

## The influence of divalent ions on the rejection of carbamazepine in the presence of humic acid by nanofiltration

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### ABSTRACT

Effect of calcium and magnesium ions and Natural Organic Matter (NOM) on the removal of carbamazepine (CBZ) was investigated by nanofiltration in this study. Water matrix which was used in these experiments was Tehran tap water and deionised water (DI) as control group. Effect of magnesium and calcium ions were examined by doubling the amount of target ions in tap water and Humic Acid (HA) was used as NOM. All the experiments have been conducted at three pressures to have more diverse operational condition. Rejection of carbamazepine in the presence of HA increased both in DI water and tap water; however, rejection was decreased in higher pressure due to concentration polarization. Both  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  decreased the CBZ rejection by reduction of CBZ-HA complexation; particularly,  $\text{Ca}^{2+}$  was more effective.

**Key words** | carbamazepine, cations, humic acid, nanofiltration, pharmaceutically active compounds

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### INTRODUCTION

With the world's growing population, human need for water has increased accordingly, especially in the recent decades. International Agricultural Research Consultants predict the number of people residing in arid regions will reach 2.7 billions by the year 2025 (Radjenović *et al.* 2008). On the other hand, limitation of drinking water resources to surface and underground water and contamination of these supplies with chemical contaminants adds to the depth of the problem. Frequent reports of environmental centers from different places around the world demonstrate that Pharmaceutically Active Compounds (PHACs) and chemical compounds in trace amounts in the surface water, drinking water, and wastewater effluents, (Kuch & Ballschmitter 2001; Kolpin *et al.* 2002; Stackelberg *et al.* 2004; Lindqvist *et al.* 2005; Lishman *et al.* 2006; Loraine & Pettigrove 2006) affect ecosystems and threaten human health (Colborn *et al.* 1993; Gagné *et al.* 2006; Zhang *et al.* 2008). Among these compounds, Carbamazepine (CBZ)

is an anti-epileptic PHAC compound which has a high persistence in the environment. As a result, it has been accepted as a criterion for detecting the PHACs in water bodies (Reinstorf *et al.* 2008). Likewise, Clara *et al.* (2004) concluded that Carbamazepine seems to be sufficiently persistent in the environment, thus qualifying as a suitable marker for anthropogenic influences in the aquatic environment. According to present European legislation on the classification and labeling of chemicals (92/32/EEC), CBZ has been classified as "R52/53 Harmful to aquatic organisms that may cause long term adverse effects in the aquatic environment." (Zhang *et al.* 2008).

Since the common methods of removal are not efficient for removal of the PHACs, nanofiltration (NF) has become a promising method of removal of pharmaceutical from water. Snyder *et al.* (2007) found that although compounds are detectable at trace levels in permeates, nanofiltration and reverse osmosis are capable of notable rejection of

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almost all PHACs. Removal of various PhACs like CBZ by NF has been investigated by many researchers. Yoon *et al.* (2006) investigated the removal of 27 PhACs including CBZ and found that 45% of CBZ on the average and maximum 65% was rejected by NF. Also, Verliefe *et al.* (2009) investigated the removal of CBZ by NF and found that it can reject CBZ about 85% if using clean NF and 10% lower if applying fouled NF. Wastewater treatment plants are only capable of removing of 10 to 20% of CBZ in influent (Pérez & Barceló 2007; Radjenović *et al.* 2007).

There is lack of research on the influence of natural water matrices on EDC and PhACs rejection by membranes and available data are inconsistent (Comerton *et al.* 2009). On the other hand, there are controversies over the effect of water ions on efficacy of PhACs removal by nanofiltration. While (Nghiem *et al.* 2005a) found no effect of ions on the PhACs removal, others (Devitt *et al.* 1998; Plakas *et al.* 2006) found its effect. Zhang *et al.* (2004) concluded that a water matrix has a significant influence on the rejection of pesticides. Indeed, higher rejection was obtained from river water and tap water than from distilled water. In addition, Comerton *et al.* (2009) demonstrated that NOM can increase the PhACs removal by nanofiltration and cations ( $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Na^+$ ) have adverse effect on the CBZ rejection in the presence of NOM by NF. Nghiem *et al.* (2008) found that calcium ion could be a major factor governing the HA fouling process by NF in the removal of bisphenol A.

There are two hypotheses over the effect of NOM on removal of PHACs by nanofiltration. First, improving membrane surface charge, pore restriction and enhance concentration polarization by membrane fouling with NOM (Nghiem & Hawkes 2007; Xu *et al.* 2006); second, via producing NOM-PhACs complexes which are larger, have more negative charge and have more tendency to adsorb to membrane surface when compared with compounds alone (Devitt *et al.* 1998; Zhang *et al.* 2004; Plakas *et al.* 2006).

Results in literature show the effect of cations and NOM on the removal of PHACs by nanofiltration; however, the effect of ions is result of overall amount of cations and the effect of kind of ions needs to be investigated.

The goal of this study is to investigate the effect of  $Mg^{2+}$  and  $Ca^{2+}$  ions, and HA as NOM on removal of CBZ from Tehran tap water by nanofiltration. In addition, all this experiments were conducted in different operation condition to examine the effect of cations and HA on removal of carbamazepine.

## MATERIAL AND METHODS

### Material

#### Feed water characteristics

Since the result of PhACs removal from natural waters are different from deionized waters, the effect of NOM and cations on Tehran tap water was examined and compared with deionized water. Tehran tap water characteristics described in Table 1. To investigate the effect of  $Mg^{2+}$  and  $Ca^{2+}$  on CBZ rejection, the amount of these ions was doubled in tap water. 30 mg CBZ 99.9% was dissolved in 10 ml acetonitrile and the solution was added to the storage tank (volume: 30 lit) containing the Tehran tap water or deionized water. To examine the effect of the NOM on CBZ removal 10 mg/l HA was added to feed tank. Likewise, to examine the effect of  $Mg^{2+}$  and  $Ca^{2+}$  on rejection of CBZ, the concentration of ions were doubled in tap water and 5.514 g  $CaCl_2 \cdot 2H_2O$  (as 50 mg/l  $Ca^{2+}$ ) and 5.225 g  $MgCl_2 \cdot 6H_2O$  (as 25 mg/l  $Mg^{2+}$ ) were added to the storage tank. Feed water characteristics is presented in Table 2

#### Nanofiltration membrane

Filtration experiments were performed using the nanofiltration membrane (NF90 from Dow/FilmTec). The molecular weight cut off for this NF membrane is reported by the

**Table 1** | Tehran tap water characteristics\*

Water	$Ca^{2+}$ (mg/l)	$Mg^{2+}$ (mg/l)	$K^+$ (mg/l)	$Na^+$ (mg/l)	$Cl^-$ (mg/l)	$NO_3^-$ (mg/l)	$SO_4^{2-}$ (mg/l)	EC ( $\mu S/cm$ )
Tehran tap water	53	13.7	0.7	8.7	19.5	8	53.5	235

\*Measured at laboratory of graduate faculty of environment in Tehran.

**Table 2** | Feed water characteristics

Parameter	Conductivity ( $\mu\text{S}/\text{cm}$ )	Calcium (mg/l)	Magnesium (mg/l)	UV <sup>254</sup>	Humic acid HA (mg/l)	pH
Deionized water (DW)						8
DW	120*	ND <sup>†</sup>	ND	–	–	8
DW + HA	120*	ND	ND	0.171	10	8
Tap water (TW)						8
TW	235	53	13.7	0.003	–	8
TW + HA	235	53	13.3	0.171	10	8
TW + Ca <sup>2+</sup>	475	105.2	13	0.003	–	8
TW + Mg <sup>2+</sup>	341	52	27.2	0.003	–	8
TW + HA + Ca <sup>2+</sup>	475	102.6	12.5	0.170	10	8
TW + HA + Mg <sup>2+</sup>	344	55.1	28.1	0.173	10	8

\*Spiked with 1 mM sodium bicarbonate (Nghiem *et al.* 2005b).

<sup>†</sup>Not detected.

manufacturer to be 200 Da. Membrane sheets were cut into smaller pieces in order to fit the pressure vessel 140 cm<sup>2</sup> of active membrane area and were stored dry at 4°C. Membrane characteristic as reported by manufacturer is illustrated in Table 3

### Material characteristic

All standards and reagents used were the highest purity commercially available. Acetonitrile, ethanol, chloridric acid and water are bought from Merck and they are HPLC grade. Standard is taken from Sobhan Pharmaceutical Company with purity of 99.99%. Table 4 provided general information about Carbamazepine.

### Method

#### Nanofiltration apparatus

Experiments were performed using a cross-flow filtration cell. NF90 membrane was used for experiments. Active membrane area of the cross-flow cell was 140 cm<sup>2</sup>. In all cases, experiments were performed at 25 ± 1°C. Prior to each experiment; membranes were dipped into 50% ethanol for 10 min and then flushed with ultra pure water.

For precompaction, membrane compacted for approximately 15 h by passing ultra pure water by 20 bar pressure through the system, until a constant permeate flux (initial clean water flux) was achieved. Following this process, ultra pure water was replaced by feed water. To ensure the system reached the steady state, EC of permeate stream and feed tank was measured and sampling was done after 18 hr. Flow rate of feed stream was 11 L/min and specific flux was calculated 2.5 L/m<sup>2</sup> h bar (line slope of flux-pressure curve). Filtration was carried out at 7, 10 and 13 bar pressures to have different operation condition. The membrane system was operated in a recycle mode in which all concentrate and permeate were returned to the feed tank. After each run, the membrane was replaced with a new membrane. Schematic of bench-scale nanofiltration system is illustrated in Figure 1.

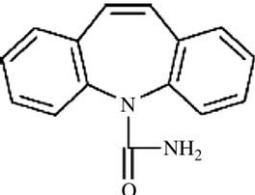
#### Analytical method

HPLC was performed on an Agilent/HP 1100 Series for detection of CBZ. The separation was achieved on an analytical column discovery C18 (5 mm, 25 cm long, 4.6 mm ID) and operated at a temperature of 25°C; the injection volume was 20  $\mu\text{l}$ . A mixture of water and acetonitrile

**Table 3** | Membrane characteristic as reported by manufacturer

Membrane	MWCO (Da)	Water flux (Lm <sup>-2</sup> h <sup>-1</sup> bar <sup>-1</sup> )	Max. pressure (bar)	Surface charge	Max temp (C°)
NF90	200	6.4	41	Negative	40

**Table 4** | General characteristic of Carbamazepine

Compound	CAS number	Molecular weight (g/mol)	Chemical formula	Log $k_{ow}$	pK <sub>a</sub>	Solubility* (mg/l)	Dipole moment (μ (D))	Chemical structure
Carbamazepine	298-46-4	236.3	C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> O	2.45 <sup>†</sup>	2.3 <sup>‡</sup>	17.7 <sup>†</sup>	693.3 <sup>†</sup>	

\*Reported in Nghiem *et al.* (2005b).<sup>†</sup>Reported in Comerton *et al.* (2009).<sup>‡</sup>Water solubility reported at 20°C.

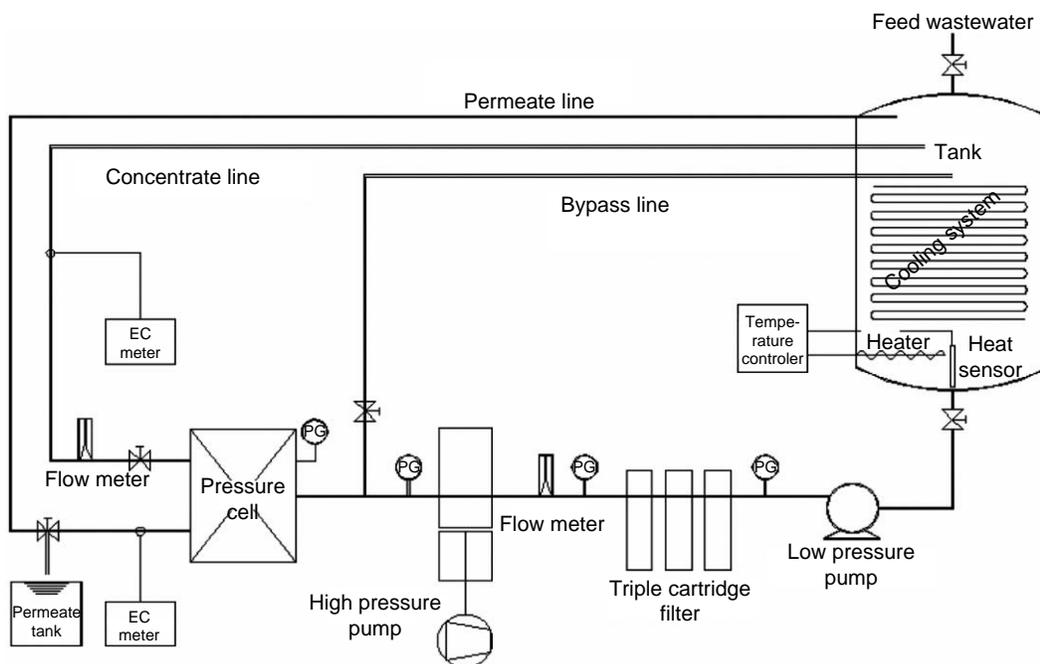
(20:80 v/v) was used as mobile phase. Flow rate was 1.5 ml/min.  $\lambda_{max} = 210 \text{ nm}$  and total runtime was 10 min.

## RESULTS AND DISCUSSION

### Effect of operation variable on carbamazepine rejection

A summary of the rejection of the CBZ by the NF90 membrane for the eight water matrices examined is presented in Table 5. After applying three different pressures in these experiments, the maximum CBZ rejection from

tap water alone was seen under 10 bar pressure with 89.7% rejection and the least was seen under 13 bar with 86.4%. In other words, pressure increase caused the rejection to increase till 10 bar and had adverse effect by further pressure increase to 13 bar. According to results shown in Table 5, it can be inferred that water matrices had a significant effect on removal of carbamazepine when other effective factors like operating variable is constant and when operating variable and water matrices was altered rejection of carbamazepine was varied in wide rang up to about 14%. Although 3 bar in pressure was

**Figure 1** | Schematic of bench-scale nanofiltration system.

**Table 5** | Summary of CBZ rejection by NF in different water matrices

Feed water	Rejection		
	Applied pressure (bar)		
	7	10	13
Deionized water (DW)			
DW + CBZ	82 + 0.1	83.5 + 1	80 + 0.8
DW + CBZ + HA	93 + 0.2	90.2 + 0.3	88 + 0.9
Tap water (TW)			
TW + CBZ	87.3 + 0.4	89.7 + 1	86.4 + 1.8
TW + CBZ + HA	91.6 + 0.3	89.7 + 0.2	87.4 + 0.6
TW + CBZ + Ca <sup>2+</sup>	82 + 0.3	83.4 + 0.5	84.9 + 0.4
TW + CBZ + Mg <sup>2+</sup>	81.8 + 2	80.5 + 2.2	78 + 0.3
TW + CBZ + HA + Ca <sup>2+</sup>	82.7 + 0.3	84.8 + 0.8	82.3 + 0.6
TW + CBZ + HA + Mg <sup>2+</sup>	84.1 + 0.3	86.6 + 1.3	81.4 + 0.4

Note: Results are the average of three rejections.

not significant, the difference in rejection is notable. Regardless of water matrices, pressure had slight effect on rejection.

Nghiem *et al.* (2004) stated, in general, solute retention increases with pressure up to an asymptotic value. However, for organic solutes that have a strong interaction with membrane polymers, retention may decrease with pressure. The reduction of rejection by increasing in pressure may be the result of two factors. First, particularly for organic solute, the higher the pressure, the greater the permeate flux; as a result, drag force within the membrane pores is increased. Hence, desorption of solute can be enhanced or time for adsorption reduced which may results in rejection reduction. Second, generally, the higher the pressure, the higher the permeate recovery, and the lower the rejection. Nghiem *et al.* (2004) concluded that rejection of organic solutes (estrone, chloroform, chlorophenol, nonyl phenol) which have strong affinity to adsorb to membrane surface, may be reduced by desorption of solute as a result of increase in pressure, however, carbamazepine as a neutral pharmaceutical which has a moderate to low affinity to membrane surface adsorption was either affected by pressure. Results in the first and third row of Table 5 show this phenomenon. Effect of pressure on rejection of carbamazepine in the presence of humic acid which has hydrophobic organic acid and has affinity to adsorb to membrane surface may be different from when there was no

HA. Not only the Presence of HA in water and adsorption to membrane surface may cause adsorption of carbamazepine to membrane surface but also it may cause the fouling of membrane. This fouling can affect the rejection of PhACs by nanofiltration. It was hypothesized that such influence was result of three distinctive mechanisms: modification of the membrane charge surface, pore restriction, concentration polarization enhancement due to cake formation (Xu *et al.* 2006; Agenson & Uruse 2007; Nghiem & Hawkes 2007). Nghiem & Hawkes (2007) found that, cake enhanced concentration polarization effect is the main mechanism for smaller pore size, NF 90 membranes. Generally, in membrane filtration solvent molecules permeate the membrane, but the larger solutes (here carbamazepine and especially HA) accumulate at the membrane surface and their concentration at the membrane surface is typically 20–50 times higher than the feed solution concentration. These solutes become so concentrated at the membrane surface that a gel layer is formed and becomes a secondary barrier to flow through the membrane. Increase in pressure can accelerate the cake formation which is resulted in flux and rejection reduction of solute. (Baker 2004). As it shown in second and fourth row of Table 5 by increase in pressure from 7 to 13 bar rejection of carbamazepine was reduced straightly, this may be the result of presence of HA to enhanced cake formation and additional effect of pressure which was discussed before.

Comparing the result of experiments related to deionized water (DI) and tap water showed the difference between the rejections of carbamazepine. This may be the result of presence of divalent and monovalent ions and other complex component which was in tap water. These results are in line with the literature (Zhang *et al.* 2004; Nghiem *et al.* 2005b; Comerton *et al.* 2009).

### Effect of humic acid on carbamazepine rejection

The presence of HA spiked into tap water and DI water resulted in an increase in CBZ NF rejection due to CBZ-HA complexation. These results are in accordance with Dewitt *et al.* (1998), Nghiem *et al.* (2005a), Comerton *et al.* (2009) and Plakas *et al.* (2006). CBZ is a base with a  $pK_a = 2.3$  and it is uncharged at all conditions typical of natural water or wastewater as well as tap water. Because of its relatively low  $\log K_{ow}$  value, CBZ has a low affinity to the membrane polymer (Nghiem *et al.* 2005b). At approximately similar experimental condition by experiments in this paper. Nghiem *et al.* (2005b) found that CBZ did not adsorb to the membrane surface.

As it was discussed before, HA have strong affinity to adsorb to membrane surface and also make hydrogen binding with organic compound in water. The NOM was assumed to enhance the adsorption of pesticides onto membranes surface, increased the size exclusion and electrostatic repulsion (Zhang *et al.* 2004). Hence, complexation of CBZ and HA leads to make larger molecule that has higher tendency to adsorb to membrane surface and reject easier via size exclusion mechanism which improves the CBZ rejection.

### Effect of ionic environment and cations on carbamazepine rejection

As it was mentioned, effect of ionic strength on removal PhACs and Endocrine Disruptor Compounds (EDCs) by nanofiltration have been examined in literature; however, data for the effect of kind of ions was absent. To evaluate the effect of Ca and Mg on removal of CBZ by nanofiltration the amount of  $Mg^{+2}$  and  $Ca^{+2}$  in tap water, were doubled (25 mg/l  $Mg^{2+}$  and 50 mg/l  $Ca^{2+}$  added to tap water). Doubling the amount of Ca and Mg in tap water resulted in

decrease in removal of CBZ. Results are illustrated in Table 5 four last rows.

This is consistent with Comerton *et al.* (2009) results that concluded  $Mg^{2+}$  and  $Ca^{2+}$  caused decrease in the CBZ rejection in the presence of HA. Verliefe *et al.* (2008) suggested that divalent ions, such as  $Ca^{2+}$ , seems to reduce the thickness of the electric double layer at the membrane surface and shield the membrane surface charge and this shielding of the membrane charge generally leads to a decrease in electrostatic interactions with charged species, but according to neutral nature of CBZ this mechanism seems not to be much effective here and the main effect of  $Ca^{2+}$  and  $Mg^{2+}$  is on the complexation of CBZ with HA. It has been shown that divalent cations can turn stretched and linear configuration of NOM to more rigid, compact and coiled configuration (Braghetta *et al.* 1997; Hong & Elimelech 1997) and this change may alter the availability of sites for compound association with NOM macromolecular and leads to reduction in NOM–compound complexation (Devitt *et al.* 1998). This mechanism may represent the reduction in CBZ rejection in more ionic environment.

Furthermore, Plakas & Karabelas (2009) concluded that the humic substances acidity (total, carboxylic and phenolic) exhibits a weak correlation with atrazine (a kind of common pesticide) rejection by nanofiltration. However, the conformation of humic species appears to play a more significant role. Hence, change in configuration of HA as a result of the presence of divalent ions, is the key factor on the reduction of CBZ rejection.

$Mg^{2+}$  and  $Ca^{2+}$  are the main cations in tap water and have obvious effect on removal of PhACs by nanofiltration. Impact of magnesium and calcium ions in the presence of HA on removal of CBZ by nanofiltration is shown in Table 5 two last rows. There is a slight difference between the results from the impact of  $Ca^{2+}$  and  $Mg^{2+}$ . That is, calcium ion has reduced the rejection of CBZ more than  $Mg^{2+}$  has. Based on what was stated about the effect of cations on the altering the configuration of HA and reduction of producing the HA-CBZ complex, it seems that calcium ion is more effective on reduction of production of HA-CBZ than magnesium ion. It has been reported that calcium and magnesium ions has interaction with HA. Both of calcium and magnesium could form complexes with carboxyl group of the HA (solute-solute interactions), resulting in

a reduction in electrostatic repulsion between the functional groups, consequently leading to the formation of small and coiled HA macromolecules (Nghiem *et al.* 2008). Furthermore,  $\text{Ca}^{2+}$  has looser second hydration shell structure than  $\text{Mg}^{2+}$  has; hence its association with carboxyl groups of HA is stronger than  $\text{Mg}^{2+}$ . In addition, the decreased mobility (diffusion coefficients) of the  $\text{Ca}^{2+}$  bound to the HA, presents stronger Ca-HA complexation, (Ahn *et al.* 2008) which can occupy the available sites for binding CBZ with HA.

There is inconsistent data regarding the effect of  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  on removal of carbamazepine in the absence of HA. The rejection of CBZ is increased by increase in pressure in the presence of  $\text{Ca}^{2+}$ , however, the rejection of CBZ is decline in same condition in the presence of magnesium ion. It is important to say that the values of rejection are less than when the CBZ was filtrated alone. Regarding to this fact that 3 pressures is not sufficient to conclude a pattern for rejection under different pressures. Further investigation on effect of cations and HA with wide range of pressure and different cross flow velocities is needed to clarifying the impact of these variables.

## CONCLUSION

Experiments in this study were conducted to examine the effect of NOM and calcium and magnesium ions on rejection of carbamazepine by nanofiltration. To investigate the effect of target ions on results of carbamazepine rejection in different operational condition, all the experiments have done in three pressures. Based on literature, it has been shown that PhACs rejection results from natural waters are different from laboratory water. Hence, removal of carbamazepine from Tehran tap water as a natural water was investigated and compared with laboratory water.

Results in this research confirm previous hypothesis studies that carbamazepine rejection efficiency is higher in natural waters (tap water) than laboratory water. The presence of NOM has increased the rejection of carbamazepine both in tap water and laboratory water. Furthermore, calcium and magnesium ions could reduce the association between the carbamazepine and HA to produce HA-CBZ complex and results in reduction of

carbamazepine rejection.  $\text{Ca}^{2+}$  compared to  $\text{Mg}^{2+}$  was more effective on reduction of carbamazepine in similar condition. In addition, results from experiments in different pressure imply that, operational condition has undeniable impact on rejection of carbamazepine especially in the presence of NOM which may accelerate the concentration polarization.

To sum up, according to these results it may be concluded that effect of divalent ions on rejection of organic compounds like PhACs in the presence of humic substance depends on the compound physicochemical properties (i.e. size, steric characteristics,  $\log K_{ow}$ ), nanofiltration condition (i.e. pressure, cross flow velocity), humic substance conformation and water environment. To investigate the effect of operational variable on the rejection of PhACs in the presence of NOM and cations, and find the pattern of rejection in wide range of pressures, further studies would be necessary.

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