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A Study on Behavior, Interaction and Rejection of Paracetamol, Diclofenac and Ibuprofen (PhACs) from Wastewater by Nanofiltration Membranes

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Abstract:

Along with many other Pharmaceutically Active Compounds (PhACs), Diclofenac (DIC), Ibuprofen (IBU) and Paracetamol (PARA) are the most common type of Non-steroidal anti-inflammatory drugs (NSAIDs), which are frequently reported in drinking and treated waters. Membranes can be used to inhibit the passage of these organic micropollutants (Pharmaceuticals) into water that can be further reused. In this study, two types of loose nanofiltration membranes, that usually are applied for large molecular weight organics, were tested for the filtration of selected small molecular weight drugs from synthetic wastewater. Effect of pH on membrane efficiency showed that behavior of drugs altered with changing pH. Results showed impressive treatment of drugs in the order, DIC (99.7%) > IBU (81.2%) > PARA (49%) along with Total Organic Carbon (TOC) (95.3%) and Chemical Oxygen Demand (COD) (84%) removal. Interestingly, nanofiltration of wastewater containing IBU tablet increased to 90.2% as compared to pure drug (80.5%). Mixture of drugs showed decreased removal of DIC (23%) while removal rates for IBU and PARA increased to 17.1 and 67%, respectively. Moderate to high rejection percentage was not due to the molecular sizes of the model drugs but hydrophobicity of drugs played role.

Keywords: Membrane technology; nanofiltration; non-steroidal anti-inflammatory drugs; pharmaceuticals; water reuse.

1. Introduction

Pharmaceutically Active Compounds (PhACs) are persistent organic micropollutants and are frequently reported in drinking water and other water reserves around the world because drinking water and wastewater treatment plants usually lacks the ability to treat micropollutants with complex chemistry and structures (Ouyang et al., 2019; Huang, et al., 2019). The use and range of pharmaceutical is increasing in parallel with their adverse effects both directly or indirectly on ecological species every year (Wei et al., 2018). They are equally harmful for humans, animals and biota, despite their low concentrations (ng L^{-1} to $\mu\text{g L}^{-1}$) (Roig, 2010; Bellona et al., 2010, Azaïs et al., 2014; Garcia-Ivars et al., 2017). In this study three PhACs, Diclofenac (DIC), Ibuprofen (IBU) and Paracetamol (PARA) has been selected as pollutants. Nonsteroidal anti-inflammatory (NSAID), analgesic and antipyretic drugs are most frequently used and produced around the globe in hundreds of tons annually (Huang et al., 2019; Pedrouzo et l., 2011). Although their long-term effects of continuous discharge into waters are not completely known yet (Mondal et al., 2016a; Mompelat et al., 2009). Due to their biologically active nature, persistence and metabolites (Lourenção et al., 2009; Solé et al., 2010) they can affect non-target organisms, like bacteria, even at trace levels (Hernando et al., 2006; Yoon et al., 2007), therefore, elimination of these pharmaceuticals from wastewater is crucial. Not only reproductive, gastrointestinal, cardiovascular, kidney, repression in endocrine cells in humans are linked with these drugs but also, they may be the reason of genetic and systematic damage to some mussels and fish species (Ericson and Kumblad, 2010; Kristensen et al., 2018). In addition, directives related to pharmaceutical pollutants are not well established except for the most common antibiotics. UK

Environment Agency identified Diclofenac and Ibuprofen as subject of significant investigations (Yuan et al., 2017).

The removal of PhACs has been studied by means of Advance Oxidation Processes (AOPs), such as, Classic Fenton Process, Photo-Fenton Process, Modified-Fenton Systems, treatment with Photocatalysis and Ozonation. These oxidative technologies revolve around the formation and employment of a powerful oxidant, called hydroxyl radical ($\cdot\text{OH}$) (De la Cruz et al, 2012; Wols et al., 2013). However, the use of different catalysts within the system, catalyst recovery, high energy requirements, long and controlled retention time and costly disinfection of treated water as a final step of water treatment, are reported to be the major disadvantages of this treatment (de Araújo et al., 2016).

Membrane techniques show advantages over conventional wastewater treatment such as physico-chemical or biological processes (Maryam et al., 2017). Although biological treatments are cheap and show high efficiency in organic matter removal, recalcitrant compounds such as pharmaceutical are nonbiodegradable and cannot be removed completely or even found in increased quantities in the effluents of conventional WWTP as reported by Zorita et al., in 2009 due to their persistent nature, conjugation and de-conjugation. Disturbance in conjugation may results in the re-release of pharmaceuticals into the environment (Joss et al., 2008). On the other hand, chemical treatments require the addition of reagents to carry out the process. It is important to highlight that neither biological nor initial physical or chemical treatments enable the treated water to be reused (Mauter et al, 2018).

Membrane technology has been reported to be a potential alternative to the treatments currently employed to treat effluents containing pharmaceuticals. It has been found that efficiency of membranes is firmly dependent on physical properties of membrane along with the chemistry

of pollutants (Alturki et al., 2013). Microfiltration and ultrafiltration are generally low-pressure membranes largely used for particulate matter removal composed of relatively larger particles that can be seen with naked eye, whereas Nanofiltration (NF) and Reverse Osmosis membranes (RO) falls into the category of high-pressure membranes and can be used for the removal of organic and inorganic micropollutants (pharmaceuticals) divalent or multivalent ions. According to literature, the main disadvantage of the nanofiltration and reverse osmosis membrane treatment is the operational cost related to membrane fouling (Ong et al., 2012). A lot of studies have been conducted and reported their successful removal of micropollutants with especially designed tight (low molecular weight cut-off) NF membranes, that preferably worked on the principal of sieving (Bellona et al., 2010, Nghiem et al., 2007; Comerton et al., 2008; Kim et al., 2008; Chakrabarty et al., 2008; Snyder et al., 2007; Azaïs et al, 2016). Table 1 shows limited studies focused on NF membranes that generally have very low (Molecular weight cut-off) MWCO as compared to our selected membranes to remove PhACs.

Loose (high molecular weight cut-off) NF membranes were selected in the present study, as NF membranes not just carry out their operations with molecular sieving effect (steric exclusion), but they also operate on the principals of Donnan or dielectric exclusion and Adsorption (hydrophobic interactions). Mechanism of Steric exclusion in NF membranes is primarily for neutral organic molecules, baring large MW (Molecular weight) than the membrane pore size. Rejection of charged molecules by NF membranes is carried out with the help of Donnan exclusion, when positively or negatively charged molecular species present in solvent interacts with charges present on the surface or matrix of membrane by building an interface (Epsztein et al., 2018). Loose NF membranes can be equally useful for the retention of micropollutants as they work on the principle of adsorption of charged species on to the active layer. Hydrophobic

interactions, high octanol water partition coefficient ($\text{Log } K_{ow}$) and $\text{Log } D_{ow}$ can increase adsorption mechanism, at a given pH (Yoon et al., 2007; Zhao et al., 2017; Park and Snyder, 2020)

Physiochemical properties of feed like pH, hydrophobicity, concentration and type of pollutants can create an electrostatic potential that helps in rejection of pollutants by interacting with the matrix of NF membranes. Surface charge on nanofiltration membranes are usually negative, that by principle, repels negatively charged species and attract cations to maintain their electroneutrality. These electrostatic interactions reject divalent anions more efficiently rather than monovalent ions, that pass into permeate (Epsztein et al., 2018). Table 1 shows limited studies focused on NF membranes that generally have very low (Molecular weight cut-off) MWCO as compared to our selected membranes to remove PhACs.

Very few studies on the use of loose NF membranes to remove PhACs from water have been found in the literature (Radjenović et al., 2008). Type of NF membranes used in present work were not tested before against selected drugs as their use is more common in dyes and colour removal. It was implicit that loose NF membranes with bigger pore size can reject PhACs by using mechanisms of Absorption and Donnan exclusion without fouling. It has been reported that by optimization of the pH, charge effects and polarization of feed components, rejection by Sulfonated Polyethersulfone NF membranes can be increased by the dissociation of surface groups such as sulfonated or carboxyl acids, however, the efficiency of these membrane may decrease when they are subject to mixture of organic micropollutants. Hydrophilic functional groups that can be present onto Polyethersulfone are usually sulfone, carboxyl, hydroxyl, and amine function that can assist rejection by making bonds with the pollutants (Park and Snyder, 2020; Wavhal et al., 2002).

115 Considering previous studies, this work was conducted with Sulfonated Polyethersulfone
116 nanofiltration membrane having MWCO higher than the molecular weight of pharmaceuticals, by
117 because tight NF membranes with low MWCO are prone to irreversible fouling. Therefore,
118 purpose of this study was to test loose NF as equally useful and efficient as tight NF membranes
119 and to check their behavior at extreme pH values. Effect of extreme pH on the removal of Non-
120 steroidal anti-Inflammatory drugs (NSAIDs) was studied by preparing a synthetic effluent
121 containing three pure drugs (PARA, IBU, DIC). Subsequently, in case of Ibuprofen, the results
122 obtained were compared with commercially available tablet of ibuprofen. The efficiency of the
123 treatment was also determined in terms of COD and TOC removal. Finally, the membrane fouling
124 was measured by controlling changes in the permeate flux.

125 **Table 1.** Rejection of selected pharmaceuticals by Nanofiltration membranes reported in literature
126 in comparison with the present study

(PACs)	pH	Removal %	Membrane Name	Manufacturer	Material	MWCO (Da)	Reference
PARA ^a	8	47.9	NF 270	Dow Chemical Co.	Polyamide	400	(Alturki et al., 2010)
PARA	8	31.2	TS 80	TriSep, 4040-TS80-TSF, Goleta, CA	Polyamide	<200	
DIC ^b	5.6 - 6.1	100	NF 90-400	Dow FilmTec	Polyamide	200	(Radjenović et al., 2008)
		44.8					
IBU ^c	7.5	45	NF	ESNA, Hydranautics, USA	Aromatic polyamide	600 (±200)	(Yoon et al., 2007)
DIC		10					
PARA		30					
IBU	6.5 - 7.5	99	TS 80	TriSep Corporation, Goleta, CA, USA	Cross-linked aromatic polyamide top layer	200	(Verliefde et al., 2009)
DIC		99					

IBU		98	Desal HL	GE Osmonics, Fairfield, CT, USA		150–300	
	4 - 9.8	100	NF 90	Dow FilmTec (Minneapolis, MN)		200	
IBU	6.3 - 9.8	99	NF 270	Koch Membrane Systems (San Diego, CA)	Polyamide thin- film with a microporous Polysulfone	200-300	(Nghiem et al., 2007)
	9.8	84	TFC-SR2			-	
DIC	Neutral	93	ESNA	Hydranautics, Oceanside, CA	Polyamide TFC	200	(Kimura et al., 2003)
PARA	6.5	44	NF 270	-	Polyamide		(Bellona et al., 2010)
PARA IBU	7	22 89	NF 200	Dow-FilmTec, Midland, MI	Aromatic polyamide	~300	(Yangali Quintanilla et al., 2010)
PARA IBU	6 - 7	75 96	NF 90			~200	
PARA IBU		0 99			Thin aromatic or semi- aromatic polyamide	200–300	
DIC	7.4 - 7.6	95	NF 270	Dow FilmTec (Minneapolis, MN, USA)			(Alturki et al., 2010)
PARA IBU		99	NF 90		Polyamide	~200	
DIC		90					
PARA DIC IBU	6.3	0 100 100	NF 4040	Dow/Filmtec	Polypiperazine- amid thin-film composite	-	(Bellona et al., 2007)
		31	NF 270		Polypiperazine with polymeric active layer	220	
PARA	7			DOW Filmtec	Polyamide supported by a Polysulfone	102	(Azaïs et al., 2014)
		91	NF 90				
PARA DIC IBU	8 7 8	90 100 99	MPS-34	Koch Membrane Systems	Proprietary Polysulfone composite membrane	200	(Garcia- Ivars et al., 2017)
PARA DIC IBU	6 8 8	38 62 58	TFC-SR2	Koch Membrane Systems	Proprietary Polyamide	> 300 – 400	

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PARA	7	84			Polyamide		
DIC	7 - 8	98	NF-270	Dow FILMTEC	Thin-Film	230 -	
IBU	8	95			Composite	300	
DIC	8	61			Hydrophilic		
IBU	8	55	FM NP010	Microdyn- Nadir, GmbH, Germany	Polyethersulfon e	1000	(Vergili, 2013)
PARA	12	36.16			Sulfonated		
DIC	3	99.74	NF 50	Hydranautics HYDRACoRe, Oceanside, CA, USA	Polyethersulfon e	1000	Present work
IBU	6 - 7	80.54					

2. Materials and Methods

2.1 Chemicals and Reagents

Ibuprofen Sodium Salt (purity 99%), Acetaminophen (purity 98%) and Diclofenac Sodium Salt (purity 98%) were purchased from Sigma Aldrich and were used in the present study without further purifications. Table 2 provides the physicochemical properties and chemical structure of the model drugs. The pH of solution containing pharmaceuticals was adjusted with NaOH and HCl (Scharlau Sentmenat, Spain). Sodium hypochlorite solution (1:90 v/v) (6% – 14% active chlorine, Sigma-Aldrich) was used for the membrane cleaning.

Table 2. Physicochemical properties of selected pharmaceuticals (Analgesic/Non-steroidal anti-inflammatory drug (NSAID) (Ouyang et al., 2019; Garcia-Ivars et al., 2017; Padhye et al., 2014; Feng et al., 2013; Albero et al., 2014; Ding et al., 2011).

Compound	Diclofenac	Ibuprofen	Paracetamol (Acetaminophen)
Formula	C ₁₄ H ₁₁ C ₁₂ NO ₂	C ₁₃ H ₁₈ O ₂	C ₈ H ₉ NO
IUPAC	2-[2-(2,6-dichloroanilino)phenyl]acetic acid	(RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid	N-(4-hydroxyphenyl)ethanamide,N-(4-hydroxyphenyl)acetamide
MW (g mol ⁻¹)	318.13	206.29	151.16
Solubility in water (mgL ⁻¹)	2.37	<1, 49,	1.40×10 ⁴

Log K_{ow}	4.26/4.51	3.84/3.97	0.46-0.49
pK_a	4.15	4.52/4.91	9.86/9.38
Dipole moment	2.51	1.22	3.85
Log D_{ow}	4.28	2.67	0.91
Nature	Hydrophobic ionic	Hydrophobic ionic	Hydrophilic nonionic
Charge at pH 7	-1	-1	0

D_{ow} pH-dependent octanol-water distribution coefficient (dimensionless) (Garcia-Ivars et al., 2017)

2.2 Synthetic Effluent Preparation

Effluents with the final volume of 1 liter were prepared by adding individual concentration of 0.1g of model drugs (Diclofenac, Ibuprofen and Paracetamol) in 1 liter of distilled water, that were stirred for at least 4 hours. In case of mixture of drugs, 0.1g of each drug in total volume of one liter was used. Finally, pH and conductivity of the effluents were measured.

2.3 Membrane Treatment

Two types of loose nanofiltration membranes, HYDRACoRe 50 (NF50) and HYDRACoRe 10 (NF10) by Hydranautics (Oceanside, CA, USA) were tested. According to manufacturer's claim, these membranes are chemical and oxidant-resistant and can be applied to remove large molecular weight organic compounds from industrial, food, beverages, dyes and municipal feedwaters (Buscio et al., 2016). Selected membranes were hydrophobic, (nature of selected drugs are given in table 2) and their main characteristics are shown in Table 3 (Buscio et al., 2016). The operating parameters were selected according to the system scale and setup in given time and space, as shown in figure 1.

Table 3. Specifications of nanofiltration membranes used in the scope of present study

Membrane Characteristics	NF50	NF10
Membrane Polymer	Sulfonated Polyethersulfone	Sulfonated Polyethersulfone
Molecular Weight Cut-off	1000 Daltons	3000 Daltons
Maximum Applied Pressure	41 bar	41 bar
Maximum Operating Temperature	45 °C	45 °C
Maximum Chlorine Concentration for Cleaning	0.1 g L ⁻¹	0.1 g L ⁻¹
Operating pH Range	2–12	2–12
Cleaning pH Range	1-12	1-12

2.3.1 Membrane Pilot Plant

A pilot plant (Polymem, France) with operating volume of 0.5 L was used in experiments (Figure 1). The tests were carried out in a batch pilot plant dead-end filtration system with continuous agitation at room temperature. The pressure was set at 8 bar for all experiments. The membrane with surface area of 0.0064m² was placed over a plastic porous support at the lower end of pilot plant. Filtration experiments were performed by adding 0.4 L of synthetic effluent containing model drugs into membrane reactor until 0.1 L of permeate was collected. After each experiment, a cleaning procedure was followed to remove impurities from the surface of membrane. The washing of membrane was carried out in the following steps: 1) rinsing with distilled water 2) soaking of membrane into 0.005g L⁻¹ sodium hypochlorite solution overnight 3) Soaking in Distilled water for 10 minutes, prior to use.

Figure 1. Systematic diagram of nanofiltration membrane setup

2.4 Analytical Methods and Measurements

The permeate flux was determined according to the equation (1).

$$J = V / (A \times \Delta t) \quad (1)$$

where J is the permeate flux ($\text{Lm}^{-2}\text{h}^{-1}$), A is the effective area of the membrane (m^2), and V is the collected volume in a time interval Δt (Lh^{-1}).

Percentage drug removal ($\%R_{\text{drug}}$) was determined by the following equation:

$$R_{\text{drug}} = \{(c_i - c_t) / c_i\} \times 100 \quad (2)$$

Where c_i is the initial drug concentration and c_t is the drug concentrations at time (t)

Shimadzu UV-VIS spectrophotometer UV-2401 (Kyoto, Japan) was used for drug absorbance measurements at the maximum wavelength of the UV-visible spectrum. The calibration curves for each drug were:

$$\text{Abs} = 0.0684x + 0.0249 \quad (R^2 = 0.998); \lambda = 243 \text{ nm (for Paracetamol)} \quad (3)$$

$$\text{Abs} = 0.0364x + 0.001 \quad (R^2 = 0.9999); \lambda = 222 \text{ nm (for Ibuprofen)} \quad (4)$$

$$\text{Abs} = 0.0328x - 0.0067 \quad (R^2 = 0.9998); \lambda = 276 \text{ nm (for Diclofenac)} \quad (5)$$

Shimadzu Total Organic Carbon Analyzer TOC-L (Kyoto, Japan) was used to carry out total organic carbon test before and after the sample treatment.

COD was determined by using standard method (Standard Methods, 2012) along with conductivity and pH by conductivity meter; GLP 31 (CRISON) and pH meter; GLP 21 (CRISON) respectively.

Scanning electron microscopy (SEM) images of membrane before and after filtration were obtained with Schottky Emission Scanning electron microscope (Model, JSM-7001F by JEOL).

3. Results and Discussion

The synthetic effluents containing 0.1 gL^{-1} of pharmaceutical standards were treated by means of two nanofiltration membranes. These micropollutants (PhACs) were selected on the bases of their unique characteristics like molecular weight, hydrophilicity/hydrophobicity and dissociation constants. Their interaction with the surface of membranes was dependent upon their nature, for instance, Diclofenac and Ibuprofen are hydrophobic in nature whereas, Paracetamol is hydrophilic (Table 2) but their nature alters with change in pH. The initial results illustrated in Figure 2, depicts the hydrophobicity dependent drug-membrane interactions at pH 6-7. NF50 membranes, with lower molecular weight cut off, showed 80.5, 43.3 and 26% of IBU, DIC and PARA removal respectively by using equation 2, whereas, the NF10 membranes, with higher molecular weight

cut off, provided less than 10% retention for all the three selected drugs with percentage values of 9.1, 9.7 and 8.1 for DIC, IBU and PARA, respectively (Figure 2). NF50 membranes had relatively lower MWCO, that represents pore size, in comparison to NF10 as given in table 3. Although in present study, MWCO played very minimal role in rejection of drugs but NF10 was unable to interact with drug molecules as permeate flux was fast and solution passed from one end to another very rapidly due to its higher MWCO.

Figure 2. Average percentage removal of three drugs with two types of Nanofiltration membranes.

In most of the studies, it has been observed that compounds with a molecular size larger than the pore size of the membrane were efficiently rejected simply with the sieving effect of the membrane polymer (Licona et al., 2018; Huang et al., 2019). This can be explained well with the idea that if the solute is neutral or have pH in the range of 6-7 along with high molar mass, rejection by nanofiltration will be finest (Park and Snyder, 2020). Therefore, with the help of membrane pore size it can be easily predicted that which compound of what molecular size can be rejected

(Verliefde et al., 2009) along with membrane efficiency. However, in present study, results indicated that sieving effect of NF membrane had not played any role as apparently, rejection of PhACs was not linked with molar mass and MWCO, because MWCO of selected membrane was far higher than the MW of selected drugs. This leads towards the other two NF membrane governing mechanisms, for instance, dielectric exclusion and Donnan exclusion (Schäfer et al., 2004; Van der Bruggen et al., 2002).

Present study is in agreement with previous studies on the aspect of steric exclusion of nanofiltration especially when molecules are charged and hydrophobic (Vergili, 2013), however, hydrophilic interactions some time show poor retentions due to opposite charges. For the studied drugs (IBU, PARA, DIC) the molecular size did not have any influence, however, their $\log K_{ow}$ values, dipole moments, functional groups and charges played a role in their rejection and flux by NF membranes. Polarity of molecules can be studied by the dipole moment of molecules (Yangali Quintanilla, 2010). Dipole moments of selected pharmaceuticals are given in Table 2, which shows PARA has highest polarity but in this case its relatively poor rejection is linked with its very low MW. Polar compounds show better retention with NF membranes (Bellona et al., 2007). Electrostatic interactions or Donnan exclusion mechanism of membrane is based on the attraction or repulsion of ions presents in solute. For instance, a membrane with a negative charge will have better rejection for negatively charged compounds because of repulsion like in the case of DIC and IBU (Vergili, 2013).

$\log K_{ow}$ is the octanol water partitioning coefficient, that represents the hydrophobicity of a compound, is also a significant factor in membrane separation technology. $\log K_{ow}$ of selected pharmaceuticals are also given in table 2. More hydrophobic compounds or compounds with the higher $\log K_{ow}$ value will show maximum adsorption on the surface of membrane (Verliefde et

al., 2009) for instance, DIC has highest Log K_{ow} value among other selected drugs, but at neutral pH (6-7) its rejection was not efficient that directs towards its pH dependent removal (Figure 2). IBU and DIC are hydrophobic and showed high removal whereas paracetamol being hydrophilic showed only 8.1 and 26.0 % removal with NF10 an NF50 respectively. Higher rejection of IBU and DIC was achieved due to their high log K_{ow} values, low dipole moments and negative charges by electrostatic repulsions from membrane surface. In literature, same trend was observed by Vergili (2013) (Vergili, 2013). Regarding TOC and COD removal, for NF50 membrane, Ibuprofen showed the higher COD removal (81.2%), followed by DIC (32.89%) and PARA (14.28%). No significant TOC and COD removal (less than 10%) was observed with NF10 membrane. The comparison of results is illustrated in Figure 3.

Figure 3. Comparison between membrane efficiencies with respect to COD and TOC tests.

pH of the solution cannot be ignored while studying application of membrane technology for the removal of Pharmaceuticals from wastewater especially when $MWCO > MW$. Nature of membrane and properties of contaminants can be altered by pH. This influence of pH and

membrane mechanism on the pharmaceutical rejection will be discussed for each selected drug in the following sections.

3.1 Effect of pH:

For Further experimentation only NF50 membrane was considered as its removal efficiency along with COD and TOC test confirmed its applicability on our set of drugs. The experiments were carried out at different pH values of 3, 6-7, and 12 showed that the nanofiltration efficiency is strongly dependent on pH (Figure 4). To understand the effect of changing pH of solute on NF, study of water partition coefficient ($\log K_{ow}$) or $\log D_{ow}$ is essential. $\log D_{ow}$ is the ratio between the charged and uncharged form of a compound, at given pH (Garcia-Ivars et al., 2017). Hydrophobicity of a solution can be inferred by these values, as $\log K_{ow}$ higher than 2 are defined as hydrophobic (Vergili, 2013). This phenomenon is also dependent on pK_a value of each compound present in solute (Nghiem and Hawkes, 2007) when the pH of the solution is more than the pK_a of compound, a release of proton will cause a negative charge or in other case, charge will be neutral, weak or positive (Ganiyu et al., 2015).

Electrostatic interactions, functional groups and hydrogen bonds of membrane surface or solute can alter hydrophobicity, which are also directly linked with a change in pH. In present study, membrane was made up of two polymers, Polysulfone, which supports hydrophobicity due to its hydrophobic nature and polyethersulfone (PES), that supports hydrophilic functional groups (Wavhal et al., 2002; Alenazi et al., 2007). This unique mechanical property of such membranes not only can assist the rejection of hydrophilic compounds but also can prevent fouling by increasing permeate flux. Solubility of charged or neutral organic compounds also varies with their acid-base solution interactions with membrane because of groups like carboxyl, hydroxyl, and

amines present on the surface of membranes (Alenazi et al., 2007), for instance, presence of groups like carboxyl and phenols helps in a negatively charged surface of membrane that repels positively charged drugs like PARA and IBU and amines aids in a positive charged surface of membrane that helps in the rejection of negatively charged drugs like DIC, IBU by releasing and gaining of protons respectively (Wavhal et al., 2002; Alenazi et al., 2007).

3.1.1 Rejection of paracetamol (non-ionic, hydrophilic compound)

Rejection of PARA under different pH with NF membrane was in the order, pH12 > pH 6-7 > pH 3 (Figure 4). As $\log K_{ow}$ of PARA is lower than 2, it is defined as hydrophilic. At pH 7 PARA is uncharged and showed 26% of retention may be because some hydrophilic molecules can be rejected due to the solute-membrane interactions between them. Maximum removal of PARA (36%) was observed at pH 12 as shown in Figure 4 along with COD and TOC. pH of the solution higher than the pK_a value generates a negative charge on the surface of drug molecules that as a result, facilitates rejection with hydrophobic membrane simply because of electrostatic interactions. Strong negative charges repeal drug molecules, not allowing them to pass through the membrane surface. Similarly, at pH 3, Dipole moment for PARA was highest and may have dissociated into a dominant positive charge which cause diffusion or adsorption on the surface of membrane by just removing a small quantity (12%). This also can generate a hydrophobic foulant layer on the surface of membrane creating higher affinity for water, thus allowing paracetamol (hydrophilic compound) to pass through membrane with water (Garcia-Ivars et al., 2017). Solubility of PARA also can vary at different pH values, results indicated that at alkaline pH solubility of PARA decreased that increased its rejection. But because of its dominant hydrophilic nature ($\log D_{ow} < 1$) and very small MW, overall poor rejection was observed. Similar results, higher removal at alkaline pH, but generally, poor rejection (below 50%) were reported by many

researchers even with the tighter NF membranes (Table 1) (Comerton et al., 2008; Bellona et al., 2010, Radjenović et al., 2008, Yangali Quintanilla, 2010).

3.1.2 Rejection of diclofenac (ionic, hydrophobic compound)

Charged (positive or negative) micropollutants (pharmaceuticals) are mainly rejected by electrostatic interactions with the charged membranes (in this case negative). Pharmaceuticals will be negatively charged at pH values, higher than their pK_a values. Diclofenac was negatively charged at pH 6-7 and 12 as these pH values are higher than their pK_a value. However, at pH 3 it can be positively charged as its pK_a value is 4.08 (lower than pH). Higher removal of Diclofenac was obtained at acidic pH (99.74%) along with higher COD (84.08 %) and TOC (95.37 %) removal. Here, under pH 3 the dipole shift on DIC molecule brings a major change in the behavior of membrane too. Under this scenario average pore size or quantity of pores on membrane surface does not play a significant role, instead because of Hydrophilic functional groups (amines) present on membrane surface and possible positive charge on DIC molecule were the reasons of maximum rejection because of repulsive forces. In the presence of carboxylic and ammonium groups, positive charge at low pH and a strong negative charge at higher pH on a hydrophobic membrane is also reported by Azais et al. (2014) as COO⁻ group at lower pH do not dissociates at lower pH and ammonium group facilitates positive charge on membrane at lower pH (acidic) (Azaïs et al., 2016; Azaïs et al., 2014). Similarly, at this pH, adsorption of DIC on to membrane surface can also play a role because of charge exclusion mechanism, that also can cause fouling. But due to hydrophilic interactions fouling was not observed (Epsztein et al., 2018). Hydrogen bonding and electrostatic interactions of pharmaceuticals and macromolecules complexes present in wastewater can increase rejection of drugs from real wastewater (Azaïs et al., 2016). At pH 12, rejection of DIC was poorest (5.3%), this can be explained by weak charge on its molecule caused by weak

dipole moment (polarity) (Garcia-Ivars et al., 2017; Vergili, 2013; Yangali Quintanilla, 2010) as mentioned in table 2. Therefore, it can be inferred that rejection of DIC with NF50 membranes was inversely proportional to the dipole moment (Vergili, 2013) At pH 6-7 rejection of DIC was 43.3% due to Donnan exclusion. Since the membrane surface was hydrophobic (negatively charged) at neutral pH because of its ionizable sulphonic or carboxylic functional groups, strong dipole interaction was present between DIC and membrane surface. Hydrophobicity allows rejection in this case but because of very loose NF overall rejection was lower at neutral pH (Verliefde et al., 2009; Verliefde, 2008; Bartels et al., 2005)

3.1.3 Rejection of ibuprofen (ionic, hydrophobic compound)

Ibuprofen exhibits a wide range of speciation properties, for instance, it is reported to be negatively charged at pH 6-7 and 12 as these pH values are higher than its pK_a value ($pH > pK_a$), however, at pH 3 they can be neutral ($pH < pK_a$), positively charged or even a mixture of both ($pH \approx pK_a$) as their pK_a values are 4.40 (Ren et al., 2017). In the case of Ibuprofen at neutral pH best results were obtained (80.5%) along with COD (81.2%) and TOC (77%) because at this pH, ibuprofen is hydrophobic and was rejected because of Donnan exclusion. At pH 3 electrostatic repulsion between ibuprofen and the membrane surface is minimal because of opposite charges, that decreases the removal rates but on the other hand, allowing uncharged or slightly charged IBU to adsorb on the surface of membrane, may have caused IBU retention (55.0%). This percentage shows the with the simultaneous occurrence of both processes (Garcia-Ivars et al., 2017; Bartels et al., 2005), IBU can be removed with NF50 membrane at pH 3, until membrane reaches its adsorption saturation. Solubility of IBU at lower pH (acidic) is also reported as low (Nghiem and Hawkes, 2007), that could be the reason of its 55% rejection at pH 3. Ibuprofen is slightly hydrophobic as its $\log D_{ow}$ is lower than 3 at higher pH values (pH 12). Therefore, because of its

low solubility and nonionic nature, ibuprofen was hydrophilic at higher pH values, as reported by other researchers (Nghiem and Hawkes, 2007; Garcia-Ivars et al., 2017). Oh et al., in 2016 also demonstrated that the solubility of ibuprofen significantly increases at basic pH conditions, resulting in a decrease in the hydrophobicity of the anionic ibuprofen (Nghiem and Hawkes, 2007; Li et al., 2004).

This change in hydrophobicity for ibuprofen at pH 12 was also therefore the reason for 34% rejection. But still 34% of IBU removal at pH 12 cannot be ignorable, change in hydrophobicity does not means a complete loss of dipole moment. Negative charges may have facilitated removal at this pH or both processes (solubility and hydrphobicity) occur simultaneously, and their contributions can be studied with the obtained rejection percentage.

Figure 4: Effect of pH on NF50 membrane efficiency

3.2 IBU Tablet and Membrane Efficiency

Performance of NF50 membrane was tested against one liter of tap water solution of crushed IBU tablet that contained 100 mg (0.1g) of IBU. The results are shown in Figure 5. The pH of

the solution was 6.5. At this pH the removal of tablet was better (90.25%) than the pure form of IBU standard (80.54%). However, TOC and COD of IBU Tablet was not efficiently removed in comparison to IBU standard. IBU tablet is almost non-charged or nearly neutral unlike pure drug and is not a pure form of drug which may also contains other organic compounds that are bonded with IBU molecule. The whole complex of IBU tablet may increase the MW of compound equal and greater than MWCO of NF50 that can support sieving effect. In case of IBU tablet, role of steric exclusion and electrostatic interaction is also important. Negative charge on drug molecule ($\text{Log } K_{ow}$ more than 2 are hydrophobic) and membrane with negative charge create electrostatic forces. In this particular case, the presence of divalent cations like Ca^{2+} and Mg^{2+} in tap water, can also change the efficiency of the treatment by not only facilitating bonds between IBU and other molecules present in solution but also by altering charge on the membrane surface (Bartels et al., 2005). The results obtained were in accordance with the results reported by Nghiem et al., (2006), Bartels et al. (2005) and Vergili (2013).

Figure 5: NF50 membrane efficiency for IBU tablet and pure IBU standard

Pure form of IBU drug is negatively charged at neutral pH, therefore, an increased rejection was expected. Neutral pH of the feed solution had a considerable effect on the hydrophobicity and solubility of IBU tablet, for instance, solubility of IBU can also be increased between pH 6.8 and 7.2 (Priyanka et al., 2017) which may have caused an improvement in rejection by absorbing on the surface of membrane. Park and Cho (2005) also obtained a higher rejection at neutral pH (70%) but at lower pH a temporary retention was observed because of adsorption on membrane surface (Park and Cho, 2005).

Figure 5: NF50 membrane efficiency for IBU tablet and pure IBU standard

3.3 Drug Mixture and Membrane Efficiency

In order to understand the behavior of drugs, a mixture of drugs was prepared. Over all, membrane performance decreased, as expected, as chemistry of drugs and membrane changed with changing pH also indicated in study performed by Alygizakis et al., (2016).

As can be observed in Figure 6, in the mixture of drugs, rejection was in the order of DIC>IBU>PARA at pH 3 with 76.62, 70.97 and 37.59% removal of DIC, IBU and PARA respectively. When they were treated individually it was found that DIC removal was 99.74%, IBU removal was 55.05% and PARA removal was 12.2% at pH 3 (Figure 4). Therefore, DIC removal was decreased whereas IBU and PARA removal was increased. A decrease in DIC removal can be attributed towards its charge shift in the presence of other drugs. But with the possible hydrophilic interactions between functional groups of membrane (carboxylic, amines and hydroxyl groups) drugs have increased the retention of IBU and PARA at pH 3. At neutral pH, mixtures of drugs followed the same removal rate order, i.e., DIC>IBU>PARA but with different removal percentages. It was observed that from individual IBU removal was decreased from 80.54% to 49.7% in a mixture, because IBU is moderately hydrophobic in their neutral form and presence of other drugs in solution has decreased its hydrophobicity even more at this operating pH. Similarly increase in solubility of IBU also increases on approaching its pK_a values (Shaw et al., 2005). However, DIC and PARA removal increased from 43.31% to 55.13% and 26% to 30.7% respectively may be because of their increased ionization. Additionally, at pH 12, removal rate for mixture of drugs was different i.e., IBU>PARA>DIC. IBU and DIC removal was increased from 34.4% to 48.3% and 5.38% to 26.3% respectively while, PARA removal was decreased from 36.16% to 28.1% probably due to its very small molecule or solubility that rapidly increases near its pK_a value (Shaw et al., 2005). It can be assumed that the more a compound adsorbs on the membrane, either it will pass through the membrane into permeate or it will cause fouling.

The results showed the importance of factors, such as pH and physicochemical properties of drugs, in a membrane treatment. The solubility of pure drug standards in distilled water and

when they mixed together can be different due to their pK_a values. The charge on the surface of membrane as well as on the molecules of drugs can also have impact on filtration at extreme pH. Likewise, dissociation constant, polarity, pH dipole moment, and hydrophobicity expressed as the octanol water partition coefficient, not only they all take part in rejection of pollutants but also, they change the flux and fouling of membrane.

Figure 6: NF50 performance with mixture of drugs

3.4 Membrane Fouling

The permeate fluxes for both membranes are shown in Figure 7. The permeate flux remained almost constant at the end and beginning of filtration with the NF50 membrane however, permeate flux changed by the end of experiments with NF10 membrane.

In the case of NF10, after all the experiment the permeate flux decreased to $0.003 \text{ Lh}^{-1}\text{m}^{-2}$ from $0.018 \text{ Lh}^{-1}\text{m}^{-2}$ in just nine minutes which represents a loss of 83.3%. But, after cleaning the membrane, the permeate flux was regained up to $0.018 \text{ Lh}^{-1}\text{m}^{-2}$. Therefore, the

fouling observed was mostly reversible. However, considering poor efficiency of NF10, experiments were not conducted with this membrane, as described in section 3.1.

The permeability flux of the NF50 membrane remained almost constant, changing from 0.0008 Lh⁻¹m⁻² to 0.0007 Lh⁻¹m⁻². Usually permeate flux decline in NF is not reported for low concentrations of drugs (Zazouli et al., 2009). NF membranes with larger MWCO (loose NF membranes) usually have higher permeate flux because of their pore size, but in present case, for all pH values (3, 6-7, 12), the permeate flux was low because of the small filtration unit, applied pressure or mode of nanofiltration. It can be observed from Figure 7 that the permeate flux was different in case of all of three model drugs. Rejections of DIC and IBU were 99% and 80%, respectively with NF50, whereas flux decline of IBU was significantly greater (0.0005 Lh⁻¹m⁻²) than flux decline of DIC (0.0009 Lh⁻¹m⁻²). Opposite results were obtained by Vergili, (2013), according to them, DIC had greater flux decline. It can be explained by the pH factor. In the present study acidic pH enhanced polarization of DIC which made filtration more effective. While in case of Paracetamol (PARA), since the drug itself is hydrophilic nonionic, it was poorly filtered by membrane polymer and passed in permeate with almost a slight change in initial flux (0.0007 Lh⁻¹m⁻²).

In present study, overall permeate flux shows a slight fouling of membrane i.e., drop in flux rate after specific time and quantity of pollutants. Filtration parameters of membranes like pressure, membrane surface, functional groups and time along with physicochemical properties of the drugs like, molecular weight, concentration and polarization affects the flux rate (Zazouli et al., 2009). Since selected membranes and drugs were hydrophobic, (negatively charged) except paracetamol, therefore, the change in flux for different drugs was expected but without fouling. When the solute passes through the membrane, firstly it dissolves in the membrane and

then by the mechanism of diffusion, it shifts towards the end point. Therefore, an increase in the adsorption of drugs over membrane surface would enhance diffusion mechanism and vice versa, resulting in a decrease or increase in rejection and fouling (Nghiem et al., 2006; Schäfer et al., 2004; Zhang et al., 2004). It is important to highlight that in this study, after every filtration step, the membrane was cleaned and reused for next treatment. After initial change in permeability flux (first 10 minutes), the flux remained stable until the end of the experiment because of lab scale NF unit.

Adsorption can play an important role in the fouling of NF membranes by organic compounds. The NF50 is negatively charged membrane therefore, the flux decline and fouling were not expected, as negatively charged drug molecules were repelled by the surface of membrane. However, adsorption can occur on the membrane surface or within the polymer structure because of electrostatic interactions (Zhang et al., 2004; Nghiem et al., 2006). The flux declines obtained from IBU studies may be attributed to adsorption of IBU ions inside the membrane pores. This agrees with the increased rejection of IBU at neutral pH described in the Section 3.1.3. Rejection of IBU was achieved by adsorption method (Ouyang et al., 2019) however, rejection of DIC was due to electrostatic interactions as its dipole moment was stronger than IBU. Highest permeate flux can be seen in figure 7b for DIC as repulsive forces between DIC molecules and membrane at pH 3 prevented drug molecules to absorb on the membrane surface.

It can be concluded that, at neutral pH, lower dipole moment of IBU and decreasing hydrophobicity caused flux decline and increased rejection. DIC being negatively charged at pH12 and 6-7 was rejected by negatively charged NF membrane by repulsive electrostatic interaction that also prevented fouling. Previous studies have suggested that anionic molecules

have lower permeability due to increased solubility (Akula et al., 2018) but in present case each drug behaved differently because of their unique properties.

Figure 7: Permeate flux of virgin and used (a) NF10 and (b) NF50 membranes for 3 model drugs

3.5 Membrane Characterization by Microscopy

Membranes characterization can be done based on permeability, flux and rejection. However, a more intensive characterization was performed by means of SEM analysis. Microscopic characterization of membranes determines their morphological properties. The changes in membrane structure and morphology are represented in Figure 8. Previous membrane separation studies have used these tools to understand membrane properties as well as fouling and cleaning processes (Kim et al., 2008; Chakrabarty et al., 2008). The visual observations obtained from SEM micrographs support the theory that surface adsorption was the dominant mechanism in NF fouling especially in the case of NF10. The SEM images of the membranes (Figure 8 a, b) illustrates that in NF50 fouling is negligible as the pore size and intensity is appeared to be same in virgin and used NF50, however, some large fragments of drugs can be seen on the surface. In the case of NF10, in Figure 8 c, large open pore system can easily be seen, that represents its higher MWCO, however, in figure 8 d, a clear fouling in the form of closed or clogged membrane pores along with undissolved drug fragments can be observed. NF10 was not efficient in terms of drug removal as either most of the drug molecules were passed through the membrane matrix or have fouled the pores by precipitation on the surface. In both membranes, fouling was reversible either by back washing (physical cleaning) or simply by soaking membranes into sodium hypochlorite solution (chemical cleaning). According to manufacturer claim, membranes with Sulfonated Polyethersulfone can be cleaned in the pH values ranging from 1-12 without damaging its polymer (Buscio et al., 2016). Initial permeate flux has been achieved after cleaning, as explained in previous section.

Figure: 8 SEM photography of nanofiltration membranes before and after filtration. (a) NF50 virgin (b) NF50 after filtration (c) NF10 virgin (d) NF10 after filtration (at 100 nm magnification)

4. Conclusions

Retention of three pharmaceuticals was influenced by characteristics, like solubility, $\log K_{ow}$, pK_a , dipole moment and charge under different pH of the solvent. The loose NF50 nanofiltration membrane treatment provided up to 99.74% Diclofenac removal at pH 3, 80.54% Ibuprofen removal at neutral pH and 36.16% paracetamol removal at pH 12. These results are quite comparable with the tight NF membranes in terms of efficiency, as sieving by pores played no role in the rejection of selected pharmaceuticals. Effect of pH influenced charged and non-charged interactions between membrane and drugs by not only changing the polarization of

drugs but also changed the charge on the membrane surface. Membrane efficiency was decreased when all drugs were mixed together. Higher removal rate was observed at pH 3 with 49.7, 55.13 and 30.7% removal of IBU, DIC and PARA respectively, however, this rate was lower than the individual treatment of drugs especially for DIC. Nanofiltration of IBU tablet was better (90.25%) than the pure IBU laboratory standard (80.54%). Although in all the tests, permeate flux rate changed because of the chemistry of drugs, no significant fouling of membranes was observed during the experiments or otherwise reversible. It can be concluded that the membranes with larger MWCO can also be a promising technique for pharmaceutical removal under controlled condition as speciation of molecules, i.e. changing of their charge under different pH influenced their retention due to the dissociation of sulfonic and carboxylic groups on membrane surface.

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Disclosure statement

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