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Removal of fluoxetine from water by nanofiltration and reverse osmosis

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ABSTRACT

This paper explores the use of nanofiltration (NF) and Reverse Osmosis (RO) to remove the pharmaceutical Fluoxetine (FLX) from water. This substance can be found in rivers and lakes and requires studies involving the application of efficient technologies for its removal or mitigation. The study evaluated NF and RO membranes as an alternative to remove Fluoxetine from water. NF removed fluoxetine within the range between 50 and 60%, and RO demonstrated higher efficiency in removing the drug (98.8%). RO is a suitable method as a complementary treatment of water to ensure a lower concentration of FLX in water.

Keywords: emerging pollutants, environment, membrane technology, water treatment.

Remoção de fluoxetina de água por nanofiltração e osmose inversa

RESUMO

Este trabalho abordou o uso de Nanofiltração e Osmose Inversa para remover o composto farmacêutico fluoxetina de água. Essa substância pode ser encontrada em rios e lagos, demandando estudos que envolvam a aplicação de tecnologias eficientes na remoção e/ou mitigação destes compostos. O objetivo deste trabalho foi avaliar a NF e RO como alternativa para remover Fluoxetina. A NF removeu a fluoxetina na faixa entre 50% e 60% e, por sua vez, a osmose inversa apresentou até 98,8% de remoção, demonstrando ser o método mais satisfatório nas condições experimentais analisadas. RO é um método adequado para complementar os sistemas de tratamento de água e garantir baixas concentrações de FLX em água.

Palavras-chave: meio ambiente, poluentes emergentes, tecnologia de membranas, tratamento de água.

1. INTRODUCTION

The presence, accumulation, and persistence of emerging pollutants in water are an international concern for governments, the scientific community, and regulatory agencies

(Foureaux *et al.*, 2018; Song *et al.*, 2020; Couto *et al.*, 2020). Emerging pollutants comprise a wide variety of chemical compounds, including pharmaceuticals (Lin, 2017; Song *et al.*, 2020), pesticides, and hormones. Generally, these pollutants are molecules with more than one ionizable group, ensuring their high persistence in water (Alonso *et al.*, 2018; Couto *et al.*, 2020). Once in the environment, individually or in synergy, they can compromise water quality, interfering with biodiversity and the balance of aquatic ecosystems (Couto *et al.*, 2020; Bhushan *et al.*, 2022).

The presence of antidepressants in water can interfere with aquatic animals' biological, reproductive, and predatory behavior, but the full impact of their effects on human health is still unknown (Zindler *et al.*, 2020). Researchers from the United States observed that fishes of the *Fathead Minnows* species exposed to Fluoxetine (FLX) have shown behavioral changes and started to become aggressive (Weinberger and Klaper 2014). Zindler *et al.* (2020) showed the bioaccumulation of FLX and metabolites in the embryonic stage of Zebrafish species at low concentrations. In addition, it has been found in surface waters, and the main route of intrusion of these pollutants into the environment comes from wastewater effluents dumped into water resources (Couto *et al.*, 2020). Thus, this study was performed with FLX as an emerging pollutant. FLX (the active compound of the trademark Prozac®) has become a symbol of prescribing antidepressants (Salahinejad *et al.*, 2022). Its molar weight is 309 g mol^{-1}, it has a pK_a of 9.8, its solubility is 17 mg L^{-1}, and its molar volume is 266 cm^3 mol^{-1} (Dalbosco *et al.*, 2021).

Conventional water treatment is not efficient in removing or degrading emerging pollutants, therefore demanding studies and applications of complementary technologies (Cadore *et al.* 2020). Thus, biological treatments, such as trickling filters or activated sludge, are mainly insufficient to remove a wide range of highly toxic contaminants, such as drugs, pesticides, and metals (Power *et al.*, 2018). Other treatments, such as coagulation and flocculation, are also insufficient to remove emerging pollutants that are dissolved in water. Ozonation and photocatalysis have the risks of generating undesirable by-products in treated water (Cadore *et al.*, 2020). On the other hand, the membrane separation methods for NF and RO (Couto *et al.*, 2020; Song *et al.*, 2020) are promising technologies, with the advantage of removing dissolved or ionic contaminants in low concentrations at high selectivity (Cadore *et al.*, 2020). Dalbosco *et al.* (2021) studied low-pressure RO membranes to separate FLX, but high-rejection membranes were not used to separate this pollutant. Taheran *et al.* (2016) reported in a literature review that several studies used membranes to separate emerging pollutants, but there were no results of the removal of FLX. Thus, there are still technical and scientific gaps regarding the removal of pharmaceutical pollutants from water.

The study aimed to evaluate membrane technologies such as NF and RO in removing FLX from water to help the understanding of the separation by both membranes.

2. MATERIALS AND METHODS

2.1. Fluoxetine

Pharmacological FLX (purity > 98%) was acquired in the pharmaceutical market locally. The test solutions were prepared using Milli-Q water (electrical conductivity less than 4 μS cm^{-1}) in different concentrations according to the experiments to be performed, and their pH varied from 6.8 to 7.1. Table 1 shows the conditions using the test solutions. In NF experiments, different concentrations were assessed to evaluate the capacity of the membrane to retain lower concentrations of FLX in the permeate. In RO experiments, the concentration was kept constant, and the effect of pressure on permeate flux and membrane rejection was evaluated.

Table 1. Operating condition and composition of the test solutions.

	Pressure (kPa)	FLX concentration (mg L^{-1})	Temperature (ºC)	pH
NF	600	1.0; 5.0; 10; 15; 20	25 ± 2ºC	6.8 to 7.1
RO	600; 800; 1000; 1300;1500	20	25 ± 2ºC	6.8 to 7.1

2.2. Equipment and configuration of the NF and RO system

The experiments were conducted in an automated pilot module provided by WGM Systems (São Paulo, Brazil). The equipment diagram and the operating procedure details are found in Brião *et al.* (2019) and were adapted according to Figure 1.

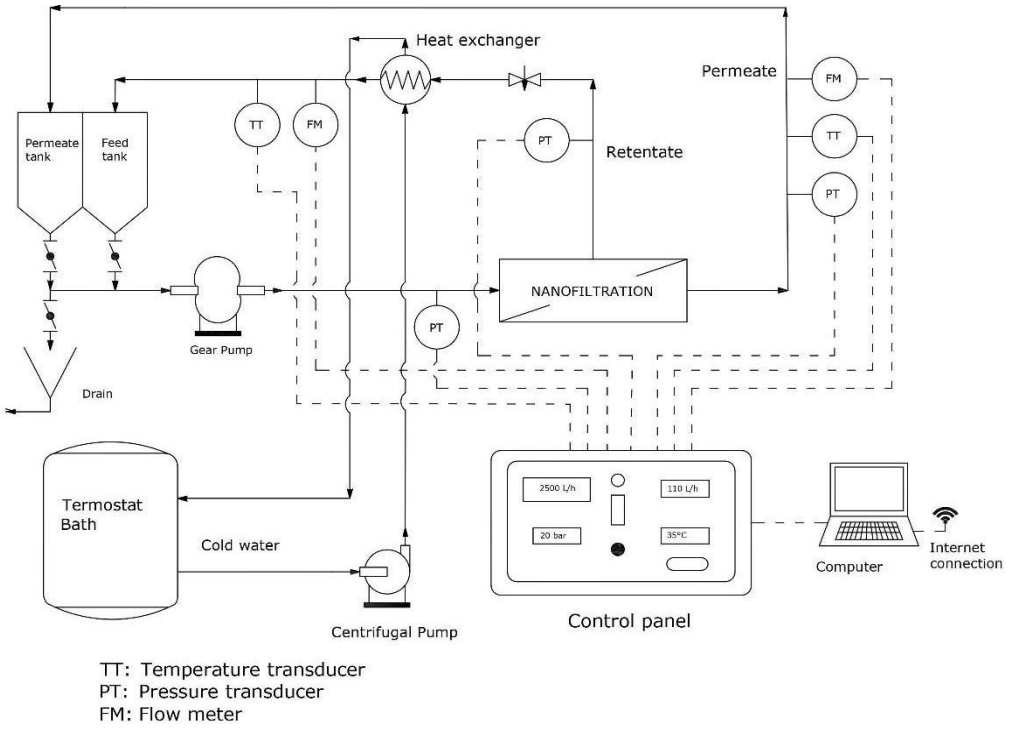

Figure 1. Diagram of the pilot equipment used.
Source: Adapted from Brião *et al.* (2019).

The FLX solution (15 L) was added in the feed tank, and the gear pump moved the fluid toward the membrane that separates the permeate and the retentate. The equipment is an automated model that collects data on temperature, pressure, and flow and sends them to the author's email via an internet connection. The operating conditions were adjusted with total recovery, returning permeate and retentate to the feed tank. The temperature was kept at 25 ± 2ºC by a heat exchanger.

The NF and RO membranes (Koch model 2538-SR3D-VYV and 2538-HRX-VYV, respectively) are constituted of aromatic polyamide (PA) with a polysulfone (PS) support in spiral wound configuration with an area of 1.8 m². The permeability of RO and NF membranes using Milli-Q water is 1.9 L h^{-1} m^{-2} bar $^{-1}$ and 6.9 L h^{-1} m^{-2} bar $^{-1}$, respectively. After each experiment, membranes were cleaned by an alkaline solution (NaOH in pH 10.5) and acid solution (HNO_3 in pH 3.0) and rinsed with permeate Milli-Q water.

2.3. Experiments using the NF membrane

The procedure was conducted with different concentrations of FLX: 1.0 mg L^{-1}, 5.0 mg L^{-1}, 10 mg L^{-1}, 15 mg L^{-1}, and 20 mg L^{-1} in two replicates. This step was performed at a constant pressure of 600 kPa to compare the separation with the low-pressure RO membrane used by Dalbosco *et al.* (2021) to remove FLX from water. The permeate flux was calculated

using Equation 1.

$$J = \left(\frac{Flow}{Am}\right) \quad (1)$$

Where: J is the permeate flux (L/m^{2}h) and A_m is the membrane area (m^2). The volumetric flow rate was read on the instrument of the pilot rig equipment.

After 1 hour of recirculation, retentate and permeate were collected for analysis. Membrane rejection was calculated using Equation 2.

$$R = \left(1 - \frac{Cp}{Cr}\right) . 100 \quad (2)$$

Where: R is the rejection coefficient of the membrane, C_p is the concentration of permeate (mg L^{-1}), and C_r is the retentate concentration (mg L^{-1}) (Miorando *et al.*, 2017).

2.4. Experiments using the RO membrane

Solutions with 20 mg L^{-1} of FLX were prepared in duplicate and assessed at different operating pressures (600 kPa, 800 kPa, 1000 kPa, 1300 kPa, and 1500 kPa). After 1 hour of recirculation, retentate and permeate samples were collected for analysis, and membrane rejection of FLX was calculated using Equation 2.

2.5. Analysis

The analysis of the samples used the LC - MS/MS system from Shimadzu (Japan) equipped with liquid chromatograph Nexera X2™ with a binary pump, triple quadrupole detector LCMS-8040™ MS/MS, and LabSolutions software for system control and data acquisition. A nitrogen generator model NM30L-MS from Peak Scientific (Scotland) and argon 6.0 as collision gas was also used.

The analyses were performed on an XR-ODS III column (150 x 2.0 mm, 2 μm) with a temperature controller adjusted to 40°C. The mobile phase consisted of (A) formic acid 0.1% (v / v) and (B) methanol. In the gradient elution program, the percentage of the organic phase was: 0 min, 5% B; 2 min, 5% B; 3.5 min, 90% B, kept up to 6.5 min; and 8 min, 5% B, remaining constant up to 10 min. The flux rate was constant at 0.3 L min^{-1}, and the injection volume was 10 μL.

The quadrupole mass spectrometer operated in the selected reaction monitoring mode (SRM), using protonated molecule 311 m z^{-1} as a precursor and 44 m z^{-1} as a product. The instrument was operated using an electrospray ionization (ESI) source in positive. The flux of desolvation gas (nitrogen) was fixed at 15 L min^{-1}, and the flux of nebulization gas was fixed at 0.3 L min^{-1}.

2.6. Data analysis

The membrane rejection and permeate flux were the response variables of the system. The results were submitted to statistical analysis of Variance (ANOVA), followed by the comparison of Tukey's test at 5% significance.

3. RESULTS AND DISCUSSION

Figure 2 shows the permeate flux across the NF membrane using different concentrations of FLX at a constant pressure of 600 kPa. The permeate flux decreases as the FLX concentration increases in the feed solution. Reverse linearity was observed between FLX concentration and permeate flux ($R^2 > 0.9$).

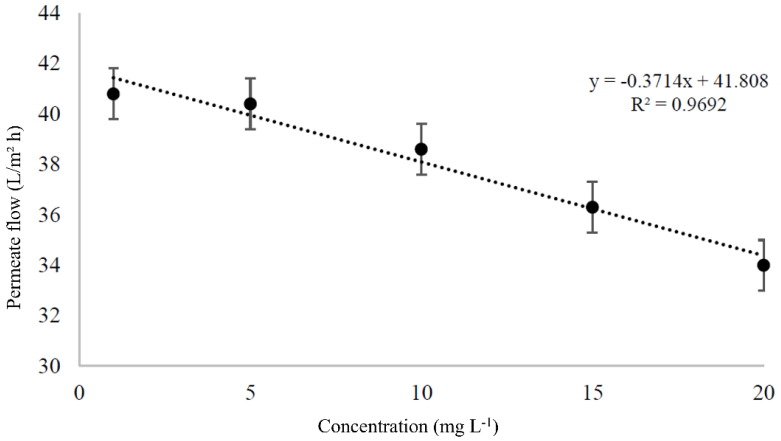

Figure 2. Permeate flux across the NF membrane at different concentrations of fluoxetine after 1 h.

Foureaux *et al.* (2018) attributed the decline of the permeate flux to the concentration polarization when they performed NF experiments on surface water to remove pharmaceutical compounds. The increase of the concentration of solutes on the retentate side of the membrane makes it difficult for water to permeate through the membrane as concentration polarization was already established and the gradient concentration occurs, and this driving force generates a back flux from the membrane toward the bulk solution. Thus, the higher the solute available, the more solute molecules are retained on the membrane surface, which reduces the permeate passage. The higher the concentration in the system feed, the lower the permeate flux due to fouling on the membrane, which can be attributed to the increase in concentration polarization on the membrane surface (Justino *et al.*, 2021).

It is suggested that the membrane should become more effective in rejecting large contaminants as it becomes fouled. However, this can cause a negative effect on permeate flux of NF. In addition, FLX molecules can be adsorbed onto membrane polymers, as shown by Dalbosco *et al.* (2021). Consequently, the pores of fouled membranes, theoretically, would only allow the passage of molecules smaller than their porosity size (Couto *et al.*, 2020).

Table 2 shows the removal of FLX by NF membrane at different concentrations at a constant pressure of 600 kPa. There is no significant difference of FLX rejection by the NF membrane in different concentrations.

Table 2. FLX rejection by NF at different concentrations.

Concentration (mg L^{-1})	1.0	5.0	10.0	15.0	20.0
Rejection (%)	59.9±4.7[a]	59.9±0.7[a]	56.0±2.5[a]	56.5±1.5[a]	56.1±2.7[a]

[a] Indicates statistically similar values on the same row.

NF is an intermediate process between RO and ultrafiltration (UF), and it can retain dissolved molecules with molar mass ranging from 200 to 1,000 g mol^{-1} and multivalent ions (Gomes *et al.*, 2020). Many works have shown that the membrane separation process is efficient for the tertiary treatment of effluents (Cadore *et al.*, 2020), including NF. A similar result was reported by Azaïs *et al.* (2014) when they used NF for the separation of carbamazepine, and the rejection was 60%. Other studies used NF for the separation of different pharmaceuticals. Couto *et al.* (2020) studied the rejection of betamethasone and fluconazole by NF membrane rejection decreased throughout the NF performance test. They suggested that size exclusion is the predominant separation mechanism and, supposedly, there is diffusion through pores and the membrane polymer matrix towards the permeate side. In hypothesis, all pharmaceuticals can interact physically or chemically with the membrane material leading to its adsorption into the

polymer matrix and potentially impacting its rejection (Couto *et al.*, 2020).

The molar mass of fluoxetine is 309 g mol^{-1}, and the molecular weight cut-off (MWCO) of the NF membrane used in the experiments is 200 g mol^{-1}. However, the molecule is not a perfect sphere, and its structure can be shaped by pressure across the membrane pores. Both charges of membrane and molecule can help the separation by charge repulsion. However, FLX is neutral in 6.8<pH<7.0, and this charge repulsion is less important than size exclusion. Licona *et al.* (2018) evaluated the separation of some pharmaceutical compounds, and NF was able to separate the hydrophobic diclofenac (in pH 4.0) with the rejection of approximately 95% by the NF90 membrane from Dow Filmtec. Thus, each compound is separated by NF by two main mechanisms (size exclusion and charge repulsion), but the membrane charge, hydrophobicity of the compound, and pH of the solution are important variables and interfere with the membrane rejection (Taheran *et al.*, 2016).

The NF membrane can be also compared to ultra-low-pressure RO membranes as they have higher permeated flux and lower rejection than high-rejection RO membranes. Dalbosco *et al.* (2021) tested the ULP-2012 RO membrane from Vontron manufacturer to remove FLX, and the permeate flux was less than 16 L h^{-1} m^{-2} in 600 kPa (less than 50% of the permeate flux of this study). On the other hand, the rejection of FLX was 99.5% (50% higher than the rejection of this study). Thus, choosing the appropriate membrane using rational methods between membrane selectivity and productivity is necessary. Song *et al.* (2020) studied the removal of several pharmaceuticals from water samples, and the rejection was between 30% and 85% for NF. The authors reported that NF is not always an effective process to remove all pharmaceutical compounds, it is necessary to test to evaluate the target pharmaceutical and the required efficiency of the process.

3.1. Experiments using the RO membrane

Figure 3 shows the permeate flux of the RO membrane in the FLX separation at different pressures. Higher pressures promote higher permeate flux as the pressure is the driving force of the movement across the membrane. The permeability of the membrane in the FLX separation was 0.0158 L m^{-2} h^{-1} kPa^{-1} (1.58 L h^{-1} m^{-2} bar $^{-1}$), and the pure water permeability of the RO membrane was 1.9 L h^{-1} m^{-2} bar $^{-1}$. Thus, there is a reduction in permeability even if the FLX concentration is lower (only 20 mg L^{-1}).

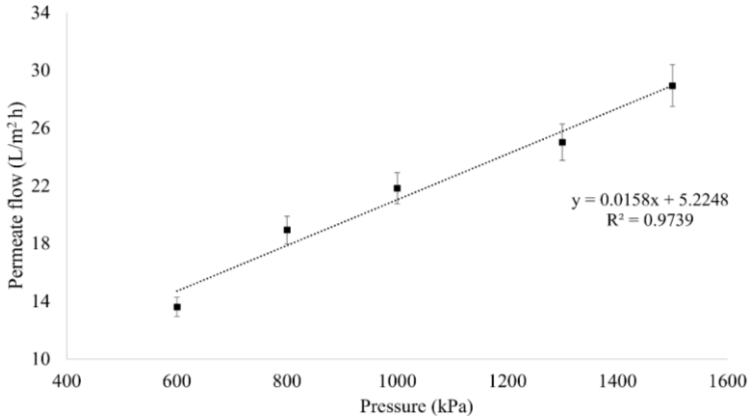

Figure 3. Permeate flux across the RO membrane at different pressures in the separation of fluoxetine (20 mg L^{-1}).

Table 3 shows removal of FLX by RO at different pressures. The rejection of FLX by the RO membrane generates polarization concentration. In addition, as the gradient concentration rises between the permeate and retentate sides, FLX passes through the membrane by diffusion (Dalbosco *et al.*, 2021).

Table 3. Rejection of FLX in the RO membrane at different pressures.

Pressure (kPa)	600	800	1000	1300	1500
Rejection (%)	98.8±0.7[a]	98.8±0.8 [a]	98.8±0.7 [a]	98.5±0.5 [a]	98.8±0.8 [a]

[a] Indicates statistically similar values on the same row.

Pressure does not affect membrane rejection, and the average removal was 98.74%. A decrease in rejection with low pressure by the so-called "dilution effect" was expected (Padilla *et al.*, 2010), but it did not occur because the solute passage followed the passage of solvent across the membrane. Dalbosco *et al.* (2021) assessed the separation of FLX using an ultra-low-pressure RO membrane, and the rejection was higher than 99%. Alonso *et al.* (2018) studied RO to remove ciprofloxacin (FLX-like structure with comparable molar mass and presence of fluoride) from water, and they reported rejections between 90 and 99%, with mass and structure similar to FLX. Song *et al.* (2020) reported rejections of RO in a range between 60% and 99%. The variations depend on the model, matrix, and characteristics of the target compounds and membrane.

Generally, the rejection of solutes by RO is influenced by the dipole moment, hydrophobicity, and molecular size of compounds. The MWCO of the RO membranes would be more useful than "salt rejection" for evaluating the rejection of drugs, although it cannot be used for precise prediction. Although many researchers have focused on the mechanisms of solute transport in NF membranes, including electrostatic interaction, hydrophobic interaction, and size exclusion, further studies are required to understand the mechanism, which is affected by solute properties, membrane parameters, feed water composition, and operating parameters (Taheran *et al.*, 2016). Lin (2017) reported that steric hindrance and electrostatic repulsion work synergistically to increase NF rejection with increased pH and membrane fouling, while steric hindrance dominates RO rejection. Steric effects are the main mechanism involved in the rejection of pharmaceutical compounds by NF and RO membranes (Couto *et al.*, 2020). The electrostatic effect is also significant in the rejection of charged compounds, justifying the high rejection of negatively charged pharmaceuticals (Foureaux *et al.*, 2018; Rigueto *et al.*, 2020), but FLX is neutral at pH 7. On the other hand, the passage of organic compounds through the membrane can also be associated with the hydrophobic part of the pollutant that interacts with the membrane matrix, while the hydrophilic part can diffuse across the membrane via hydrogen bonds with water (Couto *et al.*, 2020). FLX is hydrophobic as its pK_{ow} is higher than 2 (Licona *et al.*, 2018), but it is positively charged in pH below pK_a. The surfaces of NF and RO membranes are negatively charged at neutral pH solutions due to the deprotonation of surface carboxyl groups (Licona *et al.*, 2018). Thus, positively charged micropollutants at neutral pH are not in the best condition to be removed by NF and RO (Song *et al.*, 2020).

Thus, the higher removal of FLX by RO (>98%) than NF (between 50% and 60%) shows a sieving effect as the RO membrane pores are smaller (<1 nm) than NF, and it removes low molecular weight species such as inorganic solids (including salt ions, minerals, and metal ions) and organic molecules (Zhang *et al.*, 2020). The RO membrane produced a better permeate quality, whereas NF produced higher permeate flux (Brião *et al.*, 2019). However, any technology has advantages and limitations. Both NF and RO applied to the removal of FLX generate the retentate, and it requires another technology to treat this stream-loaded FLX. Thus, complementary technologies can be studied to treat this situation.

4. CONCLUSION

The applied technologies showed promising results and potential for application in removing FLX from water under experimental conditions.

The NF membrane obtained relatively lower removal of fluoxetine, reaching up to 59.9% rejection, which indicates physical-spatial removal. On the other hand, the RO membranes used showed high rates of FLX removal (up to 98.8%) in the tests performed.

The tests proved that the RO membrane is more effective than NF in removing FLX from water, and RO is an alternative to advanced water treatment to remove FLX from water and produces a better quality of water.

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6. ABBREVIATIONS

NF - Nanofiltration

RO - Reverse Osmosis

FLX – Fluoxetine

PA – polyamide

PS – polysulfone

ESI – electrospray ionization

MWCO – molecular weight cut-off