane cannot provide a 100% rejection of HA, it was possible to reach greater rejection of PhACs, thus the enhanced water passage across the membrane doesn't affect its efficiency. Although the feed side of the membrane became hydrophilic due to the HA deposit, the permeation of the contaminant was not affected, since the transfer of water vapour was more dominant than these contaminants of negligible volatility. However, it is possible to note from Table 18, a slightly greater passage of betamethasone. This is associated with the sum of the PhAC's properties, such as pka and $LogK_{ow}$. The greater pka (12.42) propitiates adsorption on the membrane surface/fouling layer (Figure 10) associated with the hydrophilic characteristic (log K_{ow} 1.94), that may facilitate the passage across the membrane (COUTO *et al*., 2018a).

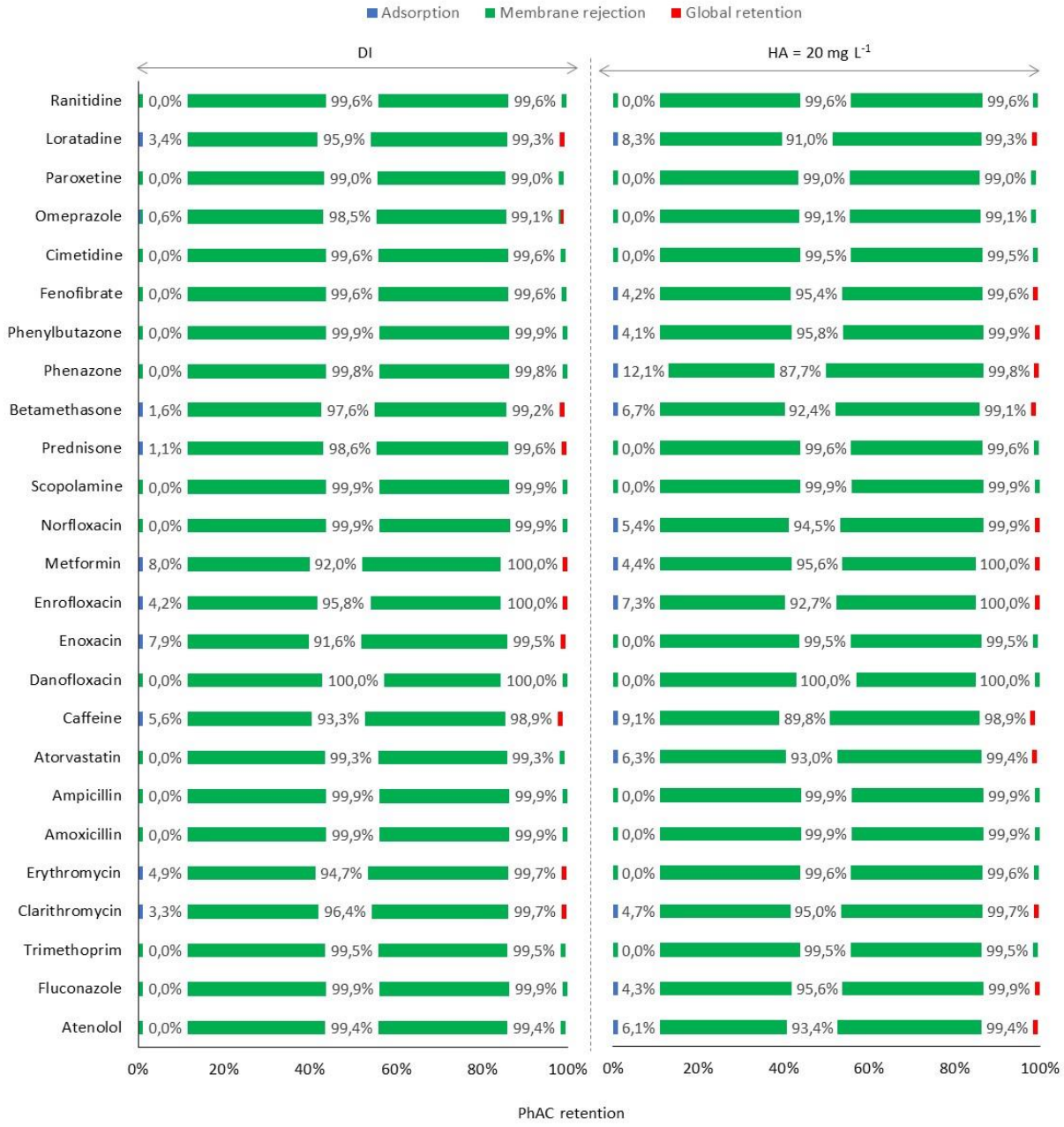
In the MD process, PhACs can be retained by the membrane retention, governed by volatility, and adsorption on the membrane surface/fouling layer. Figure 10 shows the contribution of membrane retention and adsorption to global retention of PhACs by MD process fed PhACs dissolved in DI and HA solution. The retention of PhACs by MD membrane occurs predominantly by membrane rejection which reinforces the robustness of the process and the ability to produce safe water.

The contribution of adsorption for the global was low and restricted to a few PhACs. Out of the 25 assessed PhACs only loratadine, omeprazole, betamethasone, prednisone, metformin, enrofloxacin, enoxacin, caffeine, clarithromycin and erythromycin showed interactions with the membrane (≤8%). Although it was observed a positive correlation at a p value = 0.05 between the PhACs' pka and the membrane adsorption for the DI test, no correlation was observed between the adsorption degree and the compounds' properties for the test with 20mg/L. The negative charge of the membrane plays an important role in the adsorption phenomenon. In the case of compounds having positive charges (pka greater than the solution

pH), attractive forces between the solutes and the surface of the negatively charged membrane will prevail, causing an increase in the solute concentration near the membrane surface. The opposite can be stated for the PhACs having neutral or negatively charged (pka lower than the solution pH).

Once a fouling layer was formed, the contribution of adsorption for the global was also low and restricted to a some PhACs. However, since pores wetting was observed as well as a formation of a fouling layer negatively charged due to deposition and adsorption of HA on the membrane surface, and it was associated with the change on membrane's characteristics surface, it is possible to note that the foulant layer, in general, contribute to increase the adsorption of some PhACs (loratadine, betamethasone, enrofloxacin, caffeine, clarithromycin) due to reduction of pores caused by the deposition of HA on the membrane surface (REZAEI et al., 2018) associated with an electronical attraction due to the increase of the negative charge of the membrane caused by the HA depositions; propitiated the interaction between the membrane/fouling layer of fenofibrate, phenylbutazone, phenazone, norfloxacin, atorvastatin, fluconazole, atenolol caused by the increase of electrostatic attraction; and reduce the adsorption of others, such as omeprazole, prednisone, erythromycin, metformin and enoxacin associated with electrostatic repulsion occurring between the dissociated (deprotonated) PhACs and the negatively charged membrane (COUTO *et al*., 2018), also, a reduction of the membrane contact angle caused by pores wetting may promote the lesser possibility of adsorption (REZAEI *et al*., 2018), specially PhACs with lower log K_{ow}. For this, the sum of all effects caused by the characteristics of PhACs, such as volume, pka and logk_{ow}, has a greater influence than one property alone.

Figure 10 - Effect of the presence of HA on the contribution of membrane rejection and adsorption to the global PhAC retention



4.4. Conclusion

The results here indicate that MD appears to be ideal, in terms of the sustained performance over long periods of running, for treating surface water, even at the much higher concentrations

of organic matter studied. The observed flux decline (<8%) was attributed to the membrane fouling due to the increase in the organic matter/HA mass deposited on the membrane surface. However, 100% of permeate flux was recovered suggesting the reversibility of the fouling layer.

MD also presents a high removal of organic matter (here addressed as HA) as well as ions, maintaining a low electrical conductivity. MD was also able to achieve ≥ 99% of PhACs removal for all 25 assessed PhACs, whereas 24 are below limit detection, attributing its high efficiency due to the low volatility and, to a lesser extent, by hydrophobia of the studied compounds, once again confirming the robustness of the process, propitiating a safe distillate even at higher HA concentrations. The retention of PhACs by MD membrane occurs predominantly by membrane rejection, and, although PhACs adsorption on the membrane surface had a smaller expression on the retention phenomenon, it was mainly associated with the PhACs' pka. Changes on the membrane characteristics, due to the fouling layer, changed this pattern. In general, MD is considered to be a robust process able to produce safe water, even at long-term runs.

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5. EMPIRICAL STATISTICAL MODEL THE USE OF FACTORIAL DESIGN IN THE ANALYSIS OF MEMBRANE DISTILLATION' REJECTION OF PHARMACEUTICALLY ACTIVE COMPOUNDS (PhACS) AS A FUNCTION OF ORGANIC MATTER AND SALTS

5.1. Introduction

Membrane distillation (MD) is a thermally driven process in which water is the main component to be treated. It works at low temperature where the water in vapour phase is transported through nonwetted porous of hydrophobic membranes, which is localized between de feed and the distillate streams. In fact, the membranes hydrophobicity prevents the pores wetting by the liquid or distilled feed solution in normal operational conditions. Since the water mass transfer occurs only in the gas phase, MD has a theoretically 100% rejection of all non-volatile products such as inorganic salts, organic matter and pathogenic microorganisms.

Direct contact membrane distillation (DCMD) is considered the most widely studied and used MD system configuration mainly due to its simple operation (SWAMINATHAN *et* al., 2016; CURCIO; DRIOLI, 2005). In this process, the feed solution is maintained at a higher temperature than the distillate; thus, creating a difference in vapour pressure between the feed and the distillate.

The advantages of MD processes are high separation efficiency, low propensity to scale and potentially low energy consumption (when low heat quality is readily available), thus, this technology can be used to a wide range of applications, since water desalination and domestic and industrial wastewater treatment (HAUSMANN *et al*., 2013; EL-ABBASSI *et al*., 2012; KHAING *et al.*, 2010; JACOB *et al*., 2015; WU *et al*., 2018); however, only a few studies is known to focus on the application of MD on the pharmaceutically active compounds (PhACs) removal (WIJEKOON *et al.*, 2014; ALKHUDHIRI *et al*., 2013; COUTO *et al*., 2018a).

PhACs can be found in the environment, wastewater and drinking water, all around the world (COUTO *et al*., 2018b; SANTOS *et al*., 2018), in trace concentrations, and, due to their potential risks to human and environment, they are recognized as potential threats (COUTO *et* al., 2018c; PETRIE *et al.*, 2015; TAHERAN *et al*., 2016; CAMACHO-MUNOZ *et al*., 2014). Due to its high efficiency (COUTO *et al*., 2018), MD may pose an important treatment route for the removal of these pollutants.

Due to its configuration, MD is less susceptible to membrane encrustation (ALKHUDHIRI *et al*., 2013) and its fouling layer is expected to be less compact and easily removed (ALKHUDHIRI et al., 2013). However, fouling phenomena is still the major drawback for MD's application, since it adds resistance to water permeation (thus diminishing water flux), increase heat transfer resistance and causes progressive membrane wetting (HAN *et* al., 2017; GRYTA *et al*., 2009). In this case, aqueous solution starts to penetrate the membrane pores, reducing its selectivity and impairing its goals of separation (WARSINGER *et al*., 2015).

In general, fouling can be defined as the accumulation of solutes on the surface or inside the pores of the membrane, therefore influencing its permeation flux and selectivity (GRYTA, 2007). According to Tijing *et al*. (2015), four main factors can be associated to fouling layer formation: (a) foulant characteristics; (b) membrane properties; (c) operational conditions; and (d) feed water characteristics.

In face of fouling phenomena, PhACs rejection may be compromised, since the passage of these compounds across the membrane may be enhanced along with the other and other contaminants (GUILLEN-BURRIEZA *et al*., 2014; GE *et al*., 2014; WANG; LIN, 2017). Some studies point to the occurrence of membrane fouling by NOM in MD (NAIDU *et al*., 2014; TIJING *et al*., 2015) lead to a significant flux decline (SRISURICHAN *et al*., 2005); however, Han *et* al. (2017) and Couto *et* al., (2018), affirms that that the application of humic acid lead to a flux decline from 6 up to 8%.

When inorganic fouling is concerned, it is generally referred as scaling, which is the deposition of precipitated hard minerals presented in the feed solution that involves both crystallization and transport mechanisms. According to Tijing *et al*. (2015), the most common scales in MD are $CaCO_3$, $CaSO_4$, calcium phosphate, and silicate, also, it is possible to cite other potential scale foulants, such as, $BaSO_4$, $SrSO_4$, $MgCl_2$, $MgSO_4$, ferric oxide, iron oxide and aluminium oxide. In MD systems, due to the water evaporation and temperature changes, it is possible to observe a nucleation and growth of crystals in the feed solution and to the membrane surface (ALKLAIBI and LIOR, 2005). Gryta (2010) noted a sudden decline in flux due to the deposition of $CaCO_3$ on the membrane surface in a DCMD configuration, in the other hand, He *et al*. (2009) and Han *et al*. (2017) found that the scaling produced by a feed solution rich in $CaCO_3$ did not affect the DCMD permeate flux.

Considering these divergent conclusions, studies are needed focusing on the effect of organic matter and organic salts concentration altogether on the MD membrane fouling/scale phenomena, as well as, how a cake layer formation affects the rejection of the micropollutants, especially PhACs. For this, a response surface methodology (RSM) can be applied in order to assess the relationship between one or more response variables and a set of quantitative experimental variables or factors. Nowadays, factorial designs have proved their usefulness, and are widely used in the statistical planning of experiments to obtain empirical models relating process response to process factors (ONSEKIZOGLU *et al*., 2010; CAMACHO *et al*., 2017). Thus, the objective of this work is to define an empirical statistical model in order to evaluate the effects of calcium, iron and humic acids concentration on the removal of PhACs of membrane distillation process using factorial design.

5.2. Materials and Methods

5.2.1. Selected compounds, properties and detection

The selection, standards preparations of PhACs were carried out according to item 4.2.1 and the detection was carried out according to item 3.2.2.

5.2.2. Analytical Methods

It was carried out according to item 3.2.5.

5.2.3. Experimental set-up and methods

It was carried out according to item 4.2.2.

5.2.4. Experimental procedure

It was carried out according to item 4.2.3.

To investigate the influence of organic matter and ions on the removal of PhACs and the performance of membrane distillation process, was made a synthetic composed only by deionized water (DI), humic acid sodium salt (HA, $C_9H_8Na_2O_4$), calcium chloride ($CaCl_2$), and

ferrous sulphate heptahydrate ($FeSO_4.7H_2O$) in order to allow the monitoring of the permeate quality via a conductivity meter. PhACs were added to the synthetic sample in a concentration of 1 μg/L.

5.2.5. 2^3 factorial experimental design and MD performance

A 2^3 factorial experimental design with a total of 15 experiments was developed to study the effect of HA, Ca and Fe on the MD. The variable factors with the coded and actual values are presented in Table 19. The experiments were carried out in randomized run order to determine six characteristic responses: flux (J), PhACs, TOC and EC removal, and TOC and HA adsorption on the membrane surface. The results were taken after 60% of concentration process under steady state conditions.

Table 19 - Variation levels of CCD 2^3 for the MD tests

Condition	HA (mg/L)	Ca^{2+} (mg/L)	Fe^{3+} (mg/L)
+1	80	200	200
0	50	106	106
-1	20	12	12

Table 20 shows the experimental matrix design and the results of the response variables studied. The experimental design and analysis of data were done using MINITAB® Release 14 Statistical Software.

Table 20 - Condition of factors and values of the responses chosen from factorial design 2^3 (FD 2^3) used in the MD tests to determine the main effects

Run	Condition			Responses		
	HA	Ca^{2+}	Fe^{3+}	J	BET removal	EC removal
1	-1	-1	-1	10,03	91,27	98,89
2	+1	-1	-1	9,92	91,19	99,02
3	-1	+1	-1	8,64	96,02	98,88
4	+1	+1	-1	8,48	95,36	99,01
5	-1	-1	+1	9,10	99,16	98,93
6	+1	-1	+1	8,88	99,17	99,02
7	-1	+1	+1	7,46	99,09	98,91
8	+1	+1	+1	6,92	99,18	99,08
9	-1,681	0	0	9,17	98,38	98,9
10	1,681	0	0	8,80	98,70	98,99
11	0	-1,681	0	9,35	98,35	99,05
12	0	1,681	0	7,60	98,55	98,93
13	0	0	-1,681	9,28	87,31	98,99
14	0	0	1,681	8,34	98,88	99,01
15	0	0	0	9,12	86,11	98,95
16	0	0	0	9,12	86,11	98,95
17	0	0	0	9,12	86,11	98,95
18	0	0	0	9,12	86,11	98,95
19	0	0	0	9,12	86,11	98,95
20	0	0	0	9,12	86,11	98,95

The optimization of the operating conditions of the MD process had an emphasis on flux, percentage of EC removal and percentage of BET removal. The choice of these response variables was due to the need to produce a water free of PhACs and with sufficient quality to meet the supply, as well as the smaller potential of incrustation translated here in terms of flux.

The true response surface can often be approximated over a small experimental region by a low-order polynomial. A first-order polynomial model is only able to estimate the main effects of the experimental factors and does not account for either interactions or curvilinear effects. The first-order model with interaction terms proposed for each response variable (Yi) was based on the multiple linear regression method. The empirical model in terms of coded factors was:

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 \quad (1)$$

where β_i are the values of the regression coefficients. β_0 being the constant term, β_1, β_2 and β_3 the linear effects, β_{12}, β_{13} and β_{23} the interaction effects while the x_1, x_2, x_3 are the independent coded variables (HA, Ca and Fe concentration, respectively).

The optimization results were validated experimentally by comparing the actual results, obtained in the 15 tests performed with the adjusted operating conditions, and the theoretical results, calculated by the proposed polynomial model. The validation was made based on the standard deviation between the theoretical and real answers, and the optimization will be validated if the value of this deviation is less than 10% of the value of the theoretical response. The control verification will be through control charts, where the process will be considered under control if the answers obtained are between the lower and upper control limits.

5.2.6. Calculations

It was carried out according to item 4.2.5.

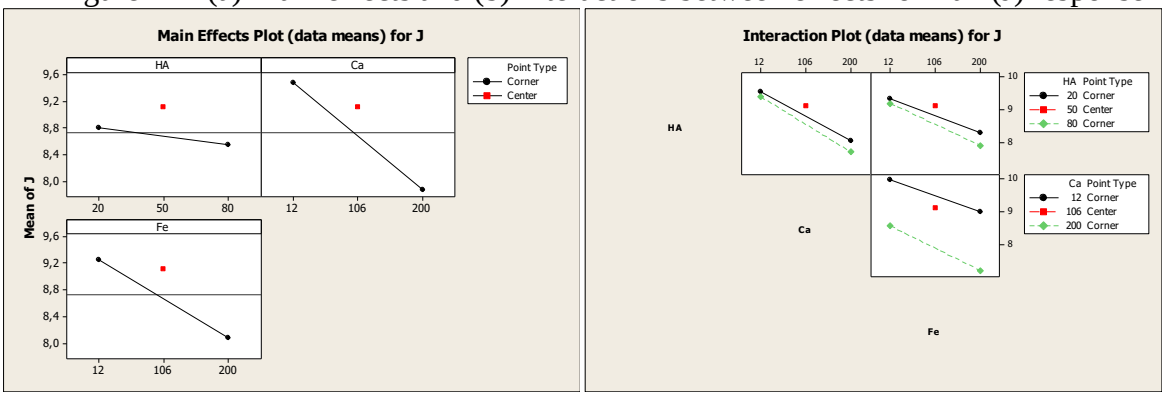
5.3. Results and discussion

5.3.1. Determination of significant factors

Flux:

Figure 11 shows the estimation of the main effects of the factors involved in the MD and their respective interactions on the flux response, when there is a change from the lowest (-) level to the highest (+) level of each factor.

Figure 11 - (a) Main effects and (b) Interactions between effects for flux (J) response



(a) (b)

According to the graphs of Main Effects and Interactions between Effects it can be observed that, according to the mean result of the central point and to the flux response, the model shows a slightly5 marked curvature, that is, the intermediate values to the limits are favorable to the response. Nevertheless, it is verified that the factors with greater potential of influence on the answer in question were the concentration of Ca and Fe.

Assessing the effects of Ca on extreme limits, increasing this factor from the lowest (12mg/L) to the highest level (200mg/L), it was observed that there was a flux decline in about 20%, from 9,5 to 7,6 kg/m^{2}h. Calcium carbonate is the most common scale in thermal desalination systems (WARSINGER *et al.*, 2015). This is associated to the fact that as MD works at high temperature (60ºC), it is more susceptible to calcium precipitation on its surface, especially when the temperature reaches the solution saturation conditions (LUO and LIOR, 2017) which may cause excessive fouling of the membranes. Calcium carbonate scale often forms after the breakdown of bicarbonate, HCO_3^-, as shown in the equation below:

$$Ca^{2+} + 2HCO_3^- \rightarrow CaCO_3 + CO_2 + H_2O \quad (2)$$

It is observed a change on solubility of $CaCO_3$ with the concentration of CO_2, and it is expected to decrease at higher temperatures as CO_2 volatilize and leaves the solution, which raises the pH (ANTONY *et al.*, 2011). Also, $CaCO_3$ has inverse solubility, i.e., at higher temperatures this salt will be less soluble irrespective of CO_2 concentration (GRYTA, 2008). Notably, at

higher temperatures, carbonate tends to hydrolyze into carbon dioxide AL-ANEZI and HILAL, 2006), as follows:

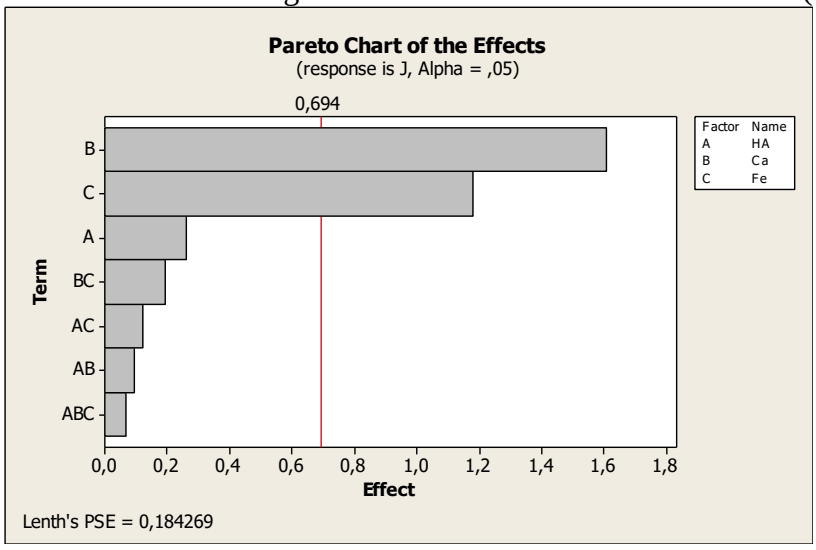
$$CO_3^{2-} + H_2O \rightarrow 2OH^- + CO_2 \quad (3)$$

This reaction makes the solution more basic, which influences the solubility of other scales such as Fe. Gryta (2007) found that when $CaCO_3$ co-precipitated with iron. Iron was found to cause a flux reduction of about 13%, from 9.2 to 8.0 kg/m^{2}h. The hydrolysis of Fe^{3+} ions can occur under heating conditions. This phenomenon can form hexaaquocation $Fe_3(H_2O)_6^{3+}$, and its H_2O ligands again experience hydrolysis, creating FeOH or Fe_2O_3 (WARSINGER *et al*., 2015). The existence of water, high or low pH, and other dissolved ions are propitiating corrosion of steel elements pieces existent in MD operations (GRYTA, 2007). It is reported that corrosion fouling not only cause clogging problems, but also may cause membrane damage by surface erosion (corroded flakes and chunks in motion through the narrow flow passages (WARSINGER *et al*., 2015). Also, Gryta (2008) reported that the iron deposits had good adherence to the feed membrane surface.

Srisurichan *et al*. (2005) reported that flux decline is expected to happen when the feed solution has Ca and HA. It is due to fouling due to the dissociation of HA in carboxyl functional groups being available for complexation with Ca^{2+}. Similar behaviour can be observed for Fe and HA.

Corroborating with Figure 2, for a significance level $\alpha = 0.05$, it is observed by the Pareto graph (Figure 12) that the flux is influenced by Ca and Fe concentrations, in this order of significance. However, HA and all factors interactions have no significant influence on this variable.

Figure 12 - Pareto chart according to the standardized effects for the flux (J) response



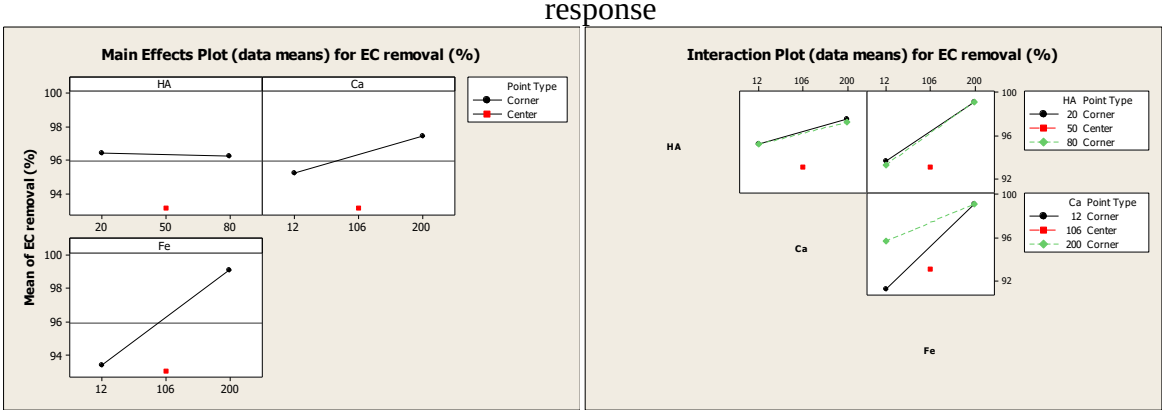
This lack of influence on MD flux by HA may be due to smaller molecular weights from synthesized chemicals used here which did not cause any flux decline. Same behavior was observed by Han *et al* (2017).

The results showed that, for the effect of flux, the most significant factors interfering in the MD were the concentration of Ca and Fe. These factors were considered main in the process due to the main objective of this treatment being flux. The results of this step were further optimized in this research with the intention of establishing a polynomial mathematical model aiming at the theoretical estimation of this response in function of the factors considered of greater influence in the process.

EC removal:

For the EC Removal response, on the graphs of Main Effects (Figure 4a) and Interactions between Effects (Figure 4b), it is possible to be observed that, according to the average result of the central point and to the EC removal (%) response, the model shows, once again, a marked curvature, that is, the intermediate values to the limits are favorable to the response. This fact also indicates that the fractional factorial design (linear adjustment) is not indicated for the optimization of this model. Nevertheless, it is verified that the factors with greater potential of influence on the answer in question were the concentration of Fe and Ca.

Figure 13 - (a) Main effects and (b) Interactions between effects for EC removal (%) response



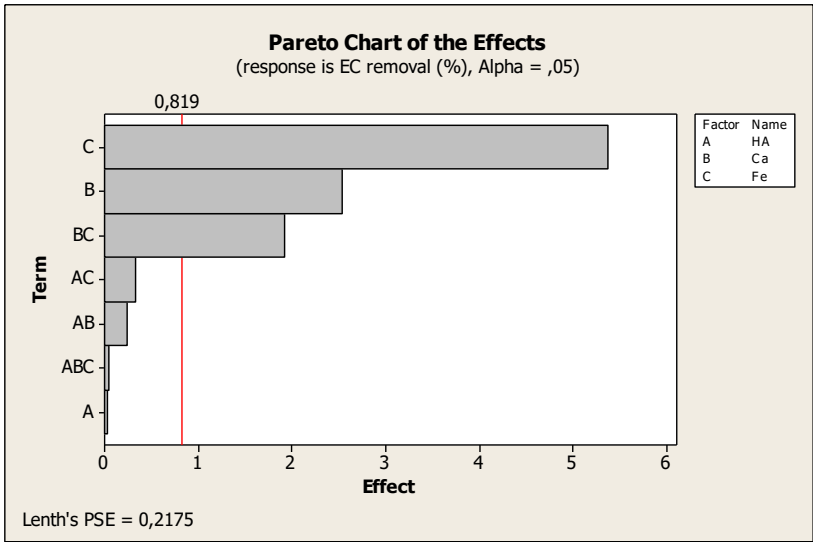
(a) (b)

Assessing the effects of Fe and Ca on extreme limits, increasing these factors from the lowest (12mg/L) to the highest level (200mg/L), it was observed that there was an increase on EC removal from 93% to 99% for Fe and 95% to 97% for Ca. Since depositions of Fe^{3+} on the membrane surface are reported to have good adherence, as well as clogging problems and membrane damage (WARSINGER *et al*., 2015; GRYTA, 2008), Fe^{3+} may be carried to the distillate side because they may dissolve in the water vapor with the lower pH because of CO_2 already dissolved due to the decomposition of $CaCO_3$. Also, the increase of CO_2 concentrations in the feed (Eq. 15) may enhance the transportation of CO_2 to the distillate in order to achieve an equilibrium, and cause the permeate conductivity to increase (QIN *et al*., 2018). However, the increase in the EC removal may be associated to the robustness of the processes. Although the feed solution had an increase in its ions concentration and the flux was deteriorated, the feed quality was maintained mainly due to material deposition on the membrane surface has narrowed the pores, hindering the passage of these ions through the membrane (WARSINGER *et al*., 2015), which corroborates to the flux decline (Figure 12).

These results provide evidence that MD is a robust process, supporting abrupt changes in feed composition thus becoming possibly a viable process for the treatment of surface water because it shows constant performance and a high quality permeate.

Corroborating with Figure 13, for a significance level $\alpha = 0.05$, it is observed by the Pareto graph (Figure 14) that the EC removal is most influenced by Fe and Ca concentrations, as well as their interactions, in this order of significance. However, HA and its interactions have no significant influence on this variable. Meng *et al*. (2014) and Han *et al*. (2017) also did not find any significant influence of HA and EC.

Figure 14 - Pareto chart according to the standardized effects for the "EC Removal (%)" response



The results indicated that, for the effect of EC removal, the most significant factors interfering in the MD were the concentration of Ca and Fe and the interactions with both factors. The results of this step were also further optimized in this research with the intention of establishing a polynomial mathematical model aiming at the theoretical estimation of this response in function of the factors considered of greater influence in the process.

PhACs Removal (%):

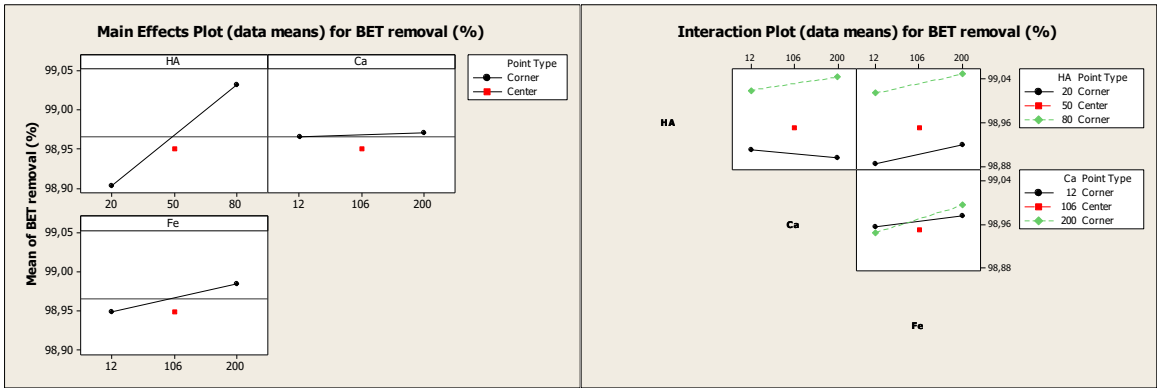
MD process showed a rejection ≥ 98% for the 25 assessed PhACs for a 60% recovery rate, since 24 out of the 25 were below limit detection, similar results were found by Woldemariam *et al*. (2016). These higher rejection results were expected since MD rejection processes are mainly governed by volatility and, to a lesser extent, by hydrophobia (which can be obtained from log K_{ow}) (WOLDEMARIAM *et al*., 2016; WIJEKOON *et al*., 2014). For the PhACs presented kH values much lower than 10^{-3} mol/m^3.Pa (Table 01) and, therefore, were classified as non-volatile compounds. Since the MD membrane only enables permeation of volatile compounds, the PhACs were concentrated in the feed solution. Similar results were also observed by Wijekoon et al. (2014) and by Couto *et al*. (2018).

Once again, it is possible to be observed that, according to the average result of the central point and to the PhACs removal (%) (here in terms of betamethasone) response, the model

shows a marked curvature. This fact also indicates that the fractional factorial design (linear adjustment) is not indicated for the optimization of this model.

It was possible to note a slightly greater passage of betamethasone through the membrane, and according to Figure 15(a), it is associated to the presence of HA on the feed solution. No changes on the rejection was observed when HA concentration raised, once again confirming that the rejections are mainly influenced by volatility. Betamethasone is accumulated on the membrane surface due to size exclusion and could eventually diffuse through the membrane polymer matrix towards the permeate side throughout the test (LICONA *et al*., 2018). Also, betamethasone seems to adsorb on membrane surface/fouling layer due to its greater pka (12.42) associated with the hydrophilic characteristic (log K_{ow} 1.94), that may facilitate the passage across the membrane according to (Chapter 4).

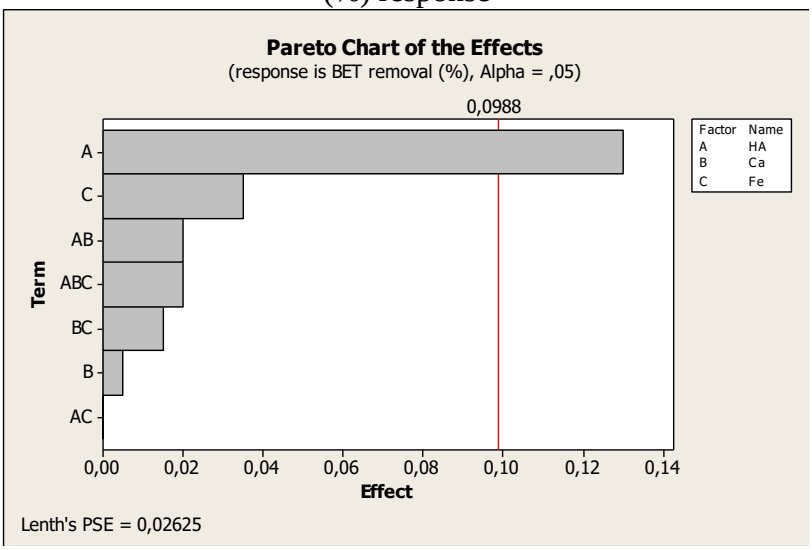
Figure 15 - (a) Main effects and (b) Interactions between effects for bethamethasone removal (%) response



(a) (b)

For a significance level α = 0.05, it is observed by the Pareto graph (Figure 16) that the betamethasone rejection is influenced only by HA concentrations. Ca and Fe or interaction between the factors don't appears to have any significant effects on the PhAC rejection.

Figure 16 - Pareto chart according to the standardized effects for the betamethasone Removal (%) response



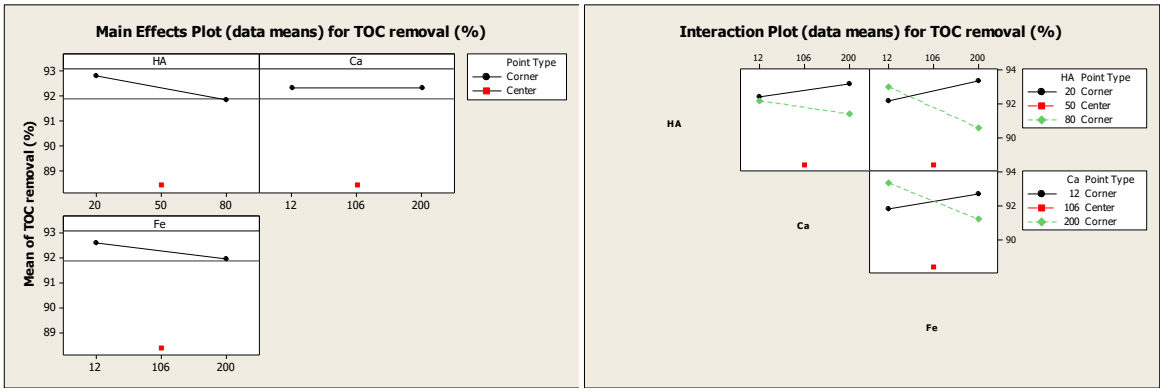
The results indicated that, for the effect of PhAC removal, the most significant factors interfering in the MD were the concentration of HA. It wasn't observed any significative interactions between the factors. The results of this step were also further optimized in this research with the intention of establishing a polynomial mathematical model aiming at the theoretical estimation of this response in function of the factors considered of greater influence in the process.

TOC Removal (%):

MD process showed a rejection ≥ 91% for organic carbon (Figure 17(a)). The presence of TOC on the distillate is due to the passage of HA across the membrane which is associated to HA's amphiphilic, i.e., while the hydrophobic part interacts with the membrane matrix, and the hydrophilic part could bond with the water molecules (via hydrogen bonding) to diffuse through the membrane (HAN *et al.*, 2017). This agrees with what was observed by Meng *et al.* (2014), however, according to Figure 18, for a significance level α = 0.25, TOC removal is not associated to any factor. The most significant factor is the interaction between HA and Fe and in less extent Fe and Ca. The depositions of Fe on the membrane surface may change its

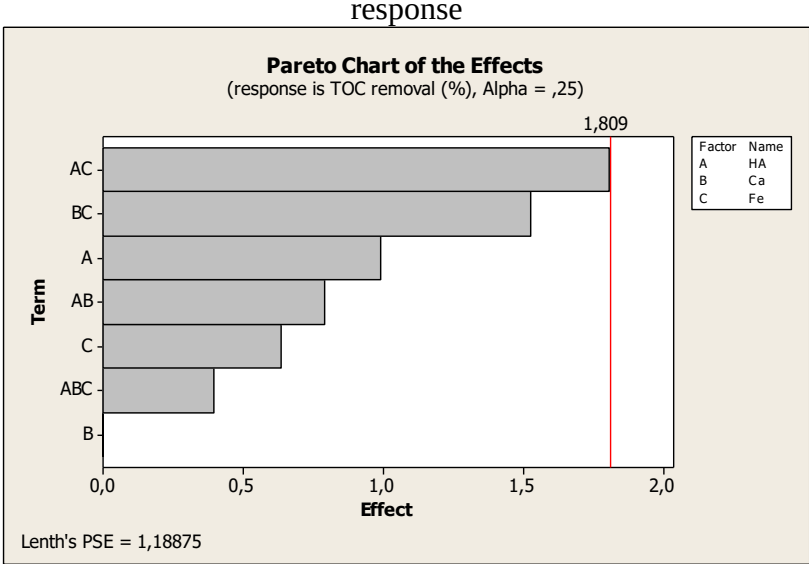
hydrophobicity characteristic (WARSINGER *et al*., 2015) increasing the permeation of HA across the membrane.

Figure 17 - (a) Main effects and (b) Interactions between effects for TOC removal (%) response



(a) (b)

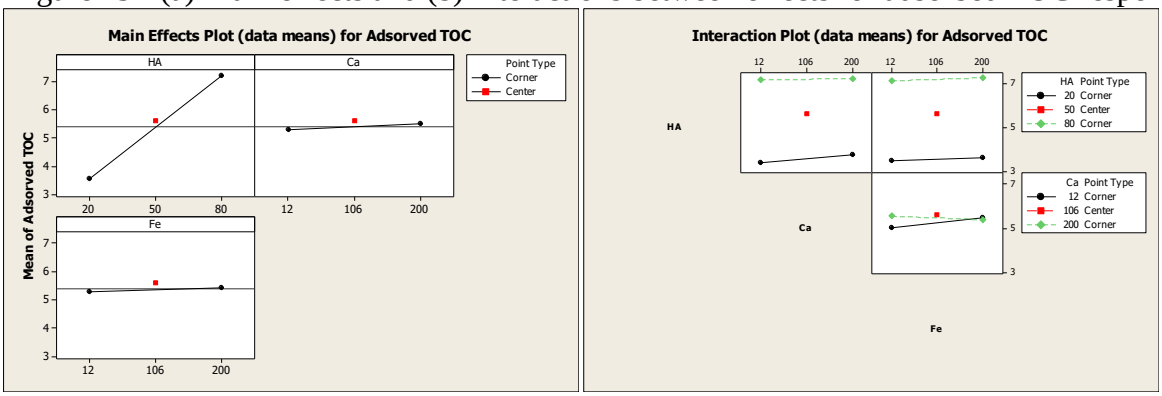
Figure 18 - Pareto chart according to the standardized effects for the TOC Removal (%) response



HA and TOC adsorbed on the membrane surface:

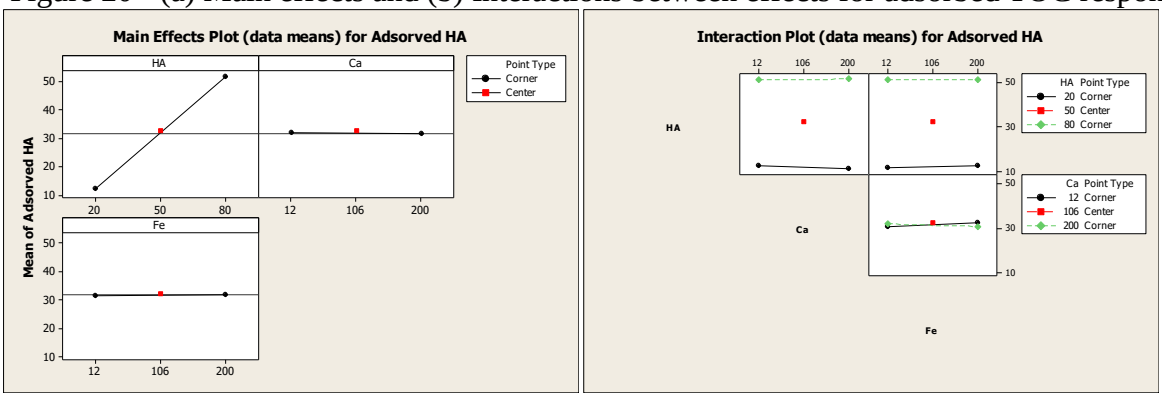
For the adsorption response of TOC and HA on the surface of the membrane, a low curvature effect was observed (Figure 19(a) and 20(a)), which indicates a trend of linear response behavior when the values of each factor are varied between the maximum and minimum levels established. It is also noted that, as expected, the concentration factor of HA has a more incisive impact in the process on the variable responses.

Figure 19 - (a) Main effects and (b) Interactions between effects for adsorbed TOC response



(a) (b)

Figure 20 - (a) Main effects and (b) Interactions between effects for adsorbed TOC response



(a) (b)

As the concentrations of HA raised from 20 to 80 mg/L, the adsorbed TOC on the membrane surface went from 3.5 to 7mg/L and the adsorbed HA increased from 10 to 50 mg/L.

The Pareto plot (Figure 21 and 22) presents the significant factors for the adsorption responses of TOC and HA. For a significance level $\alpha = 0.05$, it is observed by the Pareto graph that for

the adsorption of TOC and HA on the membrane surface, only the HA factor had significance in the process and all interactions between factors were not significant.

Figure 21 - Pareto chart according to the standardized effects for the adsorbed TOC response

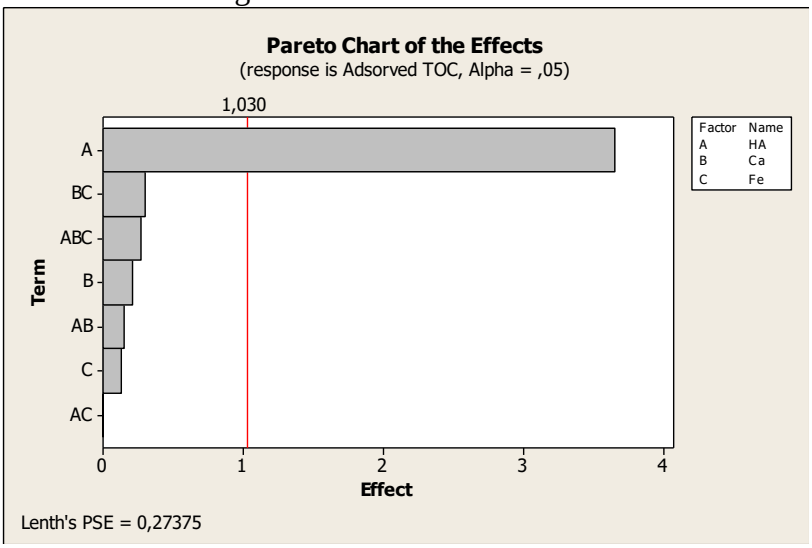
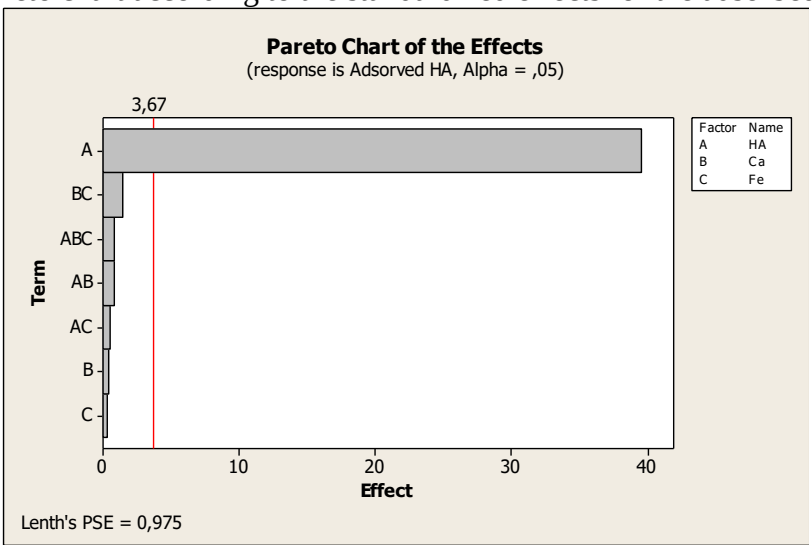


Figure 22 - Pareto chart according to the standardized effects for the adsorbed HA response



5.3.2. Critical operational conditions of significant process factors

In order to determine the critical values (which allow the greatest flux and highest EC and PhACs removal) of the factors considered as influencers of the MD process, the model was optimized using a rotational central composite design 2^3. Based on the significant effects of the model it was possible to determine a second-order polynomial mathematical model for flux (Equation 4).

$$Y(X) = 9{,}6678 - 0{,}0066X1 - 0{,}0004X_2 - 0{,}003X_3 + 0{,}005X_1^2 + 0{,}0001X_2^2 + 0{,}000X_3^2 - 0{,}000X_1X_2 + 0{,}000X_1X_3 - 0{,}000X_2X_3 \quad (4)$$

According to the coefficient of explanation of the adjusted model R^2, the polynomial function explained flux 89,9% of the total response variation, indicating a good adjustment (> 75%).

For the confirmation of the critical points of the function and if these points correspond to maximum, minimum or saddle values, the Lagrange criterion was applied to three factors. The Lagrange criterion is the calculation of the determinants Δ_1, Δ_2 and Δ_3 (Table 21).

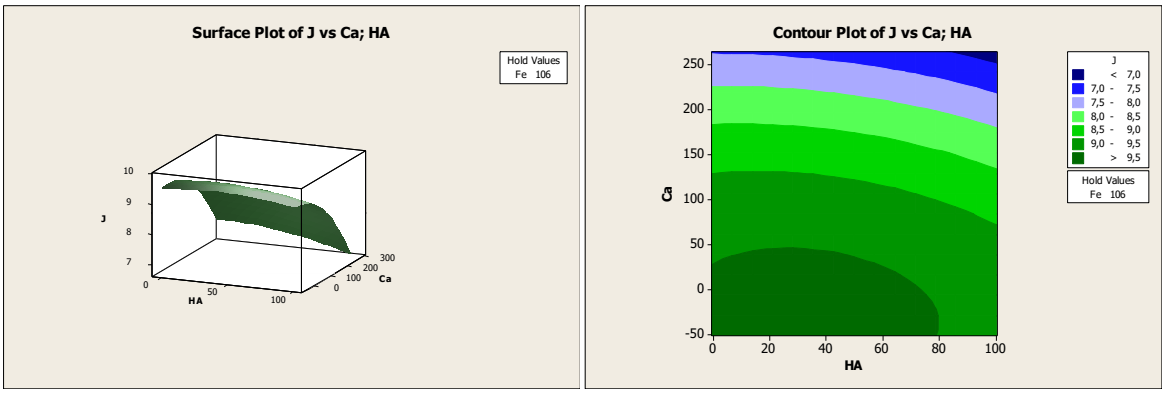
Table 21 - The Lagrange criterion for each variable response

	J (flux)	**PhAC removal**	**EC removal**
Δ_1	0.01	0	0.004
Δ_2	0.0000002	0	0
Δ_3	0	0	0

For Flux, since $\Delta_1 > 0$, $\Delta_2 > 0$ e $\Delta_3 = 0$, it is possible to affirm that there is a saddle point.

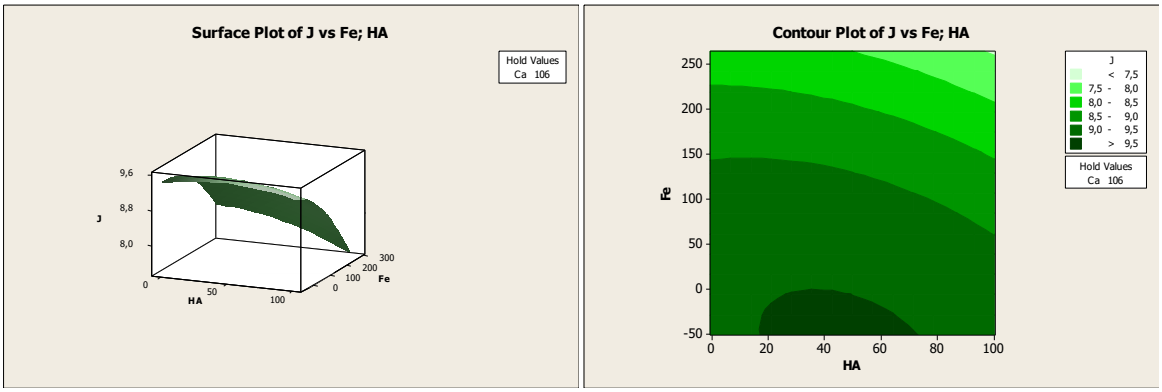
Figures 23 to 25 present the response surfaces and contour curves for the flux response as a function of HA and Ca concentrations, Ha and Fe concentrations and Ca and Fe concentration respectively.

Figure 23 - (a) surface plots and (b) contours plots for flux as a function of HA and Ca concentrations



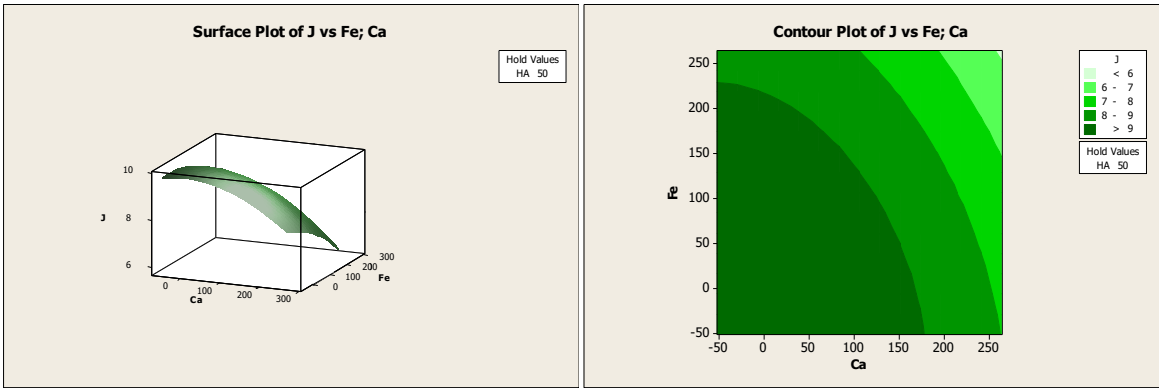
(a) (b)

Figure 24 - (a) surface plots and (b) contours plots for flux as a function of HA and Fe concentrations



(a) (b)

Figure 25 - (a) surface plots and (b)contours plots for flux as a function of Ca and Fe concentrations



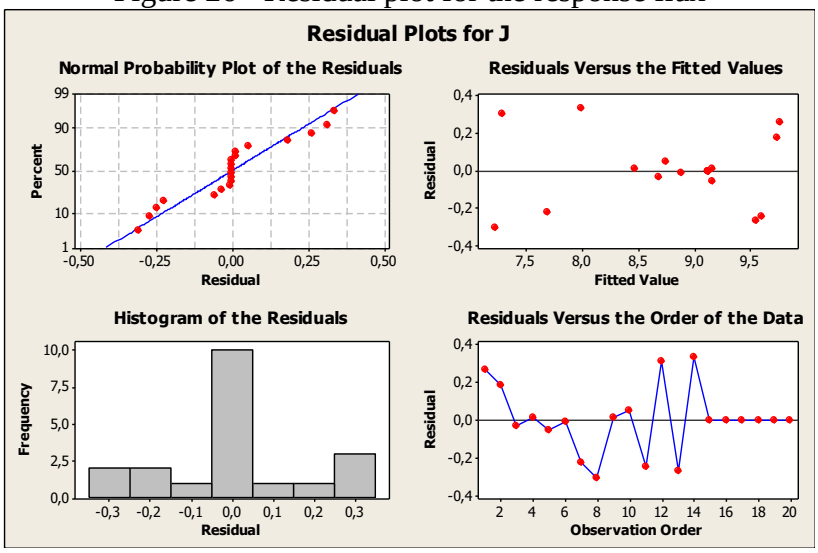
(a) (b)

Although no maximum or minimum point was possible to determine, the feed solution should not have concentrations of Ca and Fe greater than 170 and 230 mg/L, respectively, for better higher flux values, since these two factors tends to be deposited on the membrane surface and cause scaling.

The analysis of residues can be observed in Figure 26. Here, it is limited only in the verification of the independence of the residues for the response of flux. If there is an effect due to the order of data collection, the residuals would not be scattered around the line (Normal Probability graph) and randomly around zero (Waste vs. Adjusted Graph), which would allow the detection of a pattern in the graphics. The histogram corroborates this information (normal distribution),

however the Normal Probability graph is usually more informative, especially in the case of small samples.

Figure 26 - Residual plot for the response flux



Based on the significant effects of the model it was possible to determine a second-order polynomial mathematical model for EC removal (Equation 5).

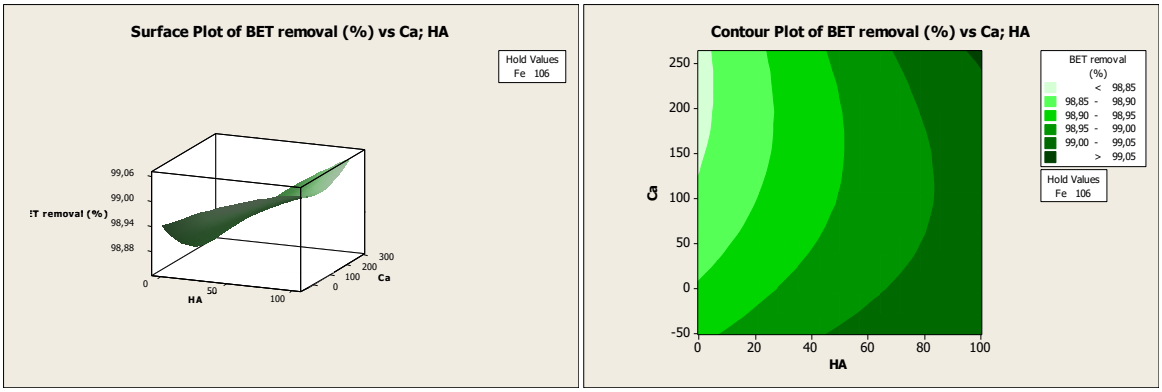
$$Y(X) = 98{,}9189 + 0{,}0018X1 - 0{,}0007X_2 - 0{,}0003X_3 - 0{,}0000X_1^2 + 0{,}0000X_2^2 + 0{,}0000X_3^2 + 0{,}0000X_1X_2 - 0{,}0000X_1X_3 + 0{,}0000X_2X_3 \quad (5)$$

For PhAC removal, the polynomial function explained 61% of the total response variation, indicating a satisfactory adjustment (> 60%).

For the confirmation of the critical points of the function it was determined Δ_1, Δ_2 and Δ_3 (Table 21), according to Lagrange criteria. For PhAC removal, since $\Delta_1 = 0$, $\Delta_2 = 0$ e $\Delta_3 = 0$, nothing is possible to affirm when a minimum or a maximum point is concerned.

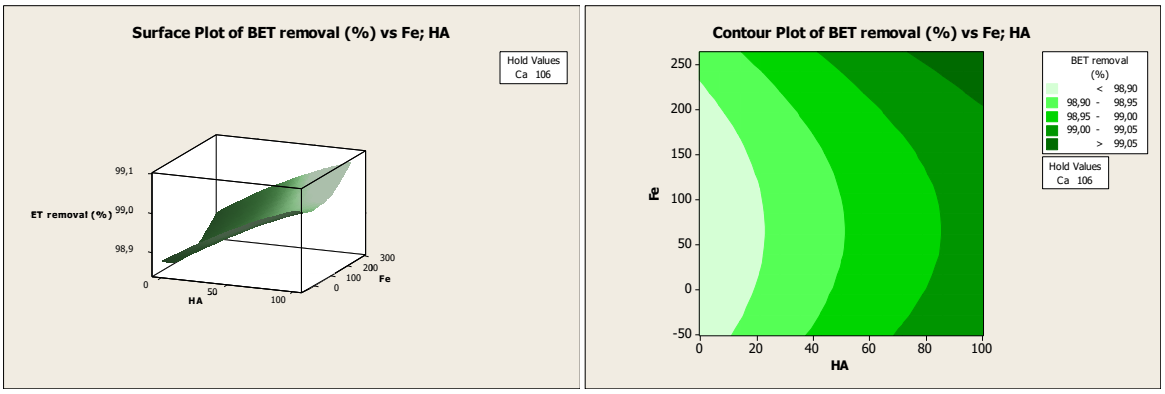
Figures 27 to 29 present the response surfaces and contour curves for the PhAC removal response as a function of HA and Ca concentrations, Ha and Fe concentrations and Ca and Fe concentration respectively.

Figure 27 - (a) surface plots and (b) contours plots for PhAC removal as a function of HA and Ca concentrations



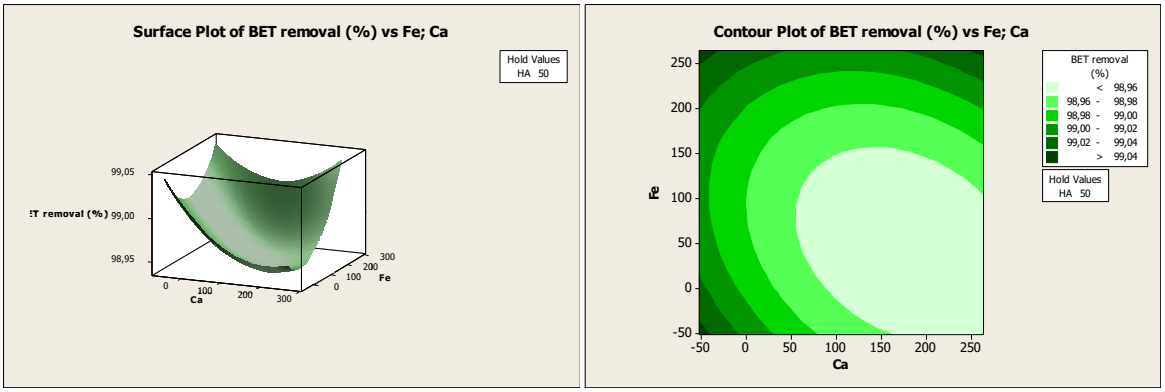
(a) (b)

Figure 28 - (a) surface plots and (b) contours plots for PhAC removal as a function of HA and Fe concentrations



(a) (b)

Figure 29 - (a) surface plots and (b) contours plots for PhAC removal as a function of Ca and Fe concentrations

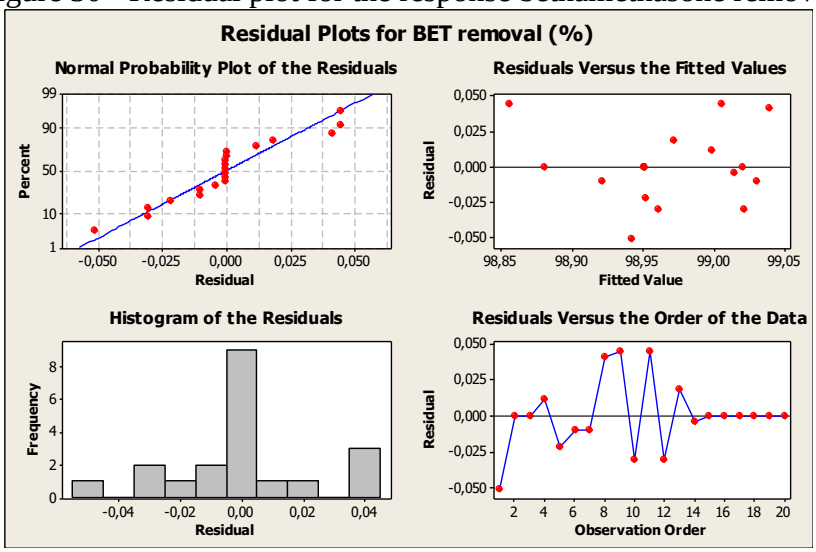


(a) (b)

Observing Figures 27-29, it is noted that the as the concentration of Ca and Fe increases along with HA concentrations, there is a decrease on betamethasone removal, until it reaches a peak concentration of <200mg/L for both Ca and Fe, where the formed cake layer may add more resistance for the passage of the PhAC across the membrane which is associated to the increase on the fouling resistance, also implicating on flux decline.

As for the analysis of residues, it is possible to observe (Figure 30), for the effect of BET Removal, a distribution of the residues around the line, which indicates normal behavior for the sludge generation response. The Residual vs. Fitted Values graph also indicates normality, presenting randomly distributed points on the zero axis and not observing a standard in this graph. The Histogram corroborates these statements.

Figure 30 - Residual plot for the response bethamethasone removal



Based on the significant effects of the model it was possible to determine a second-order polynomial mathematical model for PhAC removal (Equation 6).

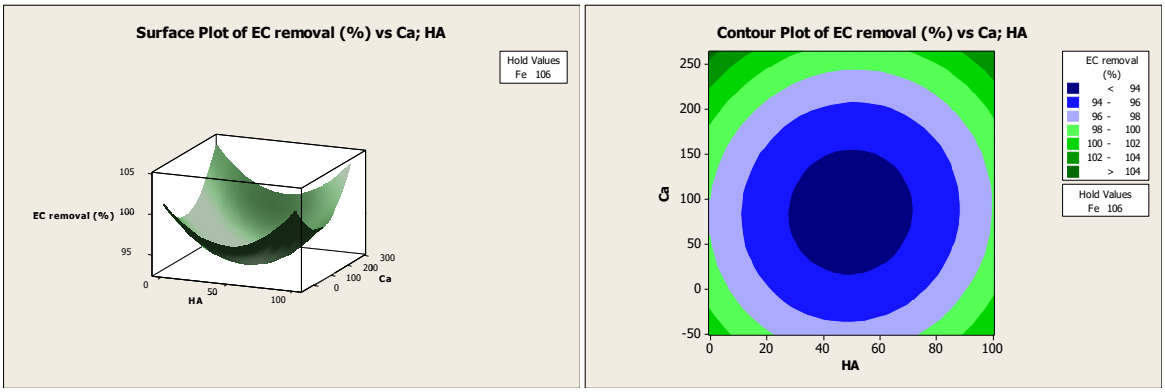
$$Y(X) = 94{,}571 - 0{,}196X1 - 0{,}019X_2 - 0{,}044X_3 + 0{,}002X_1^2 + 0{,}000X_2^2 + 0{,}000X_3^2 - 0{,}000X_1X_2 + 0{,}000X_1X_3 - 0{,}000X_2X_3 \quad (6)$$

For EC removal, the polynomial function explained 92,9% of the total response variation, indicating a good adjustment (> 75%).

For the confirmation of the critical points of the function it was determined Δ_1, Δ_2 and Δ_3 (Table 21), according to Lagrange criteria. For PhAC removal, since Δ_1= 0.004, Δ_2= 0 e Δ_3=0, nothing is possible to affirm when a minimum or a maximum point is concerned.

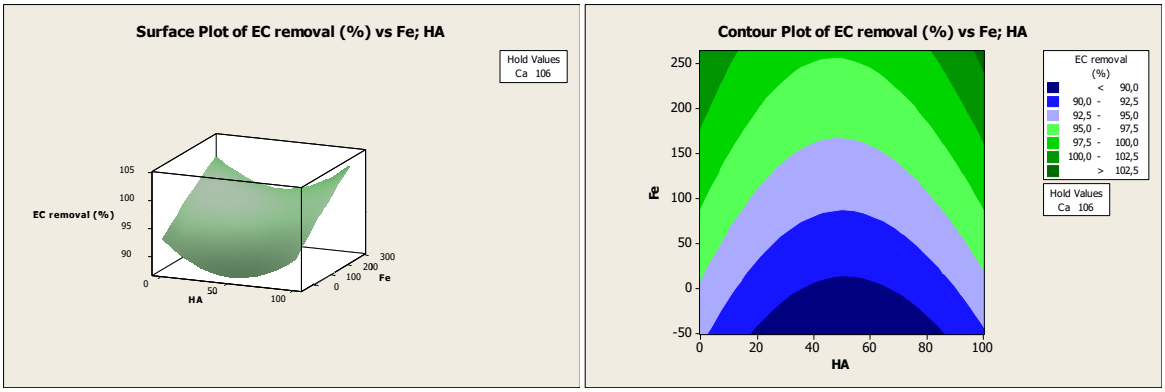
Figures 31 to 33 present the response surfaces and contour curves for the PhAC removal response as a function of HA and Ca concentrations, Ha and Fe concentrations and Ca and Fe concentration respectively.

Figure 31 - (a) surface plots and (b) contours plots for EC removal as a function of HA and Ca concentrations



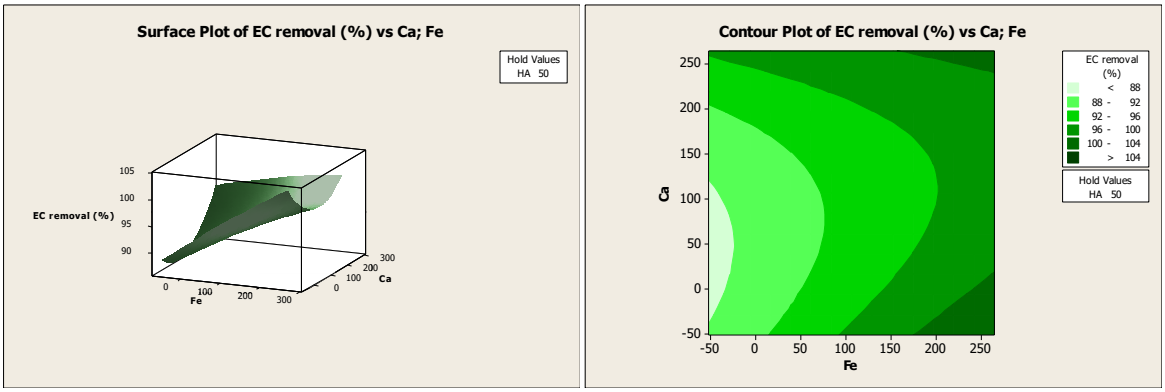
(a) (b)

Figure 32 - (a) surface plots and (b) contours plots for EC removal as a function of HA and Fe concentrations



(a) (b)

Figure 33 - (a) surface plots and (b) contours plots for EC removal as a function of Ca and Fe concentrations



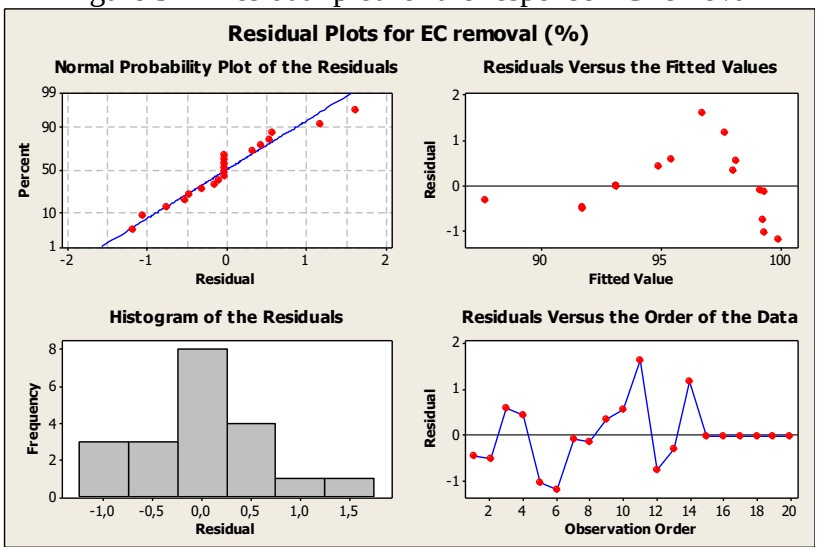
(a) (b)

Figures 31-33 shows that, once again, the increase the ion concentration in feed solution promotes a greater removal (%) of EC, which is associated to the robustness of the process, being able to dampen peaks of ions, generating a distillate with good quality. This is mainly possible due to material deposition on the membrane surface has narrowed the pores, hindering the passage of these ions through the membrane (WARSINGER *et al*., 2015), however, as the increase in the of ions on the feed side happens and the depositions of ions on the membrane surface raises, it is reported to cause decreases the membrane hydrophobicity, causing the membrane wetting. In this case, liquid starts to penetrate the membrane pores, reducing its selectivity and impairing its goals of separation (WARSINGER *et al*., 2015) which may reduce ions rejection since compounds are able to pass through the membrane along with the other and other contaminants.

The analysis of residues showed, for the effect of EC Removal (Figure 34), a distribution of the residues around the line, which indicates normal behavior for the sludge generation

response. The Residual vs. Fitted Values graph also indicates normality, presenting randomly distributed points on the zero axis and not observing a standard in this graph. The Histogram corroborates these statements.

Figure 34 - Residual plot for the response EC removal



5.3.3. Simultaneous optimization

Simultaneous optimization was performed in order to determine a favourable condition for the flow and removal of PhAC and EC altogether. Taking into account that each variable has its optimal point (Item 5.3.2), it was possible to translate into one mathematical model all three variables.

It was considered here that PhAC and EC removal are more important than flux, so weight 2 was assigned to the former two factors and 1 for the last, according to Eq. 7.

$$Final\ score = J + 2xEC + 2xPhAC \quad (7)$$

Where the final score is the response of the three variables together according to Table 22, J is the variable flux, EC is the variable EC removal and PhAC is the variable PhAC removal.

Table 19 - Partial scores and final score for variables flux (J), EC and PhAC removal response

Score	Partial Scores			Final Score
	J	EC removal	BET removal	J + 2 x EC + 2 x BET
1	< 6.86 - 7.18	< 87.31 - 88.50	< 98.880 - 98.900	< 22.6
2	7.19 - 7.49	88.51 - 89.69	98.901 - 98.920	22.7 - 25.2

3	7.5 - 7.81	89.7 - 90.88	98.921 - 98.940	25.3 - 27.8
4	7.82 - 8.13	90.89 - 92.07	98.941 - 98.960	27.9 - 30.4
5	8.14 - 8.45	92.08 - 93.26	98.961 - 98.980	30.5 - 33
6	8.46 - 8.76	93.27 - 94.45	98.981 - 99.000	33.1 - 35.6
7	8.77 - 9.08	94.46 - 95.64	99.001 - 99.020	35.7 - 38.2
8	9.09 - 9.40	95.65 - 96.83	99.021 - 99.040	38.3 - 40.8
9	9.41 - 9.71	96.84 - 98.02	99.041 - 99.060	40.9 - 43.4
10	> 9.72	> 98.03	> 99.061	> 46

Thus, based on the significant effects of the model it was possible to determine a second-order polynomial mathematical model for the three variables response combined (Equation 8).

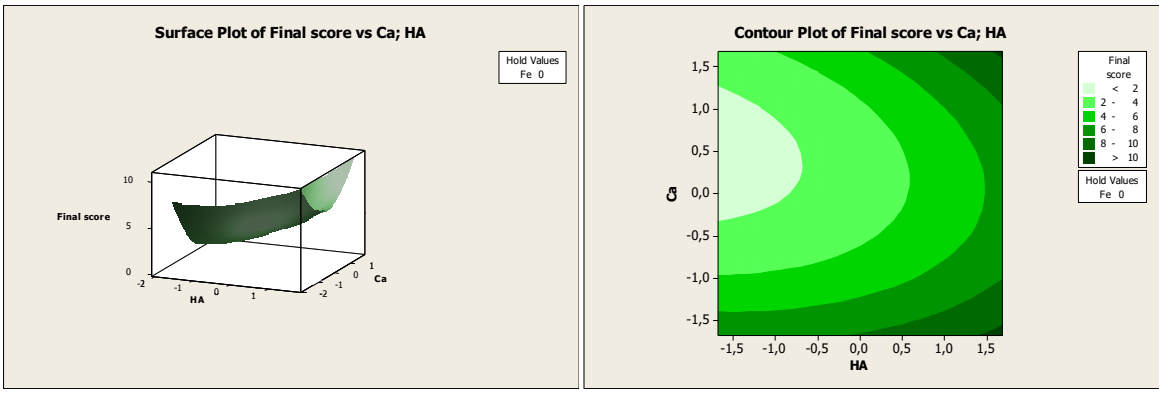
$$Y(X) = 3{,}03 + 1{,}51X1 - 0{,}68X_2 + 1{,}54X_3 + 0{,}33X_1^2 + 1{,}39X_2^2 + 0{,}51X_3^2 + 0{,}37X_1X_2 + 0{,}37X_1X_3 - 0{,}62X_2X_3 \quad (8)$$

For this, the polynomial function explained 63,7% of the total response variation, indicating a reasonable adjustment (>60%).

For the confirmation of the critical points of the function it was determined Δ_1, Δ_2 and Δ_3, according to Lagrange criteria. Since Δ_1= 0.66, Δ_2= 1.70 e Δ_3= 0.92, there is minimal point.

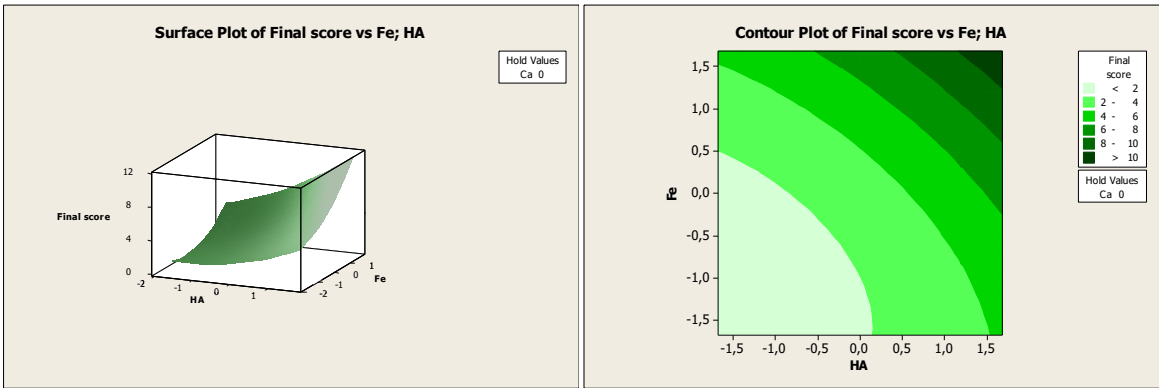
Figures 35 to 37 present the response surfaces and contour curves for the three variables response combined as a function of HA and Ca concentrations, Ha and Fe concentrations and Ca and Fe concentration respectively.

Figure 35 - (a) surface plots and (b) contours plots for three variables response as a function of HA and Ca concentrations



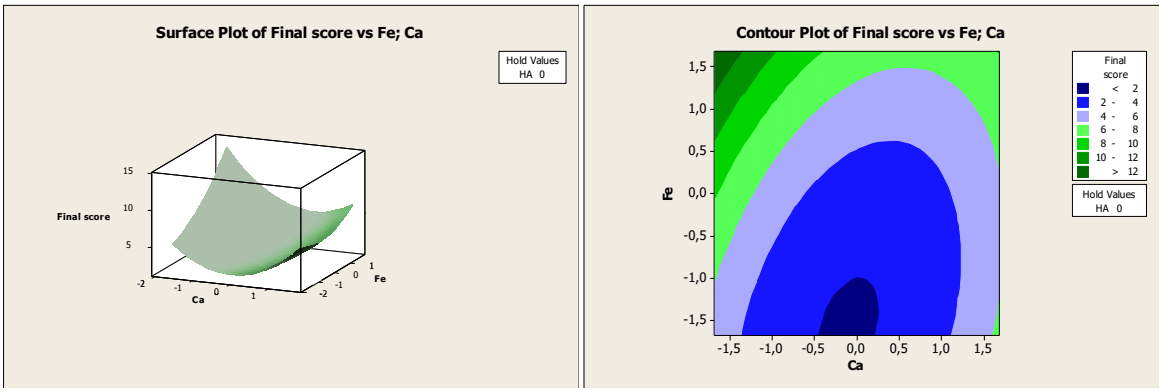
(a) (b)

Figure 36 - (a) surface plots and (b) contours plots for three variables response as a function of HA and Fe concentrations



(a) (b)

Figure 37 - (a) surface plots and (b) contours plots for three variables response as a function of Ca and Fe concentrations



(a) (b)

The identification of the coordinates of the critical point of the obtained response surface was accomplished by the resolution of a system with three linear equations and three unknowns, resulting from the application of the derivatives to the equation obtained for the surfaces.

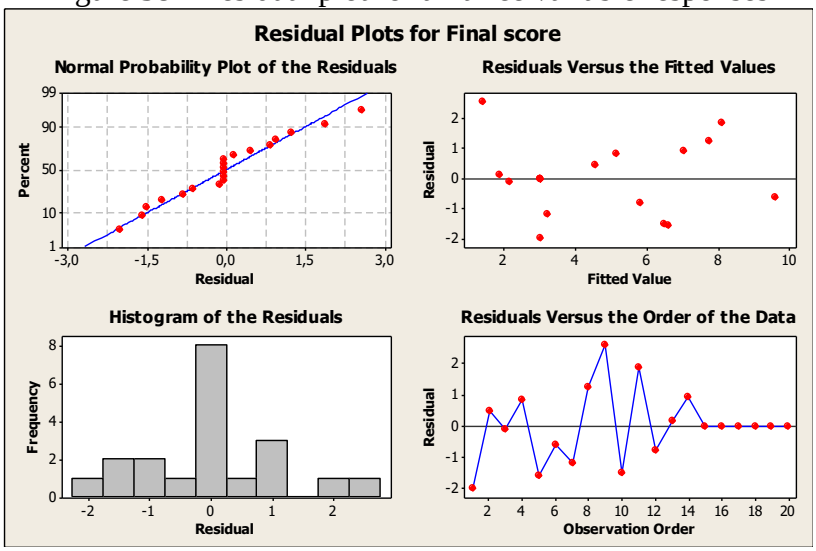
$X_1 = -2.29$; $X_2 = 0.24$; $X_3 = -1.51$

Where X_1 is HA concentrations, X_2 is Ca concentrations and X_3 is Fe concentrations. Since there is no such a thing as negative concentrations, the minimum for HA and Fe is considered 0.

The analysis of residues showed, for the effect of the combined three factors on variables response (Figure 38), a distribution of the residues around the line, which, once again, indicates

normal behavior for the sludge generation response. The Residual vs. Fitted Values graph also indicates normality, presenting randomly distributed points on the zero axis and not observing a standard in this graph. The Histogram corroborates these statements.

Figure 38 - Residual plot for all three variable responses



5.4. Conclusion

The results here indicate that MD appears to be ideal, in terms of the sustained performance even when feed with high organic and inorganic are involved, for treating surface water. MD flux is most influenced by Ca and Fe concentrations because this system is more susceptible to calcium and iron precipitation on the membrane surface, as well as EC removal which is associated to the passage of Fe3+ carried to the distillate side dissolved in the water vapor with the lower pH influenced by CO2 already dissolved due to the decomposition of CaCO3 while PhACs removal are most influenced by the presence of HA. It was found an increase on EC removal as ions concentration raised, however, flux decline was shaper due to the reduction of the pores. Wetting phenomenon can occur since a reduction on EC removal is observed when ions concentration increased.

MD was also able to achieve ≥ 99% of PhACs removal for all 25 assessed PhACs, whereas 24 are below limit detection, attributing its high efficiency due to the low volatility and, to a lesser extent, by hydrophobia of the studied. Betamethasone passage across the membrane was strongly associated to the presence of HA mainly due to the intrinsic characteristics (pka and logkow) of the compound.

The mathematical models of the critical operation conditions proposed here, it was observed a satisfactory adjustment (> 60%) to all three response variables, where flux polynomial function could explain 89%. The mathematical model proposed here for simultaneous optimization, explained 63,7% of the total response variation, indicating a reasonable adjustment. In general, MD is considered to be a robust process able to produce safe water, even at long-term runs and submitted to high organic and inorganic loads.

5.5. References

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6. FINAL CONSIDERATIONS

Pharmaceutically active compounds are a real threat all around the world, including in brazil. Trace levels of pharmaceuticals were detected in superficial water in Doce river where fluconazole and betamethasone were the main compounds found.

NF, RO, and MD are efficient single step technologies for treatment of surface water to achieve drinking water quality and PhAC removal. The rejection of PhACs by NF and RO is mainly due to size exclusion and hydrophobic interactions, whereas MD rejection is mainly attributed to low volatility of PhACs. All evaluated processes lead to a high toxicological risk reduction. In addition to presenting the highest PhAC removal, MD did not present fouling tendency which was the principal cause of flux decline in RO and NF. The NF and RO membrane fouling occurred due to deposition and/or pore blocking by natural organic matter since the water salts concentration is low.

Opex were estimated at 0.13 to 0.16, 0.123 and 2.00 US$/m3 for NF, RO and MD respectively. Although the MD process is more robust, the practical application is restricted by the high cost. Moreover, the costs for MD can be further reduced by utilizing low cost energy such as solar energy or residual heat. Future prospect for MD membrane relies on membrane permeability improvement. And, NF and RO are feasible alternative to remove PhACs from drinking water.

When assessing the influence of organic matter on MD performance in order to achieve PhACs rejections, again it was proved that MD appears to be ideal, in terms of the sustained performance over long periods of running, for treating surface water, even at the much higher concentrations of organic matter studied. The observed flux decline (<8%) was attributed to the membrane fouling due to the increase in the organic matter/HA mass deposited on the membrane surface. However, 100% of permeate flux was recovered suggesting the reversibility of the fouling layer.

MD also presents a high removal of organic matter (here addressed as HA) as well as ions, maintaining a low electrical conductivity. MD was also able to achieve ≥ 99% of PhACs removal for all 25 assessed PhACs, whereas 24 are below limit detection, attributing its high efficiency due to the low volatility and, to a lesser extent, by hydrophobia of the studied compounds, once again confirming the robustness of the process, propitiating a safe distillate even at higher HA concentrations. The retention of PhACs by MD membrane occurs predominantly by membrane rejection, and, although PhACs adsorption on the membrane

surface had a smaller expression on the retention phenomenon, it was mainly associated with the PhACs' pka. Changes on the membrane characteristics, due to the fouling layer, changed this pattern. In general, MD is considered to be a robust process able to produce safe water, even at long-term runs.

MD flux is most influenced by Ca and Fe concentrations because this system is more susceptible to calcium and iron precipitation on the membrane surface, as well as EC removal which is associated to the passage of Fe^{3+} carried to the distillate side dissolved in the water vapor with the lower pH influenced by CO_2 already dissolved due to the decomposition of $CaCO_3$ while PhACs removal are most influenced by the presence of HA.

For the mathematical model of the critical operation conditions proposed here, it was observed a satisfactory adjustment (> 60%) to all three response variables, however, it was not possible to observed a minimum or a maximum value for none of the assessed conditions. The mathematical model proposed here for all three variables together, explained 63,7% of the total response variation, indicating a reasonable adjustment.

In recent years the mostly used and advised to be applied is the RO system, due to the smaller price as well as more knowledge on the application of this technique. Also, the Doce River's water quality is still good enough to apply RO as a single step. However, once the water quality decrease, a more robust process will be required.

In general, although MD is the most expensive process, especially due to energy consumption, it is the process that presents greater robustness, even before feeding with high concentration of salts and organic matter and great RR. Despite being little studied, it presents great versatility and capacity to completely remove PhACs, having potential to be applied for the production of drinking water, and although there is a high removal of salts, it can be compensated by adding salts to the water. In addition, MD shows a good performance considering the reversable of the fouling layer, which corroborates with the persistence of the process.

Also, more studies should be focused on the utilization of renewable energy in order to reduce costs associated to the application of MD as well as treatment routs to remove from MSPs concentrates.

Appendix 01

OCCURRENCE, FATE AND REMOVAL OF PHARMACEUTICALLY ACTIVE COMPOUNDS (PhACs) IN WATER AND WASTEWATER TREATMENT PLANTS – A REVIEW

Carolina F. Couto[a], Lisete C. Lange[a], Miriam C. S. Amaral[a]

[a]Department of Sanitary and Environmental Engineering, Federal University of Minas Gerais, P.O. Box 1294, 31.270-901, Belo Horizonte, MG, Brazil.

Corresponding author: Telephone: +5531989381058 email: carolf.couto@hotmail.com

Abstract

This paper reviews the occurrence of Pharmaceutically active compounds (PhACs) in water and wastewater worldwide as well as their fate, focusing on the removal by conventional water and wastewater treatment plants and the risk imposed to human health associated to the presence of PhACs in raw and drinking water. For this, it was assessed 23 drinking water treatment plants and 30 municipal wastewater treatment plants around the world of different capacities. Due to the high stability, intrinsic characteristics and low concentration, adsorption to the sludge and biodegradation are the most used path to remove of these compounds in wastewater treatment plants (WWTP). In water treatment plants (WTP), chlorination and application of activated granular carbon are the processes associated with the highest removal of pharmaceutical compounds, but, in general, conventional WTPs are able to reduce but not completely remove PhACs in potable water. Carbamazepine, gemfizobril and fenofibrate are found to be the PhACs that risks to human health could not be excluded. This indicates the necessity of investments in advanced techniques for the treatment of water and wastewater. The results also point to the need for more studies focusing on the determination of guideline values for drinking water of more PhACs.

KEYWORDS: Pharmaceutically active compounds; PhACs; water treatment; wastewater treatment; risk assessment; emerging pollutants.

1. Introduction

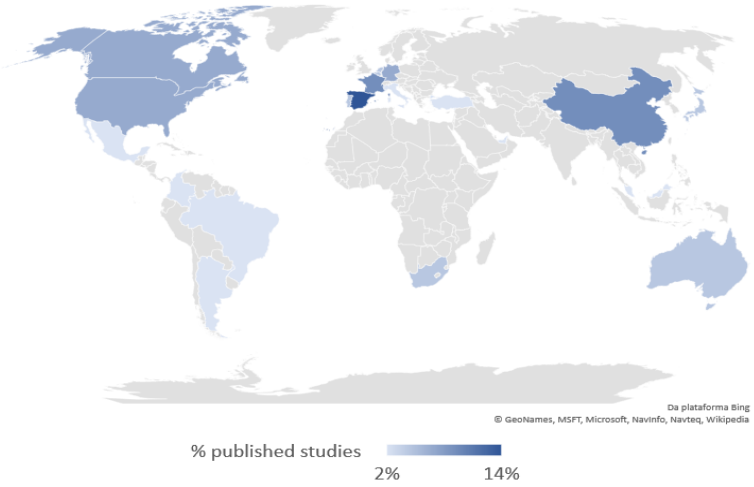
Worldwide, pharmaceutical products, such as, analgesics, anti-inflammatory drugs, antibiotics, lipid regulators, beta-blockers and X-rays contrast media, have become more and more a part of the daily routine life, being used in human and animal for health treatment, to improve life quality and to increase their life span. In 2017, it was estimated that it was spent a total of US$1135 billion on prescription medications (OECD, 2017). With the aging population combined with improvements in health standards specially in developing countries, the consumption of pharmaceutically active compounds (PhACs) is set to increase in future years (Verlicchi et al., 2012). In the year of 2013 alone, over 100 new formulations or chemical entities were approved by the US Food and Drug Administration (FDA) for clinical use (Peake et al., 2016).

These compounds reach water systems from different sources such as human excretion (sewage), wrongful disposal, landfill leachate, drain water, or from industries (Archer et al., 2017). PhACs have been found in wastewater effluent, drinking water, rivers and dams in many different places such as Asia (Saravanan et al., 2014; Shanmugam et al., 2014; Chen et al., 2015; Jindal et al., 2015), America (Qin et al., 2015; Sarmah et al., 2006; Kümmerer, 2009; Caracciolo et al., 2015), Australia (Sarmah et al., 2006; Kümmerer, 2009; Caracciolo et al., 2015; Watkinson et al., 2009) and Europe (Sarmah et al., 2006; Kümmerer, 2009; Radjenovic et al., 2009; Salgado et al., 2012; Valcarcel et al., 2013; Frederic and Yves., 2014; Net et al., 2015) and Africa (Gumbi et al., 2017) at low concentration (ng/l to μg/l range) and the increase in the production, consumption and therefore discharge to the environment has been raising global attention and concern.

The presence of PhACs in the water cycle has been increasing the concern about the efficacy of water and wastewater treatment processes in removing these compounds. Several papers were published about the presence of PhACs in the environment, in drinking water and wastewater treatment plants. A research on Scopus was done in order to rise how many studies have been carried out in the last decade (2008-2018) about the subject, using the keywords “pharmaceutically active compounds and drinking water” and “pharmaceutically active

compounds and wastewater". The majority of the studies are located in Europe, Asia and North America (Figure 1). Thus, this paper reviews the occurrence of PhACs worldwide, their fate in the environment, focusing on the removal by the conventional water and wastewater plants and the risk imposed on human by the presence of these compounds in drinking water. For this, among more than 4000 papers, it was selected 99 papers on the subject using the key words "pharmaceutically active compounds and drinking water" and "pharmaceutically active compounds and wastewater" where it was possible to observe PhACs concentration before and after the treatment. It was assessed 23 drinking water treatment plants and 30 municipal wastewater treatment plants around the world of different sizes. It was selected the papers published no earlier than 2000.

Figure 1 – Global distribution of studies about occurrence of PhACs in drinking water and wastewater



2. Environmental/ Health issues and regulations related to PhACs

Over 200 different PhACs were observed in surface, ground water and sewage (Petrie et al., 2014; Taheran et al., 2016) and it is still unclear the levels and effects as well as the fate of these compounds on the human health and wildlife, however it has been found their potential to cause aquatic toxicity, development of resistance in pathogenic microbes; genotoxicity and endocrine disruption (Taheran et al., 2016; Khetan et al., 2007; Martín et al., 2012) Also, the release of PhACs in the environment is not regulated and covered by the existing water quality Ma et al., 2017).

Verlicchi et al. (2012) assessed the environmental risk posed by PhACs in secondary effluent. It was concluded that 14, out of 51 assessed compounds, pose a high environmental risk: 7 antibiotics, 2 psychiatric drugs, 2 analgesic/anti-inflammatory and 3 lipid regulators. However, most of the toxicity data refer to acute rather than chronic effects, which limits the assessment. Long term effects are of hugely importance to understand of PhACs fate and effect on the environment and public health.

Many researches have been carried out to assess the effects of the exposure to PhACs. Chen et al. (2016) assessed the effects of hormones on sexual behaviours of *O. melastigma*. It was observed that sexual behaviour was induced in the fish groups submitted to hormones, increasing the duration of "dancing". Also, estrogenic pharmaceutical compounds are found to cause an increase in the vitellogenin levels in male fish, as well as decreased levels of vitellogenin and estradiol in the plasma of female fish. These findings were associated with immature gonads and lower gonadosomatic index in *G. brasiliensis* adult females, as well as histological changes, such as degeneration of germ cells (Yamamoto et al., 2017). Also, diclofenac was found to cause vitellogenin in male Japanese medaka fish (Lacey et al., 2012), and ibuprofen, naproxen and diclofenac destabilize DMPS bilayers affecting their thermodynamic properties (Manrique-Moreno et al., 2016). Diclofenac and the carbamazepine were found to decrease the emergence ratio and reduce the growth of the midges of *Chironomus riparius*, respectively (Nieto et al., 2017). PhACs were also associated to impact microbial communities by changing the ability of microbes to metabolize different carbon sources, thus affecting the metabolic diversity of the soil community (Pino-Otín et al., 2017). Thus, this study suggests that the repeated amendment of agricultural soils with biosolids, sludges or even irrigation of wastewater rich in PhACs residuals may result in an increase of concentration of these compounds in the soil throughout the time and impact key ecological functions (i.e. the carbon cycle) (Pino-Otín et al., 2017).

Due to this fact, some worldwide recognised agencies have been trying to either banish or stimulate the establishment of limits of the usage or discharge of some PhACs. For instance, the European Union (EU., 2018) listed 45 priority compounds with environmental quality standard (EQS) to be respected in aquatic environments and listed 8 others on contemporary watch list (Decision 2018/840, published on 5th June 2018). Similar regulations were followed by Switzerland for several ECs. In 1995, the European Union (EU) set 10 ngL^{-1} and 10 μgkg^{-1} as the concentration of PhACs and PCPs (personal care products) in surface water and soil. The U.S. Food and Drug Administration (FDA, USA) publicized directions for the evaluation of human drugs. Environmental assessment has reported the expected introduction concentration of pharmaceuticals in the aquatic environment as $\geq 1\ \mu gL^{-1}$. (USEPA, 2012)

The Water Framework Directive included anti-inflammatory diclofenac or the synthetic hormones Ethynylestradiol (EE2) in the supposed 'watch list' of priority compounds to address the risk posed by these substances (EU, 2018; Collado et al., 2014). [30,32] Various PhACs and EDCs (endocrine disrupting compounds), were enlisted in the Drinking Water Contaminant Candidate List (GWRC, 2008). Different PhACs, for example, carbamazepine, naproxen, sulfamethoxazole, ibuprofen, gemfibrozil, atenolol, diclofenac, erythromycin and bezafibrate have been rated prime concern pharmaceuticals to the water cycle by the Global Water Research Coalition (GWRC, 2008).

3. **Advances in analytical and detection methods**

The PhACs differ greatly in their physicochemical properties; also, they are found at very low levels (ng L^{-1} to $\mu g\ L^{-1}$) and in complex matrices that require highly selective and sensitive methods.

For determination of the concentration in water and wastewater as well as the confirmation of these compounds, elaborate and time-consuming extraction and purification steps followed by chromatographic techniques often coupled to mass spectrometry are required. In Table 1 it is possible to observe the techniques used for the determination of PhACs in water and wastewater used in this research. It is noted that the liquid chromatograph (LC), high-performance (HPLC) or ultra-performance liquid chromatography (UPLC) coupled to mass spectrometer, are the most used for both sewage and drinking water if compared to gas chromatography mass spectrometry (GCMS). The selection of methods is dependent on the

physic-chemical characteristic of the PhAC. Liquid chromatography (LC, HPLC or UPLC) coupled to mass spectrometer technique is more suitable for quantification of PhAC more polar and highly soluble in water, whereas gas GC-MS/MS is better for more volatile PhAC. Thus, considering all the many available methods as well as different PhACs concentrations, properties and matrix complexity, researchers should be encouraged to report the performance of their methods.

Table 1 – Number of studies for each analytical method used for the quantification and confirmation of PhACs in drinking water and wastewater

PhACs	Focus gas-chromatograph-MS	LC-MS/MS	LC/MS	HPLC-MS/MS	UPLC-MS/MS	References
Acethaminophen	1		3	2	1	Wilkinson et al., (2017); Vulliet et al., (2011); Kleywegt et al., (2011); Huerta-Fontela et al., (2011); Azzouz and Ballestero (2013); Semerjian et al., (2018); Botero-Coy et al., (2016); Rivera-Jaimes et al., (2018); Komesli et al. (2015); Leusch et al., (2018)
Acebutolol					1	Huerta-Fontela et al., (2011)
Alprazolam			1			Wu et al., (2015)
Amitriptyline			1			Wu et al., (2015)
Amlodipine		1			1	Yan et al., (2014); Huerta-Fontela et al., (2011)
Ampicilin		1				Salgado et al. [14]
Atenolol		1	7	1	1	Huerta-Fontela et al., (2011); Vulliet et al., (2011); Subedi et al., (2015); Inyang et al., (2016); Salgado et al., (2012); Leusch et al., (2018)
Atravastatin		1				Yan et al., (2014)
Azithromycin		1				Yan et al., (2014)
Bezafibrate		1	3			Rivera-Jaimes et al., (2018); Yan et al., (2014)

Bromazepam					1	Wu et al., (2015)
Captopril		1				Salgado et al., (2012)
Carbamaz epoxide					1	Huerta-Fontela et al., (2011)
Carbamazepine	1	1	14	5	2	Simazaki et al., (2015); Huerta-Fontela et al., (2011); Wu et al., (2015); Azzouz and Ballestero (2013); Rivera-Jaimes et al., (2018); Gaffiney et al., (2015); Kleywegt et al.(2011); Wang et al., (2011); Subedi et al., (2015); Lin et al., (2016); Wang et al., (2014); Lajeunesse et al., (2012); Yan et al., (2014); Radjenovic et al., (2009); Komesli et al., (2015); Wu et al., (2015); Inyang et al., (2016); Leusch et al., (2018)
Chlordiazepoxide					1	Huerta-Fontela et al., (2011)
Chlorpromazine					1	Huerta-Fontela et al., (2011)
Clarithromycin			1	1	1	Botero-Coy et al., (2016); Lin et al., (2016); Boleda et al., (2011)
Clopidogrel					1	Huerta-Fontela et al., (2011)
Clorazepate		1				Salgado et al., (2012)
Desmethylvenlafaxine					1	Huerta-Fontela et al., (2011)
Diazepam			12		1	Huerta-Fontela et al., (2011); Wu et al., (2015); Leusch et al., (2018)

Diclofenac	1	2	7	2	1	Wilkinson et al., (2017); Carmona et al., (2014); Praveena et al., (2018); Caldas et al., (2013); Azzouz and Ballestero (2013); Vulliet et al., (2011); Boleda et al., (2011); Salgado et al., (2012); Yan et al., (2014); Leusch et al., (2018)
Diltiazem					1	Huerta-Fontela et al., (2011)
Domperidone				1		Van De Steene et al., (2010)
Doxepin			1			Wu et al., (2015)
Erythromycin		1	1	1	2	Boleda et al., (2011); Gaffiney et al., (2015); Kleywegt et al., (2011); Semerjian et al., (2018); Yan et al., (2014)
Estazolam			1			Wu et al., (2015)
Estriol					1	Huerta-Fontela et al., (2011)
Estrone				1	1	Huerta-Fontela et al., (2011); Komesli et al., (2015)
Ethinyl estradiol	1			1	1	Azzouz and Ballestero (2013); Wilkinson et al., (2017); Huerta-Fontela et al., (2011)
Fenofibrate			1			Simazaki et al., (2015)
Fluoxetine		1	3			Lajeunesse et al., (2012); Salgado et al., (2012); Wu et al., (2015); Inyang et al., (2016)
Furosemide					1	Huerta-Fontela et al. [74]

Gemfibrozil		1	2	1	2	Boleda et al., (2011); Carmona et al., (2014); Kleywegt et al., (2011); Radjenovic et al., (2009); Rivera-Jaimes et al., (2018); Yan et al., (2013)
Hydrochlorthiazide					1	Huerta-Fontela et al., (2011)
Ibuprofen	1	2	5		1	Carmona et al., (2014); Azzouz and Ballestero (2013); Vulliet et al., (2011); Kleywegt et al., (2011); Wang et al., (2011); Inyang et al., (2016); Rivera-Jaimes et al., (2018); Salgado et al., (2012); Yan et al., (2014)
Indomethacin			1		2	Carmona et al., (2014); Gaffiney et al., (2015); Simazaki et al., (2015)
Ketoprofen		1				Salgado et al., (2012)
Lorazepam			1			Wu et al., (2015)
Metoprolol		1		1	1	Wang et al., (2014); Semerjian et al., (2018); Yan et al., (2014)
Mianserin			1			Wu et al., (2015)
Moxifloxacin		1				Yan et al., (2014)
Naproxen	1		3		2	Carmona et al., (2014); Azzouz and Ballestero (2013); Vulliet et al., (2011); Boleda et al., (2011); Rivera-Jaimes et al., (2018); Inyang et al., (2016)
Nimesulide			1			Caldas et al., (2013)
Nordiazepam			1			Wu et al., (2015)

Norflaxacin		1				Yan et al., (2014)
Norfluoxitine			1			Lajeunesse et al, (2012)
Oflaxacin		1			1	Semerjian et al., (2018); Yan et al., (2014)
Oxazepam			2			Hass et al., (2012); Wu et al., (2015)
Pipamperone				1		Van De Steene et al., (2010)
Progesterone			1	1		Vulliet et al, (2011); Komesli et al., (2015)
Propanolol					1	Huerta-Fontela et al., (2011)
Roxithromycin		1				Yan et al., (2014)
Sivastatin		1				Yan et al., (2014)
Sotalol					1	Huerta-Fontela et al., (2011)
Sulfadiazine		1				Yan et al., (2014)
Sulfadimethoxine					1	Boleda et al., (2011)
Sulfamethazine		1				Yan et al., (2014)
Sulfamethoxazole		1	4	4	2	Simazaki et al., (2015); Praveena et al., (2018); Boleda et al., (2011); Vulliet et al., (2011); Kleywegt et al., (2011); Subedi et al., (2015); Lin et al., (2016); Rivera-Jaimes et al., (2018); Yan et al., (2014); Brown and Wong, (2018); Radjenovic et al., (2009); Semerjian et al., (2018)
Sulpiride				1		Wang et al., (2014)
Tamoxifen					1	Huerta-Fontela et al., (2011)

Temazepam			1			Wu et al., (2015)
Testosterone			1			Vulliet et al., (2011)
Trimethoprim		1	4	2	1	Kleywegt et al., (2011); Wang et al., (2011); Lin et al., (2016); Boleda et al., (2011); Inyang et al., (2016); Rivera-Jaimes et al., (2018), Wang et al., (2014); Yan et al., (2014)
Warfarin					2	Carmona et al., (2014); Huerta-Fontela et al., (2011)

drinking water; wastewater; drinking water and wastewater

Currently, there is no standardized protocol for the sampling, extraction and analytical determination of pharmaceuticals in water or wastewater that ensures the comparability and quality of the data generated. A large range of detection limits are observed for the PhACs, even when the same analytical methods are applied. Many factors can be associated to this phenomenon. As sample preparation procedures are divided into multiple steps, it is possible that several problems associated with quantification occur, directly impacting the reliability of the compounds analysed. Thus, according to Konieczka and Namieśnik (2010), there is no "measure without error", which implies that every analytical result is inseparably associated with the term "measurement error" directly impacting the limits of detection. Thus, the final quantification results of the compounds analysed can be affected by a large sum of several errors and, finally, do not reflect the actual concentrations of the pharmaceutical compounds in the environmental samples (Borecka et al., 2013).

4. The current panorama of PhACs on wastewater

Municipal wastewater treatment plants (WWTPs) is the major barriers that can prevent contaminants in wastewater from entering the receiving environment. However, WWTPs are designed aiming the removal of easily or moderately biodegradable carbon, nitrogen and phosphorus compounds and microbiological organisms, which regularly arrive at the WWTP in concentrations to the order of mg L^{-1} and at least 10^6 MPN/100 mL, respectively, WWTPs are not equipped to deal with complex compounds in low concentrations, such as, pharmaceuticals (Garcia-Ivars et al., 2017; Verlicchi et al., 2012). Since PhACs are not removed in the conventional treatment process applied to the urban wastewater, they are continuously discharged into aquatic ecosystems, which makes WWTP effluents the main source of human pharmaceuticals in the environment (Valdés et al., 2014).

Generally, municipal wastewater treatment plants include screening, degritting, primary sedimentation, secondary treatment, and final sedimentation show low efficiency in removing PhACs. The capabilities of primary treatment processes (i.e., sedimentation) in removing PhACs are very limited (Luo et al., 2014), since adsorption is one of the main mechanisms of PhACs removal in these processes and most PhACs have hydrophilic nature. Secondary treatment involves biological process. In biological processes removal of PhACs can occur through partition, adsorption, biotransformation, and biodegradation (Jelić et al., 2011).

Biodegradation is the breakdown of complex molecules, which can or cannot confer the property of toxicity into simples, less toxic products by the activity of microorganisms using these compounds as a donator of electrons in order to produce energy. This mechanism is the key processes of a biological treatment system. The biodegradation of pharmaceutical residues in the WWTP occurs by two main mechanisms, that is, by co-metabolism, in which the pharmaceutical pollutant has been degraded by enzymes secreted by the microbial community present in biological sludge, or by degradation of substrate sludge, in which the targeted compounds are the sludge carbon and energy source for microbes. Studies conducted by Jiang et al. (2014) have shown that the *Trametes Versicolor* fungus achieved an efficient removal of carbamazepine due to the secretion of laccase and peroxidase enzymes (Jelić et al., 2011).

Several strains of Pseudomonas are reported to use the antibiotic sulfamethoxazole as the sole carbon and energy source (Jiang et al., 2014). A comparative study between the co-metabolic and single substrate degradation process concluded that the co-metabolic biodegradation process was the main mechanism of removal of ibuprofen, bezafibrate and naproxen, while ketoprofen was partially degraded as the only substrate (Quintana et al., 2005). It is observed that pharmaceutical products belonging to the same therapeutic group may present considerable variation in their removal mechanisms. The rate of degradation and removal efficiency of each compound may vary beyond depending on the type of digestion, be it aerobic or anaerobic digestion; may also vary according to the structure and functional group of the compounds. For example, the efficiency in the degradation of chlorinated compounds in aerobic digestion processes is faster than anaerobic digestion; however, the rate of degradation of the polyhalogenated compounds is slower in aerobic digestion (Schwarzenbach et al., 2005). Long chain aliphatic compounds are more biodegradable than sulphate or halogen group aromatic compounds in their complex ring structure (Schwarzenbach et al., 2005).

Biodegradation of PhACs is found to be dependent on their structure and bioavailability since it follows a first order kinetics. Its degradability also depends on the characteristics of the medium as well as the redox potential of the pH, its own stereo chemical structure and the chemical properties of the sorbent and sorbent molecules since these molecules favour the intercalation. The biodegradability is governed by complexity and stability of compounds (Schwarzenbach et al., 2005). Short side chains and unsaturated aliphatic compounds are more readily biodegradable than aromatic or highly branched side chain compounds (Tiwari et al., 2017). The mechanism of destination and removal of pharmaceutical pollutants in the WWTP

is also governed by the presence of electron withdrawal/donation groups in its structure (Wijekoon et al., 2013). The low removal of pharmaceutical products at the WWTP was due to the transformation of human metabolites and the conversion of metabolites formed into parent compounds (Tiwari et al., 2017).

Table 2 summarizes the occurrence of PhACs as influents and effluents of WWTPs worldwide.

The removal efficiency also changes as a function of the solids retention time (SRT) and hydraulic retention time (HRT), and the tertiary treatment process. The increase of some compounds in the WWTPs effluents can be associated either to analytical deviations and/or cleavage of conjugates (glucuronides, sulfates) of target compounds (Galán et al., 2012). Diversity and size of the microbial community in WWTP are controlled by the sludge retention time. It was observed an increase of PhACs removal with a longer SRT (26d), whereas decreased removal with shorter SRT of 8 d (Lesjean et al., 2004). Hydrophobic compounds can be removed using a high sludge retention time (SRT), it has been reported that with an SRT of at least 10 days there is effective removal (Clara et al., 2005) as well as the transformation of ibuprofen, sulfamethoxazole, acetylsalicylic acid and bezafibrate are achieved which require an SRT of 5 to 15 d (Ternes, 1998). Long SRT promotes the growth of specialized microorganisms, which, although they naturally have a slower growth, are effective in the removal of nitrogen and, therefore, can increase the removal of PhACs. However, in general, WWTPs are not planned to operate with a long enough SRT to satisfy this requirement. Besides that, some pharmaceuticals, for example, carbamazepine, are highly persistent and have been shown to be inert to the biological treatment process (Clara et al., 2005; Clara et al., 2004).

Properties such as acidity and alkalinity of influent of wastewater treatment plants may affect the nature of the pharmaceutical compound in addition to being able to influence the structure and composition of the microbial community acting in the medium and may increase or decrease the activity of the microbial enzymes released in the medium, and therefore the PhACs biodegradation. It has been found that the removal of ionizable compounds such as ibuprofen and sulfamethoxazole is highly dependent on the pH for degradation (Tiwari et al., 2017). In acidic media, these compounds are in a hydrophobic form which turns in greater elimination and therefore a higher efficiency of the process. However, compounds, such as, carbamazepine, that are non-ionizable compounds, the removal is independent of pH (Tadkaew et al., 2010).

In the biological treatment stage of WWTP, the removal of PhACs are also related to sorption to suspended solids (Nghiem et al., 2007). Adsorption is the main mechanism in the removal of micropollutants during primary treatment (Wang et al., 2014) and it is generally in agreement with their hydrophobicity (expressed by the octanol–water partition coefficient K_{ow}). Compounds with low $\log K_{ow}$ values (<3.0), such as carbamazepine (2.25-2.45), metoprolol (1.88), trimethoprim (0.91), sulpiride (1.10), and atenolol (0.16), are not expected to adsorb greatly to the particles, but to dissociate in the aqueous phase (Salgado et al., 2012). Trimethoprim is neither biodegraded nor adsorbed and carbamazepine could be hardly removed regardless of secondary treatment process applied (Wang et al., 2014). Inyang et al. (2016) in their research found that trimethoprim was removed under both anoxic and aerobic conditions and atenolol could be removed in anaerobic, anoxic and aerobic regimes. The EAWAG Biodegradation Biocatalysis Database Prediction Pathway System (EAWAG-BBD PPS) predicts that under aerobic conditions, atenolol can degrade by microbial hydrolysis of its primary amide into carboxylic acid (Radjenovic et al., 2009) proving its high removal in all studied cases (Table 2).

PhACs with $\log K_{ow}$ that varies from 3.0 to 5.9, such as diclofenac (4.51) and naproxen (3.18) corresponded to high and medium adsorption observed and, therefore, more expressive removal rates. This effect could be due to the high biodegradation rates observed for these two compounds. Ibuprofen, however, can be observed to be an exception, that although presents a medium $\log K_{ow}$ value (3.97), low adsorption is observed (Salgado et al., 2012). Under aerobic condition, the metabolization of ibuprofen yields hydroxyibuprofen and carboxy-ibuprofen metabolites (Matamoros et al., 2008), whereas biotransformation of naproxen can yield 2-(6-hyd roxynaphthalen-2-yl) propanoic acid and 1-(6-methoxynaphtha len-2-yl) ethanon as intermediates (Marco-Urrea et al., 2010). Increasing HRT of these compounds by sludge adsorption provides more time for microbial degradation, i.e., micro-pollutant gets degraded either by catabolic microbial enzymes or utilized by microorganisms as a carbon source. On the other hand, hydrophilic micro-pollutants escape from WWTP without biodegradation along with effluent and evades the biodegradation process.

Another feature related to the PhACs removal is associated to volatilization of the compound, which is defined by the Henry law constant (kH). To achieve significant volatilization, it is required kH value > $3x10^{-3}$ mol/(m^3.Pa), however in the case of pharmaceuticals, this value is normally around of kH <10^{-5} (Ternes, 2004). Thus, volatilization of PhACs in a wastewater

treatment plant can be negligible. Photo-degradation of these compounds is also considered insignificant due to the high sludge concentration, which increases the wastewater turbidity and, therefore, blocks the penetration of sunlight in the top layer (Tiwari et al., 2017).

Since WWTPs are not designed to remove PhACs, especially antibiotic, they are known to be the main source of antibiotics and antibiotic-resistance genes for surface waters (Grenni et al., 2018). Thus, more attention has to be paid to the adverse ecological effect caused by their persistence, especially throughout the WWTPs, and potential long-term effects toward the non-target aquatic organisms even at low concentrations.

It is possible to note that, in general, individual concentrations of many PhACs are higher in effluents of WWTPs than concentrations found in surface water. It is attributed to dilution as well as partial remediation by natural pathways like hydrolysis, sorption onto colloids, biodegradation natural attenuation and photolysis (Ke et al., 2012; Ziylan et al., 2011). Due to the majority PhACs' characteristics of being biorefractory, partial transformation by abiotic reactions is more likely to happen (Ganiyu et al., 2015). pH, natural organic matter (NOM) and ionic strength of the receiving media may influence the speciation and concentration level of each PhAC in the environment. Once in the water body, PhACs can take many different pathways. Some PhACs at different pH become charged and can easily absorb onto colloids, trapped by NOM or associated with cations in the water and transferred to sediments (Ke et al., 2012).

In general, the levels of the studied pharmaceutical compounds were also water source dependent, which, in turn, depends on the location, popular habits, wastewater treatment type, PhACs consumption patterns, physicochemical properties and stability as well as the season (Camacho-Muñoz et al., 2014). Rainfall or lack of therefore, might be one of the causes associated with the PhACs fluctuation concentration (Azzouz and Ballesteros, 2013; Chen et al., 2016). Increased flow caused by rainfall might have two different effects on the PhACs concentration influent to WTP. Firstly, they might dilute the PhACs concentrations on rivers bed, resulting in lower removal efficiency by WTP. Secondly it could suspend settled sediments in which pharmaceutical compounds are adsorbed and releasing them into the water stream (Ma et al., 2017). Additionally, after rainfall incidents, surface water could be polluted by WWTP overflows which might increase the PhACs concentration on water sources to WTP (Ma et al., 2017).

Some compounds have higher usage rates during winter months, for example antipyretics such as diclofenac, ibuprofen and naproxen, which are less efficiently removed during wastewater treatment in winter weather. The same can be stated to warmer seasons, where it is possible to note a pick in the consumption of antihistamines, for example, gemfibrozil, salicylic acid and acetaminophen (Camacho-Muñoz et al., 2014; Kostich et al., 2014). Also, on warmer seasons, the microbiological active is higher due to the increase in the temperature (Nelson et al., 2010; Lajeunesse et al., 2012). Other pharmaceuticals, such as antibiotics, antiepileptic or b-blockers are similarly consumed during both seasons, thus it is not observed seasonal pattern (Camacho-Muñoz et al., 2014).

Table 2: Concentrations and removal (%) of selected pharmaceuticals in WWTPs in different countries

PhAC Classes	PhACs	Treatment system	Raw Wastewater (ng/L)	Treated wastewater (ng/L)	Overall removal (%)	Limit Detection (ng/L)	Location / Monitoring Period	Reference
Anti-inflammatory drug	Ibuprofen	Biological nutrient removal (BNR) with an anaerobic configuration (Anaerobic, anoxic, aerobic). SRT of 8 days, and a HRT of 5.5 h	NA	NA	0, 0, >81	10	USA / 2016	Inyang et al., (2016)
		Conventional activated sludge treatment after aerobic and anaerobic digestion. Finally, a tertiary treatment based on UV oxidation.	1983	-	>99	12 - 7.6	Mexico / 2016	Rivera-Jaimes et al., (2018)
		Screen, primary clarifier, anaerobic tank, anoxic tank, anoxic tank, secondary clarifier and UV. HRT 0.9±0.1 days	1057	196	96.4	3	Portugal / 2011	Salgado et al., (2012)
		Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	268.0 ± 25.39	14.6 ± 1.9	94.6	2.5	China / 2012-2013	Yan et al., (2014)

	Naproxen	Conventional activated sludge treatment after aerobic and anaerobic digestion. Finally, a tertiary treatment based on UV oxidation.	2600	260	90	14 - 1.2	Mexico / 2016	Rivera-Jaimes et al., (2018)
		Biological nutrient removal (BNR) with an anaerobic configuration (Anaerobic, anoxic, aerobic). SRT of 8 days, and a HRT of 5.5 h	NA	NA	0, 0, >71	5	USA / 2016	Inyang et al., (2016)
	Diclofenac	Screen, primary clarifier, anaerobic tank, anoxic tank, anoxic tank, secondary clarifier and UV. HRT 0.9±0.1 days	131.61	8.1	94	7	Portugal / 2011	Salgado et al., (2012)
		Urban wastewater, 450,000 PE; Secondary treated effluent, post-chlorination	-	1200	-	5	Australia / 2015	Leusch et al., (2018)
		Urban wastewater, secondary treated effluent, post-chlorination	-	2000	-	5	France / 2015	Leusch et al., (2018)
		Water treatment plant filter backwash water from plant to sludge tank after settling	-	300	-	5	South Africa / 2015	Leusch et al., (2018)
		Urban wastewater, secondary treated effluent, no post-treatment	-	820	-	5	Netherlands / 2015	Leusch et al., (2018)

		Urban wastewater, 875,000 PE. Applies mechanical treatment with additional phosphate precipitation, followed by biological treatment with a denitrification/nitrification unit, equipped with a trickling filter.	-	2400	-	5	Germany / 2015	Leusch et al., (2018)
		Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	601	3.2 ± 0.4	46.8	2.5	China / 2012-2013	Yan et al., (2014)
	Ketoprofen	Screen, primary clarifier, anaerobic tank, anoxic tank, anoxic tank, secondary clarifier and UV. HRT 0.9±0.1 days	11245	146	98.7	21	Portugal / 2011	Salgado et al., (2012)
Analgesic	Acetaminophen	NA	145250	5235	96	0.1-1.5	United Arab Emirates / 2017	Semerjian et al., (2018)
		Primary treatment based on the partial removal of suspended solids and organic matter through coagulation, flocculation and sedimentation	39	30	23	-	Colombia - 2016	Botero-Coy et al., (2016)

		Conventional activated sludge treatment after aerobic and anaerobic digestion. Finally, a tertiary treatment based on UV oxidation.	11600	-	>99	67 - 21	Mexico / 2016	Rivera-Jaimes et al., (2018)
		Conventional activated sludge. SRT 3–5 days	357	7	98	2	Turkey / ND	Komesli et al., (2015)
Antibiotic	Trimethoprim	Biological nutrient removal (BNR) with an anaerobic configuration (Anaerobic, anoxic, aerobic). SRT of 8 days, and a HRT of 5.5 h	NA	NA	7, 17, 99	2.5	USA / 2016	Inyang et al., (2016)
		Conventional activated sludge treatment after aerobic and anaerobic digestion. Finally, a tertiary treatment based on UV oxidation.	145	143	1	7.8 - 1.3	Mexico / 2016	Rivera-Jaimes et al., (2018)
		Screen, primary clarifier, anaerobic tank, anoxic tank, anoxic tank, secondary clarifier and UV. SRT 20 days and HRT 13-15 h	257	186	27.6	2.1	China / 2013	Wang et al., (2014)
		Screen, primary settling, cyclic activated sludge system, disinfection with chlorination.	77.37 ± 22.72	52.6 ± 17.2	32	4	China / 2012-2013	Inyang et al., (2016)

		SRT 21.4 days and HRT 15.8 h days						
	Erythromycin	NA	785	541	31	0.1-1.5	United Arab Emirates / 2017	Semerjian et al., (2018)
		Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	254.24 ± 15.36	153.0 ± 16.5	39.8	2	China / 2012-2013	Yan et al., (2014)
	Clarithromycin	Primary treatment based on the partial removal of suspended solids and organic matter through coagulation, flocculation and sedimentation	0.32	0.31	3	1	Colombia - 2016	Botero-Coy et al., (2016)
	Roxithromycin	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	404.0 ± 34.2	347.5 ± 35.4	14	1	China / 2012-2013	Yan et al., (2014)
	Azithromycin	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	362.5 ± 21.7	81.5 ± 23.8	77.5	1.5	China / 2012-2013	Yan et al., (2014)

	Moxifloxacin	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	19.9 ± 7.4	6.6 ± 0.9	66.8	12.2	China / 2012-2013	Yan et al., (2014)
	Sulfamethoxazale	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	2935.4 ± 327.61	1147.9 ± 65.1	60.9	3	China / 2012-2013	Yan et al., (2014)
		Primary clarifier, aerobic reactor a, secondary clarifier, and tertiary UV treatment	2500	800	68	36	Canada / 2016-2017	Brown and Wong, (2018)
		Conventional activated sludge treatment after aerobic and anaerobic digestion. Finally, a tertiary treatment based on UV oxidation.	1143	730	36	33 - 13	Mexico / 2016	Rivera-Jaimes et al., (2018)
		NA	162	75	54	0.1-1.5	United Arab Emirates / 2017	Semerjian et al., (2018)
		Conventional activated sludge. SRT of approximately 10 days and HRT of 11.5 h.	93	NA	73.8 ±12.7	1.7	Spain / 2009	Radjenovic et al., (2009)

	Sulfadiazine	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	229.9 ± 22.5	155.0 ± 25.6	32.6	15	China / 2012-2013	Yan et al., (2014)
	Sulfamethazine	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	150.2 ± 20.1	39.9 ± 6.5	73.4	7.5	China / 2012-2013	Yan et al., (2014)
	Oflaxacin	NA	846	510	40	0.1-1.5	United Arab Emirates / 2017	Semerjian et al., (2018)
		Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	345.9 ± 59.4	57.9 ± 18.4	82.8	6.4	China / 2012-2013	Yan et al., (2014)
	Norflaxacin	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	203.0 ± 16.1	30.4 ± 3.8	85	17.5	China / 2012-2013	Yan et al., (2014)
	Ampicilin	Screen, primary clarifier, anaerobic tank, anoxic tank,	430	0	100	3	Portugal / 2011	Salgado et al., (2012)

		anoxic tank, secondary clarifier and UV. HRT 0.9±0.1 days						
b-Blockers	Atenolol	Biological nutrient removal (BNR) with an anaerobic configuration (Anaerobic, anoxic, aerobic). SRT of 8 days, and a HRT of 5.5 h	NA	NA	48, 89, 99	10	USA / 2016	Inyang et al., (2016)
		Urban wastewater, 450,000 PE; Secondary treated effluent, post-chlorination	-	1300	-	200	Australia / 2015	Leusch et al., (2018)
		Urban wastewater, secondary treated effluent, post-chlorination	-	720	-	200	France / 2015	Leusch et al., (2018)
		Water treatment plant filter backwash water from plant to sludge tank after settling	-	940	-	200	South Africa / 2015	Leusch et al., (2018)
		Urban wastewater, secondary treated effluent, no post-treatment	-	1000	-	200	Netherlands / 2015	Leusch et al., (2018)
		Urban wastewater, 875,000 PE. Applies mechanical treatment with additional phosphate precipitation, followed by biological treatment with a denitrification/nitrification	-	<200	-	200	Germany / 2015	Leusch et al., (2018)

		unit, equipped with a trickling filter.						
		Screen, primary clarifier, anaerobic tank, anoxic tank, anoxic tank, secondary clarifier and UV. HRT 0.9±0.1 days	5176	NA	100	3	Portugal / 2011	Salgado et al., (2012)
Cardiac	Metoprolol	Screen, primary clarifier, anaerobic tank, anoxic tank, anoxic tank, secondary clarifier and UV. SRT 20 days and HRT 13-15 h	122	126	-3.3	1.2	China / 2013	Wang et al., (2014)
		NA	92	62	33	0.1-1.5	United Arab Emirates / 2017	Semerjian et al., (2018)
		Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	50.2 ± 5.3	64.7 ± 14.8	-28.9	15	China / 2012-2013	Yan et al., (2014)
	Amlodipine	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination.	<MQL	4.9 ± 0.3	-	15	China / 2012-2013	Yan et al., (2014)

		SRT 21.4 days and HRT 15.8 h days						
	Captopril	Screen, primary clarifier, anaerobic tank, anoxic tank, anoxic tank, secondary clarifier and UV. HRT 0.9±0.1 days	4676	0	100	5	Portugal / 2011	Salgado et al., (2012)
Psychiatric	Carbamazepine	Biological nutrient removal (BNR) with an anaerobic configuration (Anaerobic, anoxic, aerobic). SRT of 8 days, and a HRT of 5.5 h	NA	NA	0, 0, 0	5	USA / 2016	Inyang et al., (2016)
		A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	68.2	27.5	59.7	2.5	China / 2014	Wu et al., (2015)
		screen, primary clarifier, anaerobic tank, anoxic tank, oxic tank, secondary clarifier and UV. SRT 20 days and HRT 13-15 h	17	18	-5.9	2.1	China / 2013	Wang et al., (2014)
		Secondary, biological nutrient removal, HRT 23 h and SRT 7.5 days	1032	723	10	0.2	Canada / 2009-2010	Lajeunesse et al., (2012)
		Screen, primary settling, cyclic activated sludge system, disinfection with chlorination.	14.5 ± 5.2	16.5 ± 3.3	-13.8	0.2	China / 2012-2013	Yan et al., (2014)

		SRT 21.4 days and HRT 15.8 h days						
		Conventional activated sludge treatment after aerobic and anaerobic digestion. Finally, a tertiary treatment based on UV oxidation.	90	138	-53	5.5 - 0.7	Mexico / 2016	Rivera-Jaimes et al., (2018)
		Conventional activated sludge. SRT 3–5 days	78	4	94.9	1.5	Turkey / NA	Komesli et al., (2015)
		Conventional activated sludge. SRT of approximately 10 days and HRT of 11.5 h.	156	NA	<10	15.8	Spain / 2009	Radjenovic et al., (2009)
	Fluoxetine	Biological nutrient removal (BNR) with an anaerobic configuration (Anaerobic, anoxic, aerobic). SRT of 8 days, and a HRT of 5.5 h	NA	NA	95, 96, 95	5	USA / 2016	Inyang et al., (2016)
		A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	1.4	1.4	0	10	China / 2014	Wu et al., (2015)
		Screen, primary clarifier, anaerobic tank, anoxic tank, oxic tank, secondary clarifier and UV. HRT 0.9±0.1 days	1310	250	80.9	17	Portugal / 2011	Salgado et al., (2012)

		Secondary, biological nutrient removal, HRT 23 h and SRT 7.5 days	16	8.6	47	0.7	Canada / 2009-2010	Lajeunesse et al., (2012)
	Pipamperone	Conventional activated sludge treatment	25	13.99	44.04	0.05	Belgium / 2009	Van De Steene et al., (2010)
	Mianserin	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	1.2	0.4	66.7	10	China / 2014	Wu et al., (2015)
	Nordiazepam	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	1	1	0	4	China / 2014	Wu et al., (2015)
	Amitriptyline	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	0.9	0.8	11.1	1	China / 2014	Wu et al., (2015)
	Doxepin	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	5.8	3.3	43.1	6	China / 2014	Wu et al., (2015)
	Clorazepate	Screen, primary clarifier, anaerobic tank, anoxic tank, anoxic tank, secondary clarifier and UV. HRT 0.9±0.1 days	507	135	73.2	17	Portugal / 2011	Salgado et al., (2012)
	Diazepam	Urban wastewater, 450,000 PE; Secondary treated effluent, post-chlorination	-	24	-	10	Australia / 2015	Leusch et al., (2018)
		Urban wastewater, secondary treated effluent, post-chlorination	-	<10	-	10	France / 2015	Leusch et al., (2018)

		Water treatment plant filter backwash water from plant to sludge tank after settling	-	<10	-	10	South Africa / 2015	Leusch et al., (2018)
		Urban wastewater, secondary treated effluent, no post-treatment	-	12	-	10	Netherlands / 2015	Leusch et al., (2018)
		Urban wastewater, 875,000 PE. Applies mechanical treatment with additional phosphate precipitation, followed by biological treatment with a denitrification/nitrification unit, equipped with a trickling filter.	-	<10	-	10	Germany / 2015	Leusch et al., (2018)
		A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	5.5	5.1	7.3	6	China / 2014	Wu et al., (2015)
	Oxazepam	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	10.8	6.5	39.8	6	China / 2014	Wu et al., (2015)
	Sulpiride	Screen, primary clarifier, anaerobic tank, anoxic tank, anoxic tank, secondary clarifier and UV. SRT 20 days and HRT 13-15 h	143	168	-17.4825	0.8	China / 2013	Wang et al. (2014)
	Estazolam	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	2.9	1.5	48.3	6	China / 2014	Wu et al., (2015)

	Norfluoxitine	Secondary, biological nutrient removal, HRT 23 h and SRT 7.5 days	10	7.6	24	0.1	Canada / 2009-2010	Lajeunesse et al., (2012)
	Temazepam	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	15	2.5	83.3	5	China / 2014	Wu et al., (2015)
	Alprazolam	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	8.6	6	30.2	7	China / 2014	Wu et al., (2015)
	Bromazepam	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	2.1	17.4	-728.6	2	China / 2014	Wu et al., (2015)
	Lorazepam	A2/O: Anaerobic-Anoxic-Oxic. SRT 12 days	40.7	1.6	96.1	12	China / 2014	Wu et al., (2015)
Hormones	Progesterone	Conventional activated sludge. SRT 3–5 days	9	4	55.6	5	Turkey / NA	Komesli et al., (2015)
	Estrone	Conventional activated sludge. SRT 3–5 days	27	7	74.1	5	Turkey / NA	Komesli et al., (2015)
Lipid regulator and metabolite	Bezafibrate	Conventional activated sludge treatment after aerobic and anaerobic digestion. Finally, a tertiary treatment based on UV oxidation.	3105	748	76	4.9 - 0.2	Mexico / 2016	Rivera-Jaimes et al., (2018)
		Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	125 ± 18.76	69.2 ± 20.0	84	12.5	China / 2012-2013	Yan et al., (2014)

	Gemfibrozil	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h	14.5 ± 2.5	2.9 ± 0.3	80	2	China / 2012-2013	Yan et al., (2014)
		Conventional activated sludge treatment after aerobic and anaerobic digestion. Finally, a tertiary treatment based on UV oxidation.	178	255	-43	11 - 6.7	Mexico / 2016	Rivera-Jaimes et al., (2018)
		Pre-treatment (settling in a primary clarifier), preliminary treatment, primary sedimentation. SRT 10 days and HRT 11.5 h unit and a secondary (biological) treatment.	2000–5900	-	0	11.5	Spain / 2007	Radjenovic et al., (2009)
	Sivastatin	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	117.5 ± 16.0	19.8 ± 10.0	83.1	15	China / 2012-2013	Yan et al., (2014)
	Atorvastatin	Screen, primary settling, cyclic activated sludge system, disinfection with chlorination. SRT 21.4 days and HRT 15.8 h days	1.5 ± 0.5	0.5	66.7	1.15	China / 2012-2013	Yan et al., (2014)

antidopaminergic	Domperidone	Conventional activated sludge treatment	37.9	15.7	58.5751979	<0.05	Belgium / 2009	Van De Steene et al., (2010)

NA – Not available

Nelson et al. (2010) assessed the distribution of PhACs concentration during the days. It was found that some compounds have broad increase/decrease in concentration over 6-15 h, such as erythromycin, azithromycin, atenolol, propranolol and gemfibrozil. The highest concentrations generally occur between 4 and 7 pm and lowest concentrations seem to occur between 8 and 11 a.m. Gemfibrozil seems to have a bimodal cycle similar to naproxen. Other compounds such as carbamazepine, primidone, fluoxetine, metoprolol, triclocarban, and phenytoin don't show any variation in their concentration along the day. Some compounds appear to have daily minima during 10-11:30 a.m. This behaviour is possible to be explained by taking into consideration that both consumption and excretion patterns of the studied population. PhACs are usually administered every 8 or 12 h, and the last intake of the day is usually at night. During the night, these compounds are accumulated in urine and faeces and are released along with the first toilet flush of the morning (Coutu et al., 2013).

Also, from Table 2, it is possible to observe that some compounds found all around the world are also listed on the watch list of EU (2018), for instance, macrolide antibiotics such as erythromycin, clarithromycin and estrone, also carbamazepine, atenolol, ibuprofen, bezafibrate, gemfizobril, sulfamethoxazole, and naproxen are classified as Class I (high priority) in Global Water Research Coalition (GWRC) (2008). This rise attention to the possibility of consumption increase and, therefore, the release in the environment of these compounds as well as their potential threat to the environment and public health. More toxicity data should be raised in order to determine the effects of these PhACs, not only in target organisms but also in non-target populations, as well as their effects as a mixture.

5. The current panorama of PhACs on drinking water

When public health is concern, drinking water treatment plants (WTP) may impose another barrier that can prevent the return of these PhACs to human body. Many studies have been carried out in order to detect PhACs in conventional WTP (Table 3). However, the conventional treatment plants that consist in coagulation, flocculation and filtration followed by a kind of disinfection, such as chlorination and ozonation, have poor removal efficiencies, especially the steps of coagulation, flocculation and sand filtration (Huerta-Fontela et al., 2011; Simazaki et al., 2015).

Prechlorinaton is found to be very efficient in removal some PhACs due to the high reactivity of chlorine with primary and secondary amines (Chamberlain et al., 2006; Westerhoff et al., 2005). According to Huerta-Fontela et al. (2011) the efficiency of the prechlorination is pH dependent, achieving higher removal at lower pHs when applied for carbamazepine, also, the same study suggests that the absence of the imidazole moiety contributed to the deactivation of the aromatic ring to the chlorine reaction when analysing the angiotensin agents' behaviour. The presence of a bromide instead of chlorine in one of the aromatic rings and the substitution of a benzene ring by a pyridine one block the reactivity of this compound through chlorine attack (Kim et al., 2007). However, the application of chlorine has no efficiency in the removal of β-blockers (Huerta-Fontela et al., 2011).

According to Stackelberg et al. (2007) the process of clarification (which consists of coagulation, flocculation, sedimentation and filtration) is generally not a primary route by which PhACs in filtered-water samples are degraded or removed mostly due to the intrinsic characteristics of the compounds. The application of ferric chloride coagulation may result in base or acid hydrolysis, however the low concentration of PhACs in superficial water and the hydrophobic behaviour of some PhACs with log K_{ow} >3.0, may explain the lower removal of PhACs through this process which could indicate removal by partitioning. Some, such as sulfamethoxazole or acetaminophen compounds can occur hydrolysis during coagulation step (Stackelberg et al., 2007).

Sand filtration is based on the sieving and, in less proportion, adsorption processes, and since PhACs have a molecular weight ranging from 100 to 800 KDa, these processes is not efficient in removing the target compounds.

Gemfibrozil, diclofenac, naproxen, propranolol, atenolol, carbamazepine, iopamidol and fenofibrate were the major compounds detected in WTP effluents (Simazaki et al., 2015; Boleda et al., 2011; Kleywegt et al., 2011; Vulliet et al., 2011). These compounds are characterized by low K_{ow} and carbamazepine is also found to be persistent throughout physic-chemical treatment. This compound is considered to be a trace of human presence (Clara et al., 2004; Nghiem et al., 2007; Wang et al., 2014).

In general, most of the PhACs removal would be dependent on chemical oxidation by chlorination and/or ozonation, adsorptive process by granular activated carbon (GAC), and membrane filtration employed at each WTP. The removal ratios of several pharmaceuticals

(i.e., ibuprofen, and fenofibrate) ranged from 10% and 80%. Ibuprofen could also be removed moderately by ozonation and activated carbon adsorption. According to Huber et al. (2003), ibuprofen was considered slow-reacting pharmaceutical during conventional ozonation and, in contrast, carbamazepine and sulfamethoxazole were considered fast-reacting pharmaceuticals, being in accordance with the results found in survey realised by Huerta-Fontela et al. (2011).

Fenofibrate, that has high hydrophobic property (log K_{ow} 5.28) and exists as neutral molecular at pH 7.0, is expected to be efficiently removed by activated carbon filtration, however, it was observed a removal of approximately 9% (Table 3); this may be due to the competition of adsorption on activated sites of GAC (Simazaki et al., 20115).

It is possible to observe a negative removal efficiency when progesterone and testosterone are concerned (Table 3). It may be due to a gap in the actual hydraulic retention time (HRT) at each WTP and estimated HRT to set sampling schedule of its source water and finished water.

Advanced treatment technologies, such as ozonation, activated carbon adsorption, and reverse osmosis (RO), are applicable to PhACs removal in WTPs (Huerta-Fontela et al., 2011; Mestankova et al., 2012; Kimura et al., 2003; Xu et al., 2016; Nguyen et al., 2013).

Ozonation is able to remove a large spectrum of contaminants found in raw waters. Although studies have demonstrated that the primary attack by ozone is sufficient to reduce specific effects, such as endocrine disruption (Huber et al., 2003), antibacterial (Dodd et al., 2006) and antiviral activity (Mestankova et al., 2012), during ozonation, a mineralization of PhACs is typically not achieved and compounds are only transformed (Hübner et al., 2015). Despite the general removal of specific effects by ozonation there is a concern about the unspecific toxicity of the mostly unknown transformation products, which rises up possible problems with the application of ozone and the consequences to human health.

Granular active carbon (GAC) filtration is also efficient to remove compounds with high hydrophobic properties (Huerta-Fontela et al., 2011).

Reverse osmosis is recognized as an effective and reliable form of being applied, mainly, in the treatment of supply water either as a polishing step or in raw water purification (Yangali-Quintanilla et al., 2010; Sadmani et al., 2014). Studies indicate that electrostatic exclusion is the predominant phenomenon in the rejection process of these membranes and, therefore, effective rejections of negative pharmaceutical compounds were observed, exceeding 95% by

RO membranes (Kimura et al., 2003; Xu et al., 2016; Nguyen et al., 2013). The results of a study on the removal of hormones and pharmaceuticals in treated wastewater indicated that treatments using ozonation, microfiltration and nanofiltration were partially effective, while the treatment with RO was the most successful in the removal of target compounds (Khan et al., 2004). Ozaki and Li (2002) investigated the rejection of various products, among them the PhACs by polyamide NF and RO membranes, and observed that the rejection of organic compounds by ultra low pressure RO (ULPRO) increased linearly with molecular weight and molecular weight of the evaluated compound.

Table 3: Concentrations and removal (%) of selected pharmaceuticals in conventional WTPs in different countries

PhAC Classes	PhACs	Treatment system	Raw Water (ng/L)	Treated Water (ng/L)	Overall removal (%)	Limit Detection (ng/L)	Location / Monitoring Period	Reference
Anti-inflammatory drug	Indomethacin	Conventional chemical coagulation, sedimentation, and rapid sand filtration	2.5	ND	>99	1.7	Japan / 2006-2019	Simazaki et al., (2015)
		Preoxidation with chlorine followed by coagulation/flocculation, sedimentation, filtration and post-chlorination	36	-	>99	10	Portugal / 2013	Gaffiney et al., (2015)
		NA	3	4	>99	1.3	Spain / 2012	Carmona et al., (2014)
	Ibuprofen	NA	830	39	95.3	5	Spain / 2012	Carmona et al., (2014)
		Preoxidation, coagulation, sedimentation, filtration in anthracite–sand media, disinfection with sodium hypochlorite	314 (257–357)	0.5 (0.4–0.6)	90.2	0.01	Spain / 2012	Azzouz and Ballestero, (2013)
		Coagulation, flocculation, sedimentation, filtration in sand, ozonation and chloration	6.6	1.3	80.3	7	France / 2007-2008	Vulliet et al., (2011)

		Filtration followed by disinfection	0.06	ND	-	0.5	Canada / NA	Kleywegt et al., (2011)
		Disinfection	16.6	8.8	47	1	US / NA	Wang et al., (2011)
	Diclofenac	Dioxychlorination, coagulation, flocculation, settling, sand filtration and groundwater dilution to improve raw water quality. Ozonation and granular activated carbon (GAC) filtration	175-292	ND	>99	3	Spain / 2010	Boleda et al., (2011)
		-	50.6	-	-	0.29	England / '-	Wilkinson et al., (2017)
		NA	49	18	63.3	1	Spain / 2012	Carmona et al., (2014)
		-	15.49	-	-	25	Malaysia / -	Praveena et al., (2018)
		NA	-	-	-	8	Brazil / 2010-2011	Caldas et al., (2013)
		Preoxidation, coagulation, sedimentation, filtration in anthracite–sand media, disinfection with sodium hypochlorite	259 (210–316)	<0.10	>99	0.02	Spain / 2012	Azzouz and Ballestero, (2013)
		Coagulation, flocculation, sedimentation, filtration in sand, ozonation and chloration	1.8	ND	>99	1	France / 2007-2008	Vulliet et al., (2011)
	Nimesulide	NA	12	-	>99	4	Brazil / 2010-2011	Caldas et al., (2013)

	Naproxen	Dioxychlorination, coagulation, flocculation, settling, sand filtration and groundwater dilution to improve raw water quality. Ozonation and granular activated carbon (GAC) filtration	99-152	ND	>99	6	Spain / 2010	Boleda et al., (2011)
		NA	278	11	96	0.5	Spain / 2012	Carmona et al., (2014)
		Preoxidation, coagulation, sedimentation, filtration in anthracite–sand media, disinfection with sodium hypochlorite	164 (71–321)	<0.06	>99	0.02	Spain / 2012	Azzouz and Ballestero, (2013)
		Coagulation, flocculation, sedimentation, filtration in sand, ozonation and chloration	3.1	ND	>99	4	France / 2007-2008	Vulliet et al., (2011)
Analgesic	Acethaminophen	Preoxidation, coagulation, sedimentation, filtration in anthracite–sand media disinfection with sodium hypochlorite	75 (55–110)	<0.03	>99	0.01	Spain / 2012	Azzouz and Ballestero, (2013)
		-	21.9	-	-	0.28	England / '-	Wilkinson et al., (2017)

		Coagulation, flocculation, sedimentation, filtration in sand, ozonation and chloration	71	ND	>99	2	France / 2007-2008	Vulliet et al., (2011)
Antibiotic	Sulfamethoxazole	Conventional chemical coagulation, sedimentation, and rapid sand filtration	4.4	ND	>99	0.9	Japan / 2006-2002	Simazaki et al., (2015)
		-	114.24	-	-	25	Malaysia / -	Praveena et al., (2018)
		Dioxychlorination, coagulation, flocculation, settling, sand filtration and groundwater dilution to improve raw water quality. Ozonation and granular activated carbon (GAC) filtration	57–149	ND	>99	1	Spain / 2010	Boleda et al., (2011)
		Coagulation, flocculation, sedimentation, filtration in sand, ozonation and chloration	4	ND	>99	0.5	France / 2007-2008	Vulliet et al., (2011)
		Filtration followed by disinfection	0.98	0.33	66.3	2	Canada / NA	Kleywegt et al., (2011)
		Filter treatment system	0.87	0.37	57.5	0.32	US / 2012	Subedi et al., (2015)
		Preozonation, coagulation, sedimentation, sand filtration, ozonation and GAC filtration	87-35.4	5.4-ND	>93.8	1.1	China / NA	Lin et al., (2016)

	Sulfadimethoxine	Dioxychlorination, coagulation, flocculation, settling, sand filtration and groundwater dilution to improve raw water quality. Ozonation and granular activated carbon (GAC) filtration	ND-8.3	ND	>99	0.8	Spain / 2010	Boleda et al., (2011)
	Clarithromycin	Dioxychlorination, coagulation, flocculation, settling, sand filtration and groundwater dilution to improve raw water quality. Ozonation and granular activated carbon (GAC) filtration	40.1–54.4	ND	>99	0.2	Spain / 2010	Boleda et al., (2011)
		Preozonation, coagulation, sedimentation, sand filtration, ozonation and GAC filtration	ND-1.5	ND-1.8	>90	0.3	China / NA	Lin et al., (2016)
	Erythromycin	Dioxychlorination, coagulation, flocculation, settling, sand filtration and groundwater dilution to improve raw water quality. Ozonation and granular activated carbon (GAC) filtration	21-33	0.8-1.4	95	0.2	Spain / 2010	Boleda et al., (2011)
		Preoxidation with chlorine followed by coagulation/flocculation,	3200	200	99.4	150	Portugal / 2013	Gaffiney et al., (2015)

		sedimentation, filtration and post-chlorination						
		Filtration followed by disinfection	0.4	0.03	92.5	10	Canada / NA	Kleywegt et al., (2011)
	Trimethoprim	Dioxychlorination, coagulation, flocculation, settling, sand filtration and groundwater dilution to improve raw water quality. Ozonation and granular activated carbon (GAC) filtration	9.5-22.8	ND	>99	0.9	Spain / 2010	Boleda et al., (2011)
		Filtration followed by disinfection	0.4	ND	-	1	Canada / NA	Kleywegt et al., (2011)
		Disinfection	4.6	ND	>99	0.3	US / NA	Wang et al., (2011)
		Preozonation, coagulation, sedimentation, sand filtration, ozonation and GAC filtration	17-4.1	3.7-ND	>78.2	0.6	China / NA	Lin et al., (2016)
b-Blockers	Acebutolol	Prechlorination followed by coagulation, flocculation and sand filtration	44	36	18.2	0.01	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Atenolol	Prechlorination followed by coagulation, flocculation and sand filtration	470	380	19.1	5	Spain / 2008-2009	Huerta-Fontela et al., (2011)

		Coagulation, flocculation, sedimentation, filtration in sand, ozonation and chloration	10.9	0.4	96.3	1	France / 2007-2008	Vulliet et al., (2011)
		Filter treatment system	6.7	3.6	46.3	0.4	US / 2012	Subedi et al., (2015)
	Propanolol	Prechlorination followed by coagulation, flocculation and sand filtration	54	26	51.9	1.1	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Sotalol	Prechlorination followed by coagulation, flocculation and sand filtration	100	53	47	0.1	Spain / 2008-2009	Huerta-Fontela et al., (2011)
Cardiac	Amlodipine	Prechlorination followed by coagulation, flocculation and sand filtration	1	ND	>99	0.01	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Clopidogrel	Prechlorination followed by coagulation, flocculation and sand filtration	2	ND	>99	0.15	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Diltiazem	Prechlorination followed by coagulation, flocculation and sand filtration	4	2	50	0.8	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Furosemide	Prechlorination followed by coagulation, flocculation and sand filtration	22	ND	>99	9	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Hydrochlorthiazide	Prechlorination followed by coagulation, flocculation and sand filtration	670	74	89	1	Spain / 2008-2009	Huerta-Fontela et al., (2011)

	Warfarin	Prechlorination followed by coagulation, flocculation and sand filtration	1	0.2	80	0.1	Spain / 2008-2009	Huerta-Fontela et al., (2011)
		NA	1	ND	>99	0.3	Spain / 2012	Carmona et al., (2014)
Psychiatric	Bromazepam	Prechlorination followed by coagulation, flocculation and sand filtration	7	ND	>99	5	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Carbamazepine	Conventional chemical coagulation, sedimentation, and rapid sand filtration	1.8	ND	>99	0.4	Japan / 2006-2009	Simazaki et al., (2015)
		NA	25.3	ND	>99	2.3	China / 2014	Wu et al., (2015)
		Prechlorination followed by coagulation, flocculation and sand filtration	13	ND	>99	1.1	Spain / 2008-2009	Huerta-Fontela et al., (2011)
		Preoxidation, coagulation, sedimentation, filtration in anthracite–sand media, disinfection with sodium hypochlorite	186 (144–215)	40.4	75.5	0.01	Spain / 2012	Azzouz and Ballestero, (2013)

		Chlorinated drinking water, sourced from a protected surface water catchment	-	<0.3	-	0.25	Australia / 2015	Leusch et al., (2018)
		10 DW France Chlorinated drinking water, sourced from a protected surface water catchment November 2015	-	<0.3	-	0.25	France / 2015	Leusch et al., (2018)
		Dam water treated by dosing with lime and flocculant, flocculation, air floatation & sand filtration simultaneously, granular activated carbon, chlorination	-	<0.3	-	0.25	South Africa / 2015	Leusch et al., (2018)
		18 DW Netherlands Non-chlorinated drinking water, sourced from open surface water November 2015	-	<0.3	-	0.25	Netherlands / 2015	Leusch et al., (2018)
		Groundwater treated by aeration for iron and manganese removal	-	<0.3	-	0.25	Germany / 2015	Leusch et al., (2018)
		Preoxidation with chlorine followed by coagulation/flocculation, sedimentation, filtration and post-chlorination	20	13	65	8	Portugal / 2013	Gaffiney et al., (2015)
		Filtration followed by disinfection	3	0.21	93	1	Canada / NA	Kleywegt et al., (2011)

		Disinfection	8.4	2.2	73.8	0.5	US / NA	Wang et al., (2011)
		Filter treatment system	0.1	ND	>99	0.03	US / 2012	Subedi et al., (2015)
		Preozonation, coagulation, sedimentation, sand filtration, ozonation and GAC filtration	0.5-1.01	ND-0.65	>35.6	0.2	China / NA	Lin et al., (2016)
	Carbamaz epoxide	Prechlorination followed by coagulation, flocculation and sand filtration	54	7	87	0.01	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Chlordiazepoxide	Prechlorination followed by coagulation, flocculation and sand filtration	54	35	35.2	1.2	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Chlorpromazine	Prechlorination followed by coagulation, flocculation and sand filtration	5	1	80	1.1	Spain / 2008-2009 Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Desmethylvenlafaxine	Prechlorination followed by coagulation, flocculation and sand filtration	5	4	20	0.02	Spain / 2007-2008	Huerta-Fontela et al., (2011)
	Oxazepam	NA	<40	<LQO	>99	40	Germany / 2011	Hass et al., (2012)
	Diazepam	Prechlorination followed by coagulation, flocculation and sand filtration	12	4	66.7	0.4	Spain / 2008-2009	Huerta-Fontela et al., (2011)
		Chlorinated drinking water, sourced from a protected surface water catchment	-	<0.5	-	0.25	Australia / 2015	Leusch et al., (2018)

		10 DW France Chlorinated drinking water, sourced from a protected surface water catchment November 2015	-	<0.5	-	0.25	France / 2015	Leusch et al., (2018)
		Dam water treated by dosing with lime and flocculant, flocculation, air floatation & sand filtration simultaneously, granular activated carbon, chlorination	-	<0.5	-	0.25	South Africa / 2015	Leusch et al., (2018)
		18 DW Netherlands Non-chlorinated drinking water, sourced from open surface water November 2015	-	<0.5	-	0.25	Netherlands / 2015	Leusch et al., (2018)
		Groundwater treated by aeration for iron and manganese removal	-	<0.5	-	0.25	Germany / 2015	Leusch et al., (2018)
		NA	24.3	1.9	92.2	0.1	China / 2014	Wu et al., (2015)
Hormones	Estrone	Prechlorination followed by coagulation, flocculation and sand filtration	0.3	ND	>99	0.2	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Estriol	Prechlorination followed by coagulation, flocculation and sand filtration	26	ND	>99	4.7	Spain / 2008-2009	Huerta-Fontela et al., (2011)
	Ethinyl estradiol	Prechlorination followed by coagulation, flocculation and sand filtration	2.5	NA	>99	0.2	Spain / 2008-2009	Huerta-Fontela et al., (2011)

		-	0.23	-	-	0.98	England / '-	Wilkinson et al., (2017)
		Preoxidation, coagulation, sedimentation, filtration in anthracite–sand media, disinfection with sodium hypochlorite	44 (10–97)	<0.20	>99	0.06	Spain / 2012	Azzouz and Ballestero, (2013)
	Progesterone	Coagulation, floculation, sedimentation, filtration in sand, ozonation and chloration	1.7	2.4	-41.2	0.02	France 2007-2008	Vulliet et al., (2011)
	Testosterone	Coagulation, floculation, sedimentation, filtration in sand, ozonation and chloration	2.8	5.9	-110.7	0.02	France / 2007-2009	Vulliet et al., (2011)
	Tamoxifen	Prechlorination followed by coagulation, flocculation and sand filtration	0.1	NA	>99	0.01	Spain / 2008-2009	Huerta-Fontela et al., (2011)
Lipid regulator and metabolite	Fenofibrate	Conventional chemical coagulation, sedimentation, and rapid sand filtration	23	21	8.7	0.2	Japan / 2006-2009	Simazaki et al., (2015)
	Gemfibrozil	Dioxychlorination, coagulation, flocculation, settling, sand filtration and groundwater dilution to improve raw water quality. Ozonation and granular activated carbon (GAC) filtration	187-326	ND	>99	2	Spain / 2010	Boleda et al., (2011)
		NA	77	2	97.4	0.3	Spain / 2012	Carmona et al., (2014)

		Filtration followed by disinfection	0.2	ND	-	1	Canda / NA	Kleywegt et al., (2011)
	Bezafibrate	Coagulation, flocculation, sedimentation, filtration in sand, ozonation and chloration	1.9	ND	>99	1	France / 2007-2008	Vulliet et al., (2011)
		Filtration followed by disinfection	0.7	0.5	28.6	0.5	Canda / NA	Kleywegt et al., (2011)

NA – Not available

ND – Not detected by the analytical method

From Table 3, it is possible to note that, as well as for the wastewater panorama, many compounds that are listed in the watch list of EU (2018) are found in the water surface, as well as in drinking water, for instance, macrolide antibiotics such as erythromycin and clarithromycin, estrone and ethinylestradiol, which confirms the necessity of increasing the efforts in order to monitor water sources and drinking water all around the world. Also, since the consumption of PhAC tends to increase throughout the time, more emphasis should be paid to non-detected or not studied PhACs as well as to developing countries, in order to fill the gaps about occurrence of PhACs in the environment, drinking water and wastewater.

A risk assessment was conducted with the concentration values of PhACs in the raw and treated water observed in Table 3. For this purpose, the Benchmark Quotient (BQ) was calculated as the ratio between the mean or maximum drinking water concentration and the drinking water guidelines values (Drinking water equivalent level - DWEL) for the compounds for which the values were available in the literature. The DWEL values were calculated by using equation 1.

$$DWEL = \frac{TDI\ x\ M\ x\ f}{V} \quad (1)$$

Where TDI , M, F and V are Tolerable Daily Intake (µg/kg bw/day) (values available in Supplementary Material), body weight (considered to be 60 kg), drinking water allocation (adopted value of 0.2) and personal drinking water consumption (2 L/day).

A BQ value of 1 represents a (drinking) water concentration equal to the guideline value (DWEL). A BQ value of ≥1 in drinking water may thus be of potential human health concern if the water were to be consumed over a lifetime period. Compounds with a BQ value ≥0.1 in drinking water require further investigation of the risk imposed. For compounds detected in raw water, surface water and groundwater, drinking water treatment may provide additional safety. For these substances it was presumed that a BQ of ≤0.2 presents absence of appreciable concern for a risk to human health (Schriks et al., 2010).

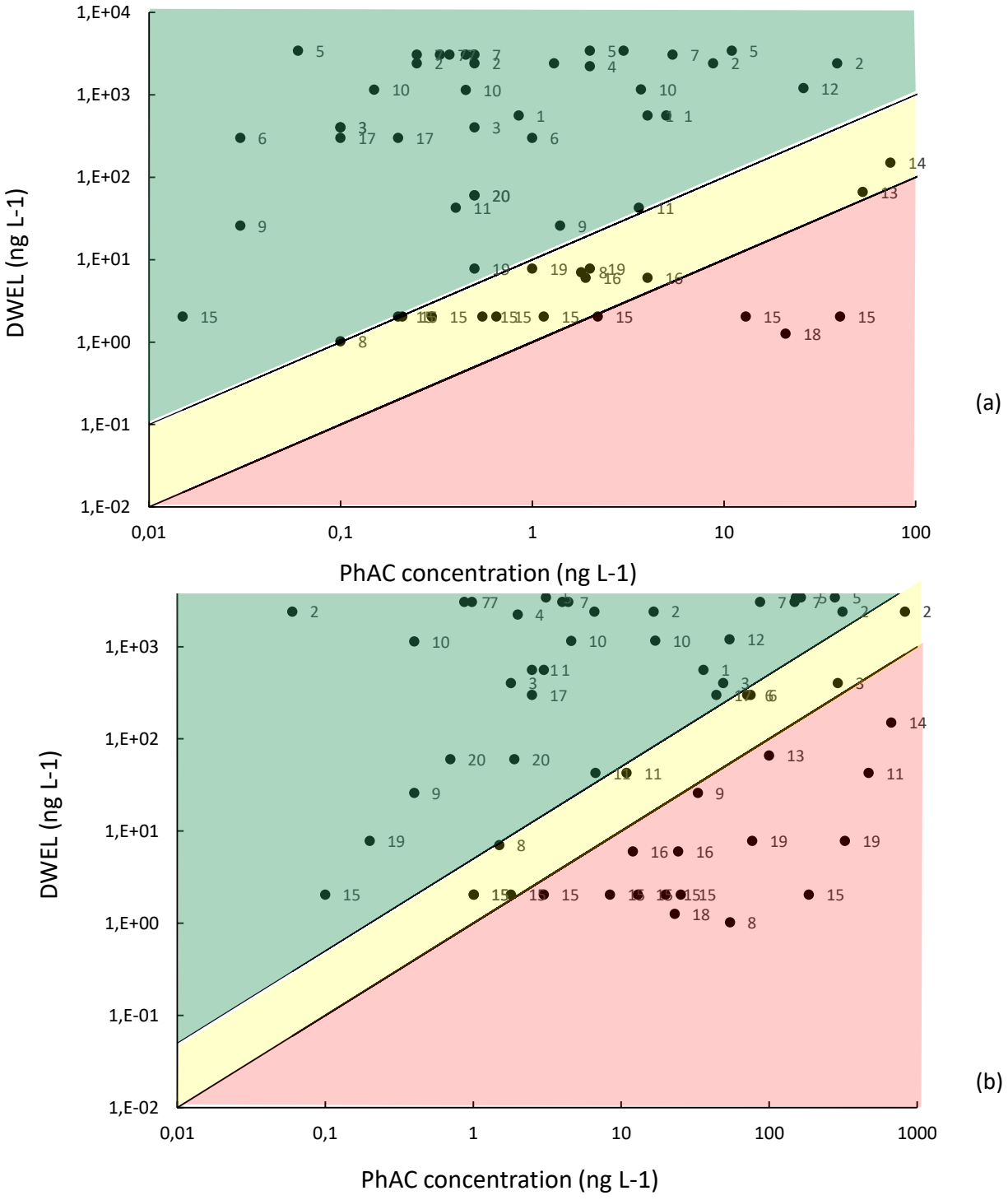
In Figure 2, the concentrations reported for drinking water (Figure 2a) and raw water (Figure 2b) are compared with DWEL. Figure 2 shows that, for most substances, BQ values are ≤0.1 or ≤0.2 for drinking raw water, respectively, representing no significant risk to human health. In the range that needs further investigation, it is possible to observe carbamazepine, diazepam, hydrochlorothiazide, clarithromycin, sotalol and gemfizobril, raising attention to the presence of these compounds in the drinking water. Also, of these compounds only clarithromycin is listed in the watch list of EU (2018) and carbamazepine and gemfizobril are listed in the GWRC

(2008) as class I (high priority) bringing special attention to explore the human exposure to these PhACs. In drinking water, three compounds were detected with a BQ ≥ 1: fenofibrate, carbamazepine and atenolol. All of the three compounds are listed as Class I in the GWRC (2008), also, their high concentration in drinking water and the inefficiency of WTP in reducing their concentrations and, therefore, risks in different parts of the globe, draws attention to the necessity of removing these PhACs and produce safer drinking water.

Also, it is possible to observe the presence of these compounds in the wastewater effluent in high concentration (Table 3), specially carbamazepine which is not considered as a highly persistent compounds and have been shown to be inert to the biological treatment process (Clara et al., 2004; Clara et al., 2005). Studies from Turkey, Mexico, Canada and 2 from China have found either carbamazepine or carbamazepine and gemfizobril in the WWTP effluent, as well as diazepam, atenolol, sulfamethoxazole, clarithromycin and erythromycin, this also brings attention to the necessity of an application of an advanced treatment for wastewater in order to reduce the possible risks associated to the higher concentrations raw surface water.

For 18 of the 38 PhACs assessed in this study, the health risk assessment for drinking water could not be carried out as toxicity data or potable water concentrations were missing. Most of these PhACs are from psychiatric, cardiac and hormones classes raising attention to the necessity of more studies focusing on the determination of guide line values for drinking water of these compounds.

Figure 2 - Comparison of reported concentrations in drinking water (a) and raw water (b) to drinking water guideline values (Drinking Water Equivalent Levels – DWEL). A BQ ≤0.1 or ≤0.2 for drinking water and wastewater respectively (indicating no potential risk to human health at lifetime consumption) is calculated for PhACs above the continuous line (green area), and a value 0.1 or 0.2 for drinking water and wastewater respectively <BQ ≥ 1 (warranting further investigation – yellow area). BQ≥1 (indicating potential human health risk – red area). Numbers corresponding to substances concentration in water and DWEL are presented in Table 3 and supplementary material, respectively.



1 - indomethacin; 2 - ibuprofen; 3 - diclofenac; 4 - nimesulide; 5 - Naproxen; 6 - acetaminophen; 7 - sulfamethoxazole; 8 - clarithromycin; 9 - trimethoprim; 10 - atenolol; 11 - propranolol; 12 - sotalol;14 -

hydrochlorothiazide; 15 - carbamazepine; 16 - diazepam; 17 - Ethinylestradiol; 18 - fenofibrate; 19 - gemfibrozil; 20 – bezafibrate

6. Future Perspectives

There are thousands of pharmaceuticals in the market that can go to the environment, but less than 2% of them have been detected and investigated for treatment (Simazaki et al., 2015). Therefore, more efforts are needed to work on detection, toxicities, persistence and priorities of other compounds. Furthermore, close attention has to be paid to the sensitive/vulnerable subpopulations (e.g., pregnant women), since these groups are not contemplated in the researches found in the literature. Also, it should be noted that the majority of the surveys are realised with target pharmaceuticals alone, which may not represent the real hazard to human health, since there is a mixture of many different PhACs in the drinking water supplies. Effects of chronic, low-level exposure to pharmaceutical, including exposure of sensitive subpopulations in a life time of consumption, should also be assessed.

Considering the difficulty in predicting the real and the full effects and risks of those trace organic substances impose either to human health or to wild life, as well as their consumption increasing trend and therefore release in the environment, the removal of these compounds of the wastewater and drinking water is paramount. Thus, due to the failure of the current WWTP and WTP in removing PhACs mainly due to the low concentration, many studies have focused on the application of advanced water treatment processes such as membrane separation processes (Garcia-Ivars et al., 2017; Nguyen et al., 2013; Hübner et al., 2015; Sadmani et al., 2014; Park et al., 2017) in order to produce water with enough quality to protect human health and wild life.

Membrane separation processes (MSP) including nanofiltration (NF) and reverse osmosis (RO) have become an important alternative to produce good quality water reaching the drinking water standards due to their higher removal rate of low molecular weight organic pollutants, minimizing the risk associated to the source and its contaminants as well as its modularity and ability to integrate with other systems. To increase its efficiency and to reduce problems with fouling, it is possible to integrate membrane systems using low pressure driven membranes such as ultrafiltration (UF) and microfiltration (MF) with NF/RO membranes.

7. Conclusion

Pharmaceutically active compounds are a real threat around the world and the increasing tendency in the consumption and, therefore, the realise of these compounds in the environment, raises a global warning, since the acute and chronical effects are still not clear.

The chemical stability associated with a low concentration of PhACs, makes conventional water and wastewater treatment not efficient processes in removing these kinds of micropollutants, what turns out to be released in the environment. Biodegradation, adsorption and chlorination are the processes associated with the highest removal of PhACs. The existence of these compounds in the domestic wastewater as well as in the superficial and ground water are linked to the location, season and populational habits.

More attention should be paid to developing countries in order to assess the real risks due to PhACs in the environment, especially due to lack of sanitation and trends of consumption increase of these compounds. Also, more efforts should be given in order to determine all the range of PhACs in the environment as well as their respective drinking water guideline value.

Although conventional drinking water treatment were able to reduce the risks associated to the PhACs in the water, carbamazepine, diazepam and genfizobril were still found with high risks associated to human health, which brings attention to the development of safer techniques for drinking water production.

More studies are still needed on the detection toxicities, persistence and priorities of other compounds specially in order to give background and subsidize decision making.

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Appendix 02

Occurrence and risk assessment of pharmaceutically active compounds in water supply systems in Brazil

Amanda Vitória Santos[a*], Carolina Fonseca Couto[a], Míriam Cristina Santos Amaral[a], Liséte Celina Lange[a], Laura Hamdan de Andrade[b], Lucilaine Valeria de Souza Santos[a,b], Ana Flávia Souza Foureaux[a], Eduarda Oliveira Reis[a], Yuri Abner Rocha Lebron[a,b], Victor Rezende Moreira[a,b]

[a]Department of Sanitary and Environmental Engineering, Federal University of Minas Gerais, P.O. Box 1294, 31.270-901, Belo Horizonte, MG, Brazil.

[b]Department of Chemical Engineering, Pontifical Catholic University of Minas Gerais, P.O. Box 1.686, 30535-901, Belo Horizonte, MG, Brazil.

Corresponding author: Telephone: +55(31)985731303; email: amandasantosenq@outlook.com

Abstract: The presence of pharmaceutically active compounds (PhACs) in water supply systems has generated a great concern. Aiming to understand the factors that influence its occurrence, the mechanisms that define its removal in conventional drinking water treatment plants (DWTP), and to assess the environmental and human health risks owing to its presence in natural waters, 80 PhACs in four Brazilian water sources were monitored in this study. Three water sources corresponded to large cities of three distinct regions and the fourth represented a medium-sized city without sewage coverage. Trace levels of pharmaceuticals were detected in superficial and drinking water in all the assessed water sources. The presence and concentration of PhACs were dependent on seasons and population habits. Betamethasone, prednisone, and fluconazole were the most common PhACs in all sources. Less than 1% of the evaluated PhACs were non-toxic to any trophic level and approximately 60% were highly toxic to at least one. Both raw and treated water from the four water sources were subject to toxicological risk at some level owing to at least one drug. The PhACs related to the highest toxicological risks to raw water were loratadine, atorvastatin, and norfloxacin. Atorvastatin presented a margin of exposure (MOE) ≤ 100 in treated water, indicating a significant risk for public health. DWTP capacity to remove PhACs and reduce toxicological risk is only partial, so drinking water is still contaminated by PhACs and poses toxicological risk both to the environment and human health.

Keywords: Pharmaceutically active compounds; Risk assessment; Drinking water treatment; Pharmaceutical removal.

1. Introduction

Pharmaceutically active compounds (PhACs) have been detected in the surface, ground, and drinking water and wastewater in many different places globally in concentrations ranging from ng/L to µg/L (SARMAH *et al.*, 2006; KÜMMERER, 2009; WATKINSON *et al.*, 2009; SARAVANAN *et al.*, 2014; NET *et al.*, 2015). PhACs reach superficial water bodies mainly by human excretion (sewage) owing to their incomplete removal in wastewater treatment plant (WWTP) facilities (ARCHER *et al.*, 2017). WWTPs are the major barrier to prevent the contamination of the environment by PhACs. However, conventional WWTPs usually employed for sewage treatment are designed to remove easily or moderately biodegradable carbon, nitrogen and phosphorus compounds and microbiological organisms (VERLICCHI *et al*., 2012; GARCIA-IVARS *et al*., 2017). As PhACs have a very stable structure, low volatility, different hydrophobicity, complex structures, and extremely low concentrations, their removal is challenging.

Drinking water treatment plants (DWTPs) may impose another barrier that can prevent the return of these PhACs to the human body. Many studies have been carried out to detect PhACs in treated water (VULLIET *et al.*, 2011; BOLEDA *et al.*, 2011; CARMONA *et al.*, 2014). The results suggest that conventional treatment processes, such as coagulation, flocculation, filtration, and chlorination, generally have poor removal efficiencies (HUERTA-FONTELA *et al.*, 2011; SIMAZAKI *et al.*, 2015), although advanced treatment technologies, such as ozonation, activated carbon adsorption and membrane separation processes (MSP) have successefully been applied to PhAC removal (KIMURA *et al*., 2005; HUERTA-FONTELA *et al*., 2011; MESTANKOVA *et al*., 2012; TAHERAM *et al*., 2016; WANG *et al*., 2018). Thus, the conjugation of conventional and advanced methods is highly indicated for efficient PhAC removal.

In general, pharmaceutical compound levels are water source-dependent, which, in turn, depends on the location, popular habits, wastewater treatment type, PhAC consumption patterns, physicochemical properties, and stability as well as the weather (CAMACHO-MUNOZ *et al.*, 2014).

PhAC contamination may be more severe in developing countries, such as Brazil, especially owing to limited or no sewage treatment. Brazil has the largest population in Latin America, as well as the largest area, and is one of the countries with the greatest availability of water per capita globally. However, according to the Brazilian National Health Interview Survey

(SISTEMA NACIONAL DE INFORMAÇÕES SOBRE SANEAMENTO, 2015), 50.3% of the Brazilian population has access to sewage collection, and only 42.67% of the country's sewage is treated. Still, only 10 cities in 100 of the largest Brazilian cities treat more than 80% of the sewage generated. Furthermore, as in other developing countries, owing to insufficient health services, people generally use drugs without medical prescriptions, resulting in a higher consumption than that of developed countries. The wastewater treatment facilities for hospital wastewater and the pharmaceutical industry are very limited. The adoption of co-treatment of these effluents with sewage is the most common practice. In some cases, this wastewater is directly released into rivers without treatment.

Thus, the presence of PhACs in natural water causes great concern, especially because they can pose toxicological risk to the environment and public health. Since PhACs are designed to be biologically active, even at trace levels, they may exhibit undesired effects on target and non-target organisms (ZHOU *et al*., 2016). For instance, diclofenac has high antiovulatory effects on aquatic vertebrates (YOKOTA *et al*., 2015). Additionally, ciprofloxacin may interfere with the photosynthesis pathway of higher plants, leading to morphological abnormalities or growth inhibition (ARISTILDE; SPOSITO, 2010). Moreover, dissemination of antibiotic-resistant bacteria in the environment caused by the presence of antibiotics is an emerging concern (MARTI *et al*., 2014). The presence of PhACs in the environment is even more concerning considering that they do not appear individually, but as a complex mixture, which could lead to unwanted synergistic effects (CLEVEURS, 2004; 2005). Considering the toxic effects and especially owing to the inadvertent exposure to pharmaceuticals via drinking water, it is important that PhAC human health risks are also assessed.

Thus, the aim of this study was to identify, quantify, and qualify PhACs in four Brazilian drinking water treatment systems and assess the environmental and human health toxicological risk posed by these PhACs. The DWTPs analyzed presented different capacities, raw water quality, and treatment processes and were localized in three different Brazilian regions (Northeast, Southeast, and South). Each region presented specific characteristics, such as climate, population habits, and social-economic conditions. To the best of our knowledge, no other study had been carried out in these regions with respect to PhAC identification, quantification, and environmental and human health risk assessment.

2. Materials and Methods

2.1. Chemicals and reagents

A total of 28 PhACs (Annex A) were selected based on the list of pharmaceuticals distributed free of charge by the Brazilian health system (SUS) to represent the Brazilian consumption pattern, as well as various classes of micropollutants. The physicochemical properties, including molecular weight, geometry, hydrophobicity/hydrophilicity, polarity, and charge of the selected PhACs are shown in Annex A. The analytical standards of the selected PhACs were obtained from Sigma-Aldrich (Steinheim, Germany). HPLC-grade formic acid and solvents were purchased from Dikma (USA). Ultrapure water (18.2 $M\Omega cm^{-1}$) was produced by a Milli-Q unit (Millipore, USA).

2.2.Study area and sample collection

Raw and treated water was collected from four Brazilian DWTPs including three different regions. Different scenarios were contemplated: DWTP 1 is in Southeast region and tropical climate (Aw), with temperatures ranging from 15 °C to 33 ºC and annual rainfall of 1060 mm; DWTP 2 is in Northeast region and equatorial climate (AF), with temperatures ranging from 21 °C to 30 °C and annual rainfall of 2145 mm; DWTP 3 is in Southeast region and DWTP 4 is in South region and both are in temperate and warm climate, with temperatures ranging from 13 °C to 29 °C and rainfall around of 1500 mm. The rivers that supply water to DWTP 1 (capacity=0.04 m^3/s) and 3 (capacity=6.5 m^3/s) basin cover urban and rural areas, industrial districts, agricultural areas, hospitals, and pharmaceutical industries, and receive discharged treated and untreated sewage. The river that fed the dam of DWTP 2 (capacity=8.5 m^3/s) covers mostly rural areas with subsistence agriculture and monoculture, mainly of manioc, and receive discharged treated and untreated sewage. The dam is used for multiple use, such as power generation, natural fishing, fish farming, sailing, and recreation. The lake that supplyes DWTP 4 (capacity0.2 m^3/s) is located in an urban area and is a tourist attraction with recreational use. The lake is supplied by a set of water sources originating from the slopes of the South, crossing the region. DWTPs 1 to 3 apply the processes coagulation, flocculation, sedimentation, sand filtration, disinfection (chlorination) and fluoridation; and DWTP 4 apply fast coagulation, pebble filtration, disinfection (chlorination) and fluoridation.

The sampling campaign was conducted in April, July and November 2016 and January and April 2017, according to the technical specification requirements for monitoring surface water and wastewater of the Standard Methods for the Examination of Water and Wastewater (APHA, 2012).

2.3.Sample preparation and instrumental analysis

PhACs were analyzed using HPLC (DGU/20A3 Prominence, Shimadzu, Japan) coupled to a micrOTOF-QII mass spectrometer (Bruker) with an electrospray ionization source (ESI). The quantification limit for each PhAC was around 8 ng/L. The uncertainty of estimation was 1% according to the validation method of the analysis protocol. Recoveries were between 86% and 100% but were compensated by the calibration, which is processed the same way as the samples. Water samples were previously filtered using a 0.45 μm hydrophilic PVDF filter. Analytes were isolated from water samples (1 L) in two steps, firstly without pH adjustment (pH 7), and then with pH adjustment to 2 by adding 0.002 mol/L H_2SO_4 solution, using a polymeric C18/18% cartridge (500 mg/6 mL – Applied Separations) preconditioned with 5 mL methanol and 5 mL ultra-pure water, and then eluted with methanol using a Aspec Gilson GX-271 Liquid Handler. Separation was achieved on a Shim-pack XR-ODS C18 column (2.0 mm; 50 mm and 2.0 μm; Shimadzu, Japan) with a mixture of 0.1% formic acid water and methanol as the mobile phase. The flow rate and injection volume were 0.1 mL/min and 10 μL, respectively. The mobile phase gradient followed an isocratic method using 95% of methanol for 15 min.

2.4.Water quality parameters

Color (2120 C), TSS (2540 B E), conductivity (2510 B), and pH (4500 H B) were measured according to the Standard Methods for the Examination of Water and Wastewater (APHA, 2012). TOC was analyzed using TOC Shimadzu TOC-V CNP. The concentrations of Cl^-, SO_4^{2-}, PO_4^{3-}, F^-, NO_3^-, NO_2^- were measured by ion chromatography (ICS-1000 ion chromatograph equipped with the Dionex AS-22 column and ICS 12a). The metals concentrations K^+, Mg^{2+}, Ca^{2+}, and Na^+ were quantified by atomic absorption spectrometry (Atomic Absorption Spectrophotometer - GBC - AVANTA).

2.5.Environmental and Human health risk assessment

The potential environmental risks posed by individual compounds were evaluated based on a hazard quotient (HQ). HQ values were calculated for acute and chronic effects by dividing measured environmental concentration (MEC) by predicted no effect concentration (PNEC), which was determined by dividing the mean effect or lethal concentration (EC50 or LC50) and non-observed effect concentration (NOEC) by safety factors, whose typical values reported in the literature are 1,000 and 10, respectively (WORLD HEALTH ORGANIZATION, 2011). For HQ calculations, the lowest PNEC values and the highest PhAC concentrations in the evaluated waters were considered to obtain a worst-case scenario. The risk was classified into the following categories: high risk ($HQ > 1$), medium risk ($0.1 \leq HQ \leq 1$), low risk ($0.01 \leq HQ < 0.1$) and negligible risk ($HQ < 0.01$) (EUROPEAN COMMISSION, 1996). E(L)C50 and NOEC values of each PhAC were collected from

the literature for three trophic levels (algae, crustaceans and fishes, whenever possible) and only values obtained with standard tests were considered, as recommended by the guidelines of the Water Framework Directive (EUROPEAN COMISSION, 2000). According to the Globally Harmonized System of Classification and Labeling of Chemicals (GHS), the compounds were classified as: (i) highly toxic: E(L)C50 ≤ 1 mg/L; (ii) toxic: 1 mg/L < E(L)C50 ≤ 10 mg/L; (iii) harmful to the aquatic ecosystem: 10 mg/L < E(L)C50 ≤ 100 mg/L (UNITED NATIONS, 2011). Some regulatory systems also include a fourth category, non-toxic compounds: E(L)C50 > 100 mg/L. These levels of toxicity have been used in previous studies (CLEUVERS, 2004; HAN *et al.*, 2006; GARCIA *et al.*, 2014).

Concerning public health, the concentration of each PhAC in drinking water samples was compared with the concentration below which the probability of adverse effects as a result of long-term (lifetime) exposure is negligible to calculate the margin of exposure (MOE). Tolerable daily intake (TDI), which was derived from the non-observed adverse effect level (NOAEL) and a safety factor equal to 100, was used to estimate the safe level of exposure (WHO, 2011). Tolerable daily intake (TDI) values for each PhAC were found in literature or derived from NOAEL, as recommended in literature (DWI, 2007). For PhACs whose NOAEL value was not found, the lowest observed adverse effect level (LOAEL) was used and an additional safety factor of 10 was applied (DWI, 2007). For the comparison, TDI was converted to a drinking water equivalent level (DWEL) in mg/L, according to Eq. 1.

$$DWEL = \frac{(TDI * bm * f)}{C} \quad (1)$$

Where bm is the body mass (60 kg), f is the relative contribution of water to exposure, which can be considered 100% since PhAC exposure from other sources is insignificant, and C is the daily water consumption (2 L) (WHO, 2011). The MOE was obtained by the ratio between DWEL and MEC.

3. Results and discussion

3.1. Water quality

The monitored water quality parameters are shown in Table 1. All water sources evaluated are classified as class 2, which requires conventional drinking water treatment, according to National Council for the Environment (CONAMA 357/2005). The detected drinking water quality parameters satisfied the standard limit values according to Brazilian legislation (Ministerial Order Nº 2914, 2011).

Characteristic	Water source 1		Water source 2		Water source 3		Water source 4		Legal limit for drinking water
	Raw	Treated	Raw	Treated	Raw	Treated	Raw	Treated	
pH	7.09 ± 0.03	7.51 ± 0.2	7.16 ± 0.04	6.14 ± 0.24	7.45 ± 0.08	8.4 ± 0.52	6.79 ± 0.09	7.31 ± 1.17	6.0 - 9.5
EC (µs/cm)	127 ± 28	289 ± 31	254 ± 134	348 ± 87	356 ± 96	498 ± 167	48 ± 11	164 ± 70	-
Color (Hz)	131 ± 53	< 2	21.75 ± 15	< 2	51.35 ± 29.45	5.41 ± 0.13	63.93 ± 39.96	< 2	15
Turbidity (uT)	22.56 ± 19.15	0.34 ± 0.73	1.549 ± 1.80	0.249 ± 0.13	4.982 ± 1.3	0.078 ± 1.5	6.635 ± 1.2	0.275 ± 0.02	1
TOC (mg/L)	1.59 ± 0.82	< 0.1	0.85 ± 0.78	< 0.1	0.35 ± 0.13	< 0.1	< 0.1	< 0.1	-
TN (mg/L)	0.78 ± 0.24	< 0.1	0.28 ± 0.25	0.33 ± 0.3	0.16 ± 0.14	< 0.1	0.14 ± 0.28	0.13 ± 0.26	-
Cl residual	-	3.2 ± 0.54	-	2.6 ± 0.21	-	2.9 ± 0.41	-	3.1 ± 0.67	> 2
Alkalinity (mg/L)	17.42 ± 10.11	6.42 ± 1.97	32.75 ± 2.63	10.75 ± 3.30	15.73 ± 1.58	5.86 ± 1.36	7.75 ± 1.50	4.50 ± 1.29	-

TS (g/L)	98 ± 61	0.316 ± 0.086	0.215 ± 0.09	0.137 ± 0.056	0.115 ± 0.15	0.089 ± 0.53	0.150 ± 0.059	0.083 ± 0.019	-

Table 1 - Main characteristics of the assessed water matrixes (average, standard deviation, n=4)

Water source 1 presents the highest values of turbidity, apparent color, TOC, total nitrogen (TN), and solids (TS). The city does not count with a WWTP and the sewer is discarded near the water adduction point, which explains the lowest water quality. Turbidity and color are parameters closely related to dissolved organic matter, and therefore can have a great influence on the presence of PhACs in water, since the compounds can bind them either via hydrogen bonds or adsorption (SADMANI *et al.*, 2014).

3.2.PhACs occurrence and concentration

Among the 28 investigated compounds, 11 were detected during the sampling campaigns. Atenolol, erythromycin, scopolamine, phenazone, fenofibrate, ranitidine, paroxetine, amoxicillin, ampicillin, enoxacin, clarithromycin, danofloxacin, trimethoprim, ketoprofen, ibuprofen, caffeine and gemfibrozil were not observed in any of the samples evaluated. These compounds likely have concentrations lower than the detection limit, which might be associated with the population consumption habits or greater propensity of these drugs to be hydrolyzed under aerobic conditions or adsorbed (RADJENOVIC *et al.*, 2009; LUO *et al.*, 2011). Same behavior of these compounds could be observed by other studies worldwide (CARMONA *et al.*, 2014; SIMAZAKI *et al.*, 2015). The compounds that were not detected or had concentrations below the MDL in all samples were not discussed in this study. The mean concentrations of PhACs observed in raw water ranged from 11 ng/L (omeprazole in water source 1) to 4,215 ng/L (fluconazole in water source 3). Betamethasone, fluconazole, atorvastatin, and prednisone were the most abundant compounds. Moreover, betamethasone, fluconazole, and prednisone were detected with high frequency in all water supply systems (Table **2**2). The prevalence of these PhACs could be explained by their low degradability and hydrophilic characteristics (VERLICCHI *et al*., 2012; GARCIA-IVARS *et al*., 2017). Sample concentrations observed in this study were compared with those reported in the literature. Fluconazole concentrations noted in this study were significantly higher than those found in rivers in Spain (28.5 ng/L), China (22.8 ng/L) and South Korea (46.2 ng/L) (CASADO *et al*., 2014; HUANG *et al*., 2013; KIM *et al*., 2009). Despite being one of the most common PhACs in this study, prednisone was not detected in any samples of U.S. surface waters (BATT *et al*., 2015). The authors also did not detect atorvastatin in any samples, in accordance with the low detection frequency of this PhAC in this study. Betamethasone concentrations were also lower in the US and German than those detected in the present study. According to Vestel *et al*. (2016), the Pharmaceutical Assessment and Transport Evaluation model estimated betamethasone concentrations to be <0.6 ng/L in 95% of all U.S. surface waters and in German the concentrations were found to be between 0.07 and 2.8 ng/L (WEIZEL *et al*., 2018). The differences between the concentrations ranges indicated variations in the consumption

pattern among different countries and highlighted the high use of these PhACs in Brazil. Loratadine, betamethasone, prednisone, fluconazole, atorvastatin and genfibrozil were the only PhACs quatified in treated water, in concentrations ranging from 8 ng/L (gemfibrozil in water source 4) to 2,811 ng/L (prednisone in water source 2).

Pharmaceutical compounds	Raw water														
	1				**2**				**3**				**4**		
	DF[a] (N=5)	C (ng/L) min-max	C (ng/L) average	C (ng/L) median	DF[a] (N=5)	C (ng/L) min-max	C (ng/L) average	C (ng/L) median	DF[a] (N=5)	C (ng/L) min-max	C (ng/L) average	C (ng/L) median	DF[a] (N=5)	C (ng/L) min-max	C (ng/L) average	C (ng/L) median
Betamethasone	3	20-701	295	165	4	34-3225	1106	559	2	622-888	755	755	3	326-878	419	473
Cimetidine	-	-	-	-	-	-	-	-	-	-	-	-	1	116	116	116
Fluconazole	3	227-573	356	266	3	83-332	206	204	2	35-4215	2125	2125	4	90-986	382	225
Omeprazole	1	11	11	11	-	-	-	-	-	-	-	-	-	-	-	-
Phenylbutazone	1	132	132	132	-	-	-	-	-	-	-	-	-	-	-	-
Loratadine	-	-	-	-	-	-	-	-	-	-	-	-	1	2481	2481	2481
Prednisone	1	233	233	233	4	2032-3556	2502	2210	2	34-883	458	458	4	327-1509	853	788
Enrofloxacin	-	-	-	-	1	14	14	14	-	-	-	-	-	-	-	-
Norfloxacin	-	-	-	-	-	-	-	-	1	134	134	134	-	-	-	-
Metformin	1	36	36	36	-	-	-	-	-	-	-	-	-	-	-	-
Atorvastatin	-	-	-	-	2	299-506	402	402	-	-	-	-	-	-	-	-
Genfibrozil	-	-	-	-	-	-	-	-	-	-	-	-	1	17	17	17
	Treated water															

	1				2				3				4			
Pharmaceutical compounds	DF[a] (N=5)	C (ng/L) min-max	C (ng/L) average	C (ng/L) median	DF[a] (N=5)	C (ng/L) min-max	C (ng/L) average	C (ng/L) median	DF[a] (N=5)	C (ng/L) min-max	C (ng/L) average	C (ng/L) median	DF[a] (N=5)	C (ng/L) min-max	C (ng/L) average	C (ng/L) median
Loratadine	-	-	-	-	-	-	-	-	-	-	-	-	1	17	17	17
Betamethasone	-	-	-	-	1	34	34	34	-	-	-	-	1	180	180	180
Prednisone	-	-	-	-	3	1650-2811	2105	1853	2	29-84	57	57	3	241-572	370	296
Fluconazole	1	151	151	151	2	349-586	468	468	1	1189	1189	1189	3	91-196	147	154
Atorvastatin	-	-	-	-	1	477	477	477	-	-	-	-	-	-	-	-
Genfibrozil	-	-	-	-	-	-	-	-	-	-	-	-	1	8	8	8

[a] Detection frequency

Table 2 - Minimum, maximum average and median concentrations of PhACs (ng /L) in raw and treated water from four Brazilian water supply systems

The presence of PhACs in natural water is susceptible to seasonality (Fig. 1) owing to their consumption pattern and microbial activity, which is higher in the warmer months. In addition, the regions' socio-economic conditions also influence the consumption pattern and contamination extent (Fig. 2).

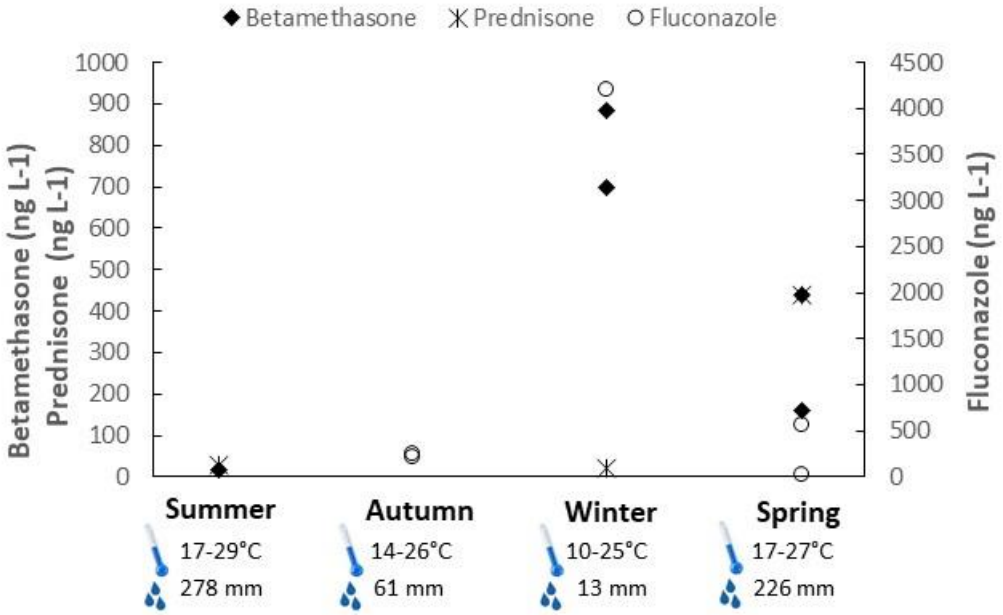

Figure 1: Betamethasone, prednisone, and fluconazole concentrations during different seasons

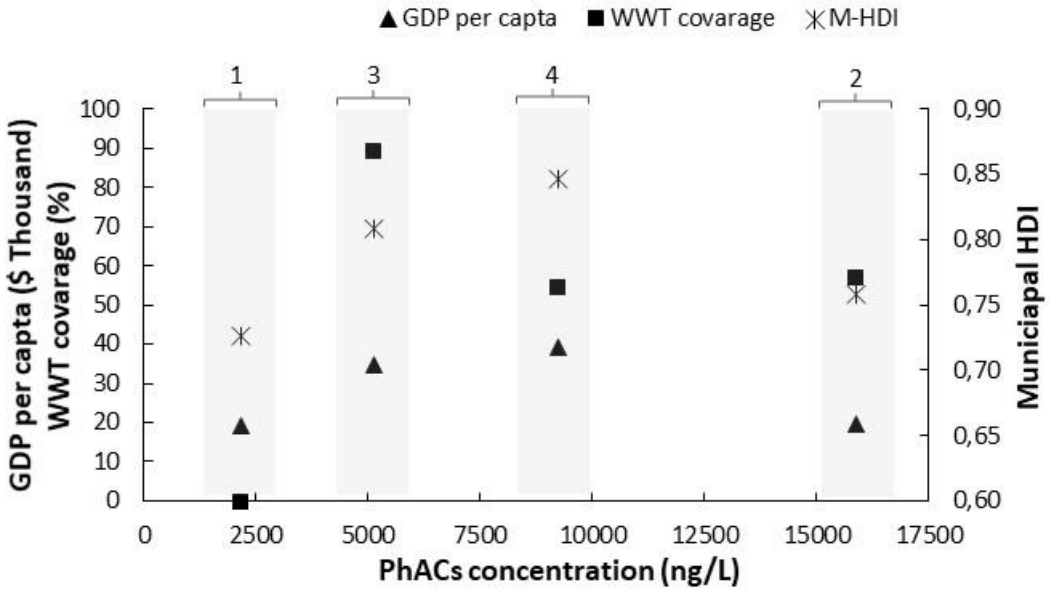

Figure 2: Correlation between accumulated PhAC concentration and wastewater treatment (WWT) coverage index, municipal human development index (HDI), and gross domestic product (GPD) per capita

It is possible to observe a seasonal pattern in PhAC concentrations in natural water sources in Fig. 1. Winter presented the greatest pick of PhACs, mostly owing to low rainfall, which reduces river flow, and therefore concentrates these pollutants. Also, the low temperatures of this season propitiate the increase in infectious diseases, and thus a higher PhACs consumption is observed. With the arrival of spring, PhAC concentration begins to decrease until its lowest values in summer, which is characterized by a high rainfall index, increasing the dilution, and high temperatures that may accelerate the biodegradation of pharmaceuticals owing to higher microbial activity (LUO *et al.*, 2011).

Besides the climate factors, social-economic aspects can also contribute to higher PhAC concentrations. As can be seen from Fig. 2, higher values of gross domestic product per capita (GDP per capita) and human development index (HDI) are associated with higher PhAC concentrations. These factors reflect the consumption capacity of the population and so it is expected that the higher the family income, the greater the health care, which directly impacts PhAC consumption. For example, although water source 1 presented the lowest WWT coverage, it also presented the lowest PhAC concentrations, which may be associated with the low values of GDP per capita and HDI. In turn, water source 4 presented higher PhAC concentrations owing to the high GDP per capita and HDI and the low WWT coverage. Water source 2 presented higher concentrations of PhACs. This could be owing to the high temperatures of this region throughout the year, which increases the evaporation rate, especially since this water source is a dam. Besides these, other factors may play important roles, such as water body preservation and wastewater treatment systems.

Removal of pharmaceuticals in the DWTP

Enrofloxacin, norfloxacin, metformin, cimetidine, phenylbutazone and omeprazole were not quantified in any of the treated water samples. The mechanisms involved in their removal may have been size retention, biodegradation in the filtration step (especially antibiotics that are more easily degraded) (HUERTA-FONTELA *et al.*, 2011; SIMAZAKI *et al.*, 2015), adsorption, and chlorine oxidation (Fig. 3).

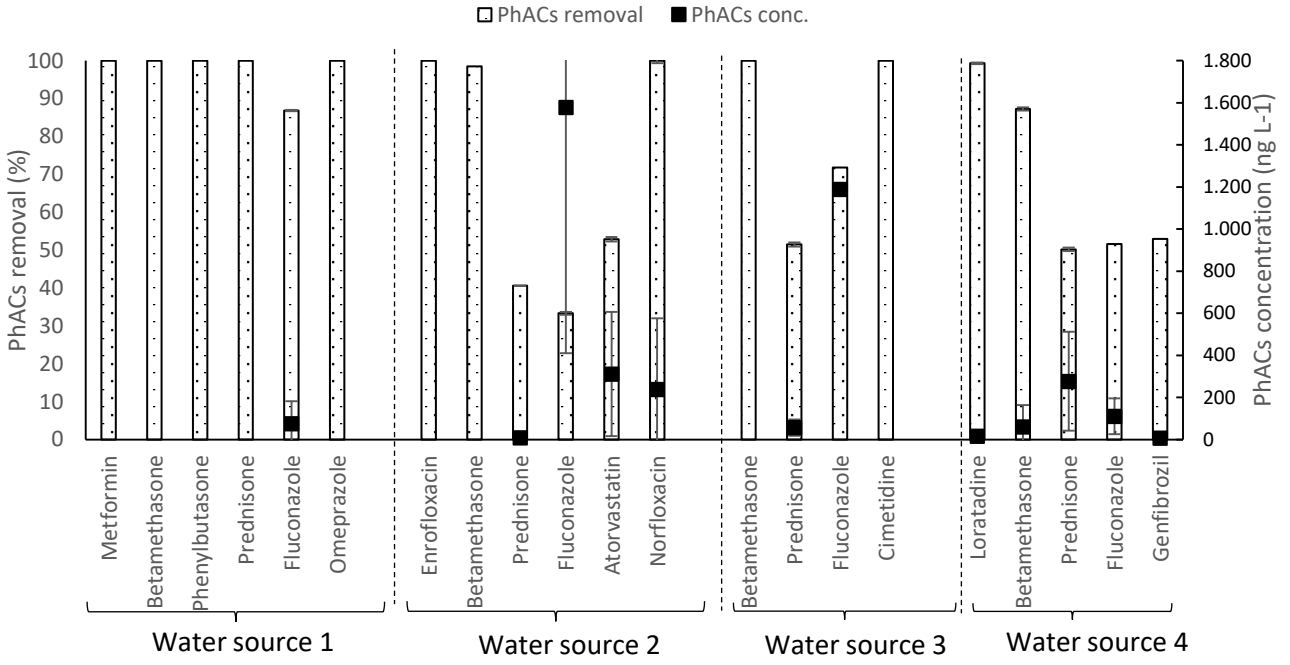

Figure 3 – PhACs concentration in treated water and removal efficiency of each evaluated DWTP

According to Stackelberg *et al.* (2007), the process of clarification (consisting of coagulation, flocculation, sedimentation, and filtration) is generally not a primary route by which PhACs in filtered-water samples are degraded or removed, mostly owing to the intrinsic characteristics of the compounds. The low concentration of PhACs in superficial water and hydrophobic behavior of some PhACs with log K_{ow}>3.0, such as atorvastatin (log K_{ow}=5.04) and gemfibrozil (log K_{ow}=4.28), may explain the lower removal of these compounds through this process. However, compounds with low log K_{ow}<3.0 are not expected to be adsorbed to the particles but to dissociate in the aqueous phase (WANG *et al.*, 2014) and evades the biodegradation/adsorption process. This can explain he lower removal efficiencies of fluconazole (log K_{ow}=0.40) and prednisone (log K_{ow}=1.46). These two PhACs were the most frequent in treated water (fluconazole was present in all water sources).

The application of ferric chloride coagulation used in water source 3 DWTP may result in base or acid hydrolysis, however it is not efficient enough to remove PhACs throughout the water treatment. Although DWTP from sources 1, 2 and 4, which apply aluminum sulfate, showed higher PhACs incidence and concentration, they were more efficient, owing to alterations to the compounds hydrophobicity, since it seems to have better affinity with PhACs.

Chlorination was found to be very efficient in the removal of some PhACs owing to the high reactivity of chlorine with primary and secondary amines (WESTERHOFF *et al.*, 2005; CHAMBERLAIN;

ADAMS, 2006). According to Huerta-Fontela *et al.* (2011), the efficiency of chlorination increases for compounds that do not have the imidazole group, since the absence of this group favors the deactivation of the aromatic ring and potentiates the reaction with chlorine. The presence of a bromide instead of chlorine in one of the aromatic rings, and substitution of a benzene ring by a pyridine one blocks the reactivity of this compound through chlorine attack (KIM *et al.*, 2007). This may explain the higher removal of enrofloxacin, betamethasone and loratadine.

Environmental and Human health risk assessment

E(L)C50, NOEC, NOAEL and TDI values for each PhAC are presented in Annex B. The predominant susceptibility order to acute toxicity effects, accounting for 46% of the PhACs, was algae> crustaceans> fishes, which is in accordance with the results found by Sanderson *et al.* (2003) and Garcia *et al.* (2014). In fact, 62.5% of the drugs for which acute toxicity data were found for fish trophic level were classified as non-toxic, according to GHS. For algae, non-toxic drugs account for only 26% of the total data, whereas 53% are highly toxic. Regarding chronic effects, fishes are the trophic level most susceptible to 62.5% of the drugs, which may be related to PhACs bioaccumulation. Atorvastatin, for example, has a logKow equal to 5.04 (Annex A) and has one of the lowest NOEC values. Toxicity indicators revealed the seriousness of PhAC toxicological potential, since less than 1% was considered non-toxic for all trophic levels and approximately 60% were classified as highly toxic for at least one. The drugs erythromycin, norfloxacin, fenofibrate, loratadine and gemfibrozil stand out owing to their high toxicological potential.

The few NOAEL/LOAEL values found make enhance the understanding of the toxicological effects of PhACs. Of the 28 drugs selected, there were NOAEL values for only seven compounds and LOAEL values for only four, which corresponds to less than 30% for both indicators (25% and 14%, respectively). For other six drugs, TDI values were found in the literature (erythromycin, trimethoprim, ibuprofen, atorvastatin, gemfibrozil and atenolol), so it was only possible to obtain TDI values for approximately 60% of the selected PhACs.

All the evaluated water sources were subject to toxicological risk, both acute and chronic, owing to at least one PhAC (Table 3). Only water source 1 was not subject to high toxicological risk. The PhACs related to the highest acute toxicity risks were loratadine in 4 (HQ = 124) and norfloxacin in 3 (HQ = 3.526). Regarding chronic toxicity, the highest risk was posed by atorvastatin in 2 (HQ = 389). In contrast, all these PhACs had low detection frequencies, which may be explained by their seasonal consumption pattern or degradability rates. Loratadine and norfloxacin were only detected in winter, when the consumption of antiallergics is higher and microbial activity is lower, decreasing

the biological degradation of antibiotics. Atorvastatin was only quantified in the Northeast region, possibly because despite being an expensive pharmaceutical product in Brazil, the government of one of this region biggest city provides it to the population. However, compounds with a high detection frequency were related to milder toxicological risks and none of them posed high risk in any of the water sources. Fluconazole and betamethasone posed low risks in all water sources, as summarized by Chen and Ying (2015) for Chinese surface waters and Vestel *et al*. (2016) for US surface waters. Regarding the human health risk assessment, it was not possible to calculate the MOE for three PhACs (omeprazole, metformin, and norfloxacin). Among the others, 11 presented MOE values higher than 1,000 and six had values higher than 100, indicating a low probability of risk to public health even before the water passes through the treatment system for 94% of the PhACs quantified in the evaluated water sources.

Conventional DWTPs were able to promote some reduction in the toxicological risk potential of PhACs (Table 3); however, water source 1 was the only one in which treated water was not subject to acute or chronic risk. The others presented toxicological environmental risk owing to at least one PhAC. Prednisone, betamethasone and fluconazole posed low or negligible risks, both for acute and chronic effects. Despite the low detection frequency, atorvastatin should b highlighted for its high toxicity potential. This PhAC posed high chronic risk (HQ = 367) and it is also related to one of the highest acute toxicity values (HQ = 0,183), only lower than loratadine (HQ = 0,838) in water source 4. Regarding human health, atorvastatin was the only drug that did not present MOE above 1,000 in treated water, with a value below 100 (MOE = 34); therefore, PhAC could pose a human health risk.

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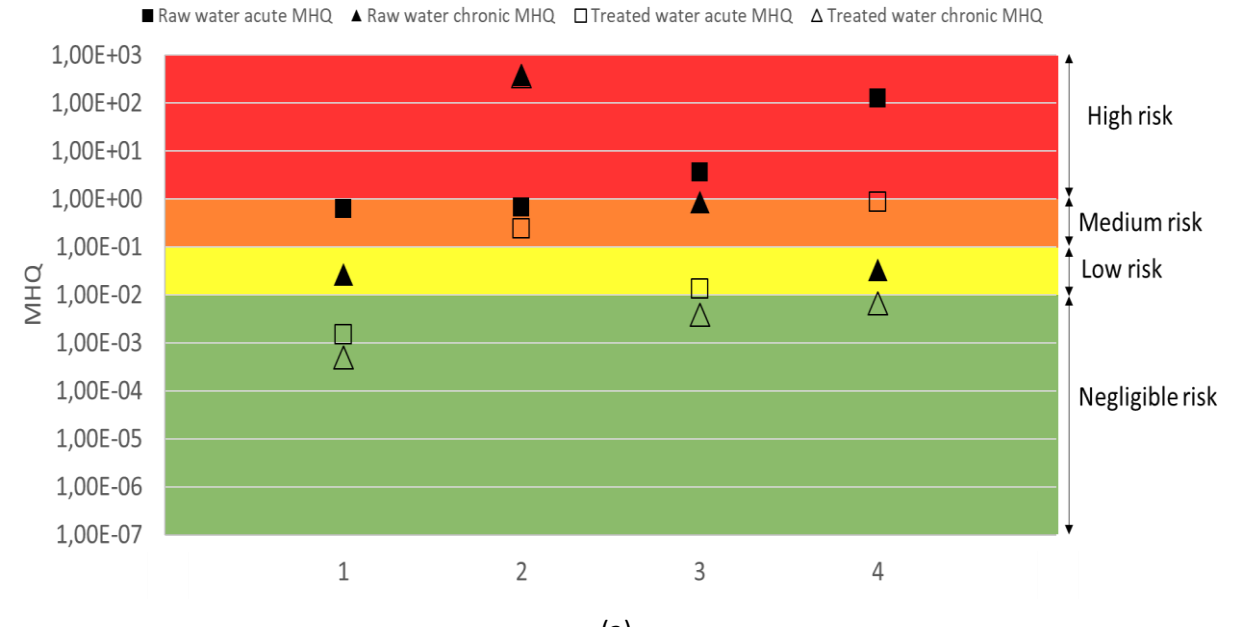
Water source	Raw water						Treated water					
	PhAC	Acute toxicity		Chronic toxicity		Human health	PhAC	Acute toxicity		Chronic toxicity		Human hea
		HQ	Classification	HQ	Classification	MOE		HQ	Classification	HQ	Classification	MOE
1	Metformin	0.001	Low risk	-	-	-	Fluconazole	0.002	Negligible risk	0.000	Negligible risk	9934
	Betamethasone	0.022	Low risk	0.001	Negligible risk	2675						
	Phenylbutasone	-	-	0.000	Negligible risk	315789						
	Prednisone	0.004	Negligible risk	-	-	25751						
	Fluconazole	0.006	Negligible risk	0.002	Negligible risk	2613						
	Omeprazole	0.579	Medium risk	0.024	Low risk	-						
2	Enrofloxacin	0.293	Medium risk	0.000	Negligible risk	104466	Betamethasone	0.001	Negligible risk	0.000	Negligible risk	54446
	Betamethasone	0.101	Medium risk	0.003	Negligible risk	581	Prednisone	0.052	Low risk	-	-	2135
	Prednisone	0.065	Low risk	-	-	1687	Fluconazole	0.006	Negligible risk	0.002	Negligible risk	2560

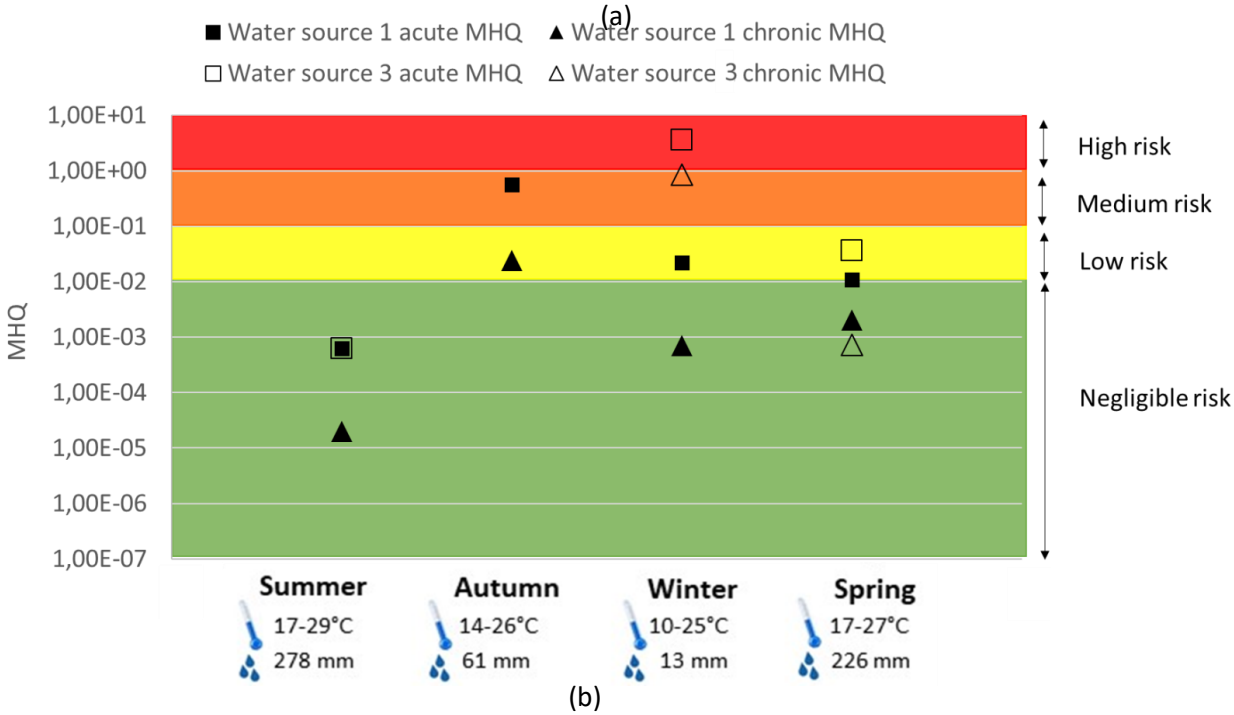
	Fluconazole	0.003	Negligible risk	0.001	Negligible risk	4520	Atorvastatin	0.183	Medium risk	367	High risk	34
	Atorvastatin	0.195	Medium risk	389	High risk	32						
3	Norfloxacin	3.526	High risk	0.838	Medium risk	-	Fluconazole	0.012	Low risk	0.004	Negligible risk	1261
	Betamethasone	0.028	Low risk	0.001	Negligible risk	2112	Prednisone	0.002	Negligible risk	-	-	71429
	Fluconazole	0.042	Low risk	0.014	Low risk	356						
	Prednisone	0.016	Low risk	-	-	371						
4	Cimetidine	0.001	Negligible risk	0.017	Low risk	753	Loratadine	0.838	Medium risk	-	-	53687
	Loratadine	124	High risk	-	-	363	Betamethasone	0.006	Negligible risk	0.000	Negligible risk	10411
	Betamethasone	0.027	Low risk	0.001	Negligible risk	2135	Prednisone	0.010	Low risk	-	-	10497
	Prednisone	0.028	Low risk	-	-	3976	Fluconazole	0.002	Negligible risk	0.001	Negligible risk	7657
	Fluconazole	0.010	Low risk	0.003	Negligible risk	1521	Genfibrozil	0.015	Low risk	0.006	Negligible risk	2100
	Genfibrozil	0.032	Low risk	0.012	Low risk	988						

Table 3 - PhACs environmental and human health risk assessment for raw and treated water from all sources evaluated

A significant point concerning the PhACs toxicological risk assessment is that, since the pattern of consumption of these compounds varies widely between different regions, depending on several socioeconomic factors (OLIVEIRA *et al.*, 2012; GODOY *et al.*, 2015), HQ and MOE values obtained for a PhAC in a specific region do not necessarily reflect the risks in other regions (CARLSSON *et al.*, 2006). Another important point is the possible contribution of each PhAC to the global risk potential of the complex mixture of compounds found in the environment, even if its individual potential is low (CLEUVERS, 2005). The mixture toxicity was estimated by using the classical concentration addition model. The mixture hazard quotients (MHQ) were calculated for each of the evaluated water sources (Fig. 4a) and seasons (Fig. 4b).



(a)



(b)

Fig. 4: Raw and treated water mixture hazard quotient (MHQ) (a) of all evaluated water sources and (b) of water sources 1 and 3 during all seasons.

All evaluated sources are subjected to both acute and chronic significant risks. Water sources 2 and 4 presented the greatest risks and water source 1 the least risks. Regarding the occurrence of PhACs, the toxicological risk is also subject to seasonality. In water source 3, it was possible to observe peaks of both acute and chronic risk in winter, following the highest PhAC concentrations observed in this season (Fig. 4b). In water source 1, the highest MHQ was observed in autumn. Winter temperatures are milder in this region, which may have caused the highest peaks in autumn, when temperatures begin to decrease and rainfall decreases considerably, increasing PhACs consumption and reducing the dilution factor. In both sources, milder risks occurred in summer months, as expected.

Conclusion

PhAC contamination is a reality in Brazilian natural waters as trace levels of pharmaceuticals were detected in superficial and drinking water in all assessed water sources. PhACs presence and concentration are subject to seasonality and to regional socio-economic aspects.

The toxicity potential confirms the concern regarding these compounds, since less than 1% of the evaluated PhACs were non-toxic to any trophic level and approximately 60% were highly toxic to at least one level. Both raw and treated water from the four evaluated water sources were subject to toxicological environmental risk at some level owing to at least one drug. In treated water, atorvastatin posed a significant human health risk; therefore, requiring special attention. Toxicological risk is also susceptible to seasonality and mixed PhAC toxicity is higher than that of individual compounds. Since the removal and risk reduction of PhACs using conventional DWTPs are only partial, the application of more efficient technologies must be considered.

Therefore, the results reported here are important as they provide comparative insight about PhAC concentration and risk assessment in water supply systems around Brazil. Besides, owing to the possibility of increased consumption of pharmaceuticals in the future, it is also important to highlight the importance of continual PhACs monitoring, to observe any increase in their concentration, which could pose even higher risks to aquatic environmental and public health.

Acknowledgments

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