Use of Membrane for Removal of Nonsteroidal Anti-inflammatory Drugs

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Contents

Abstract Nonsteroidal anti-inflammatory drugs (NSAIDs) belong to most used pharmaceuticals in human and veterinary medicine, the emerge of drugs in the environment is a concern subject. The contamination is due to the consumption and the excretion of large quantities of pharmaceuticals via urine and feces in wastewaters. In this chapter, the reader will have an overview of the use of different types of membranes and their combined method in the removal of NSAIDs and demonstration that the use of membrane could be an environment-friendly methodology that enhances its efficiency in the removal of these compounds.

Keywords Membrane bioreactor, Nanofiltration, Nonsteroidal anti-inflammatory drugs, Reverse osmosis, Ultrafiltration

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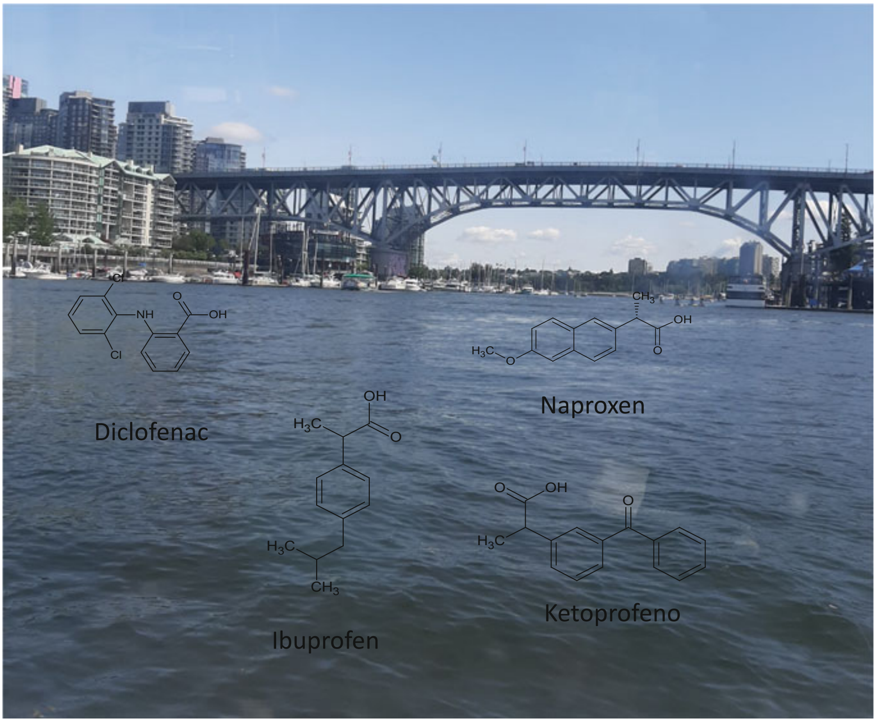
1 Introduction

In the past decades, there has been a growth in the number of published articles that have focused on the environmental monitoring of nonsteroidal anti-inflammatory drugs (NSAIDs). Among the emerging environmental contaminants, pharmaceutically active compounds have become a growing public concern because of their potential to cause undesirable ecological and human health effects. The concentrations of five common nonsteroidal anti-inflammatory drugs, diclofenac, ketoprofen, naproxen, ibuprofen, and acetylsalicylic acid, were determined in surface waters [1]. Nonsteroidal anti-inflammatory drugs are a drug class FDA approved for use as antipyretic, anti-inflammatory, and analgesic agents [2]. These effects make NSAIDs useful for the treatment of muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, and migraines and used as opioid-sparing agents in certain acute trauma cases [3–5].



It is believed that the water sources are contaminated with a variety of pharmaceutical compounds due to the absence of wastewater separation and limitation of sanitation sewer systems. Most frequently, conventional treatment processes applied at domestic wastewater treatment plants fail to remove completely pharmaceutical substances; that is why it is very important to explore a new technology using membranes and a combined membrane process in order to remove nonsteroidal anti-inflammatory drugs and improved the quality of water.

2 Consumption and Presence of NSAIDs in Wastewater

Worldwide acute or chronic pain and fever are the main symptoms of numerous disorders and are the main reasons for medical consultation. Inflammation is a pathogenetic factor in many diseases and also is an outcome of physical damage (blows and injuries, among others). In classical medicine are used drugs possessing antipyretic, analgesic and anti-inflammatory activities [6], to counteract these symptoms.

Among the most common pharmaceuticals are nonsteroidal anti-inflammatory drugs (NSAIDs), and the most consumed of these drugs in the world are diclofenac, ketoprofen, naproxen, ibuprofen, and acetylsalicylic acid. For example, in Germany in 2001, they reported a consumption of acetylsalicylic acid 836 tons, paracetamol 622 tons, ibuprofen 345 tons, and diclofenac 86 tons. In England in 2000, the use of naproxen was 35 tons [7]. The occurrence of several drugs has been reported in are sewage treatment plant (STP) effluent, as well as in surface and drinking water in Brazil, Canada, China, Germany, Italy, Spain, Switzerland and the United States [6, 8–15].

Various drugs have been extensively studied, such as ibuprofen (IBU), (RS)-2-(4-(2-methylpropyl) phenyl) propanoic acid; naproxen (NPX), (+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid; and ketoprofen (KPF), (RS)-2-(3-benzoylphenyl) propanoic acid, not only in wastewater but also in drinking water sources [14, 16, 17]. Salgado et al. [18] identified 73 pharmaceutical active compounds of diverse families in a municipal wastewater treatment plant. Shanmugam et al. [1] report presence of diclofenac, ketoprofen, naproxen, ibuprofen, and acetylsalicylic acid in surface waters from 27 locations of the Kaveri, Vellar, and Tamiraparani Rivers in Southern India. Farré et al. [19] describe a work collaboration of 13 laboratories distributed in nine European Countries exercise for the analysis of nonsteroidal anti-inflammatory drugs (NSAIDs). The compounds selected in this study were ketoprofen, naproxen, ibuprofen, and diclofenac. Analyses samples were river water, wastewater, and artificial water (fortified environmental and distilled water) with different ranges of complexity. For its part, Petrovic et al. [20] also reports presence of analgesics and anti-inflammatory drugs. Table 1 summarizes the concentration ranges of NSAIDs detected in these papers.

Some research has focused on the NSAID residues in the environment. Nishi et al. [21] monitored the concentrations of seven NSAIDs in domestic wastewater in Japan. The concentration averages of diclofenac, ibuprofen, salicylic acid, ketoprofen, mefenamic acid, felbinac, and naproxen in wastewater were, in order, 259.7, 162.9, 55.3, 48.3, 39.7, 30.8, and 11.8 mgL^{-1}, respectively. Lolić et al. [22] recognize maximum concentrations between 5.34 mg L^{-1} and 1,227 ng L^{-1} for acetylsalicylic acid and carboxyibuprofen, respectively, in seawaters of Portugal.

Table 1 Range (maximum value–minimum value) of concentration of some drugs present in wastewater (μgL^{-1})

Diclofenac	Etofenamate	Ibuprofen	Ketoprofen	Naproxen	Acetylsalicylic acid	Salicylic acid	Acetaminophen	Reference
64.5	40.2	52.2	104.1	0	0	0	0	Salgado et al. [18]
0.103	0	0.2	0.1	0.028	0.66	0	0	Shanmugam [1]
3.248	0	2.717	1.175	0.228	0	0	0	Farré [19]
4.06	0	372.619	2.792	17.062	18.93	14.1	25.96	Petrovic [20]

For zero value, it means that the NSAIDs was not analyzed

He et al. [6] reported 17 mgL^{-1} of ibuprofen and 2 mgL^{-1} for propiphenazone as the highest and lowest concentrations, respectively, with respect to the other nineteen NSAIDs found in water samples, taken from six drinking water purification plants and two water purification plants in Japan. Among all detectable NSAIDs in the environment, diclofenac and ibuprofen often showed the highest concentration and detection rates [6].

3 Mechanisms of Elimination of NSAIDs and Influence Variables

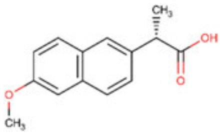
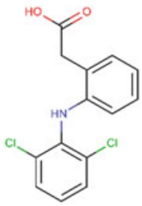
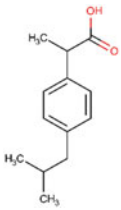
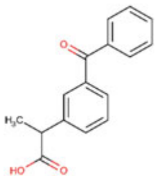
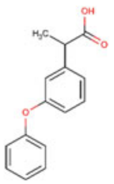
The elimination of NSAIDs can occur through various mechanisms in the activated sludge process, mainly by biodegradation, sorption, or volatilization [23]. Sewage sludge is designed to substantially degrade the organic compounds by microbial metabolism, which varies depending on operating conditions such as sludge retention time (SRT), hydraulic retention time (HRT), and temperature [16]. Longer HRTs involve mayor contact time between the activated sludge and organic compounds and thus better removal efficiency [24, 25]. Sorption onto sludge, referring to hydrophobic or electrostatic interactions with the biomass, is a common mechanism whose effectiveness depends on the physicochemical properties of the compounds and the biomass concentration [13]. Adsorption to the sludge of hydrophilic compounds is limited [26], and, consequently, their removal by sorption processes is inefficient and can impede the biodegradation of these compounds too [27].

The adsorption process also intervenes in operating conditions in the NSAID retention processes (e.g., temperature, pH, ionic strength, or porous characteristics of the adsorbent and aqueous matrix) [28]. As well, the physicochemical properties of NSAIDs interfere with the adsorption process. The NSAIDs are weak organic acids with a carboxylate moiety present in them [29, 30]. Their acid dissociation constants (pKa) range from 4.00 to 4.91, while their octanol-water partition coefficients (Kow) range from 1.10 to 3.97, implying that NSAIDs exist as dissolved neutral species under normal environmental conditions [31, 32]. Their high water solubility and polar nature lead to difficulty in their removal efficiency in wastewater treatment plants [33, 34]. The physicochemical properties relevant to their existence in water bodies are given in Table 2.

4 Filtration Method

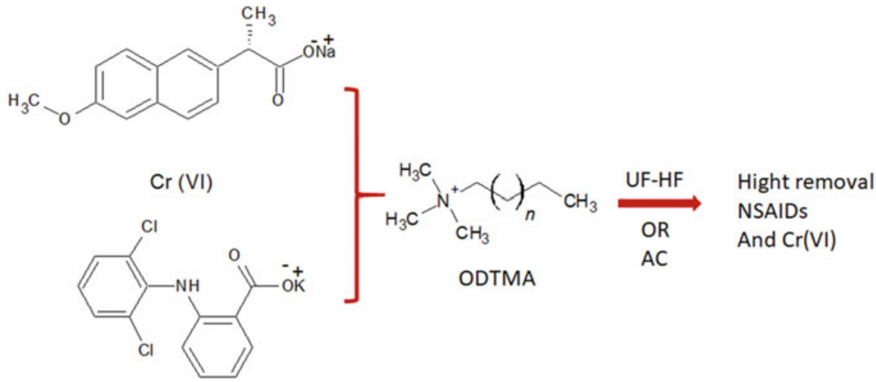
The filtration method using membranes as removal material has revolutionized the remotion of emerging contaminant from wastewater. Qurie et al. [36] reported in 2014 the combined use of membranes with adsorbent compounds had resulted as an efficient method for remotion of nonsteroidal anti-inflammatory drugs (NSAIDs);

Table 2 Chemical structures and physicochemical properties of NSAIDs

NSAIDs	Chemical structure	CAS number	Weight	Log know	pKa	Water solubility (mgL^{-1})
Naproxen		15,307–86-5	296.149	3.18	4.19	44
Diclofenac		15,307–86-5	296.149	4.51	4	10
Ibuprofen		15,687–27-1	206.2808	3.97	4.91	58
Ketoprofen		22,071–15-4	254.2806	3.12	4.45	51
Fenoprofen		29,679–58-1	242.2699	4.05	4.5	81

Information: (https://www.drugbank.ca/) assessed in the period between November and December (2019), [35]

for example, the cationic ODTMA-micelle-clay combined with ultrafiltration (UF) (hollow fiber HF and spiral wound SW) membranes, activated carbon (AC), and reverse osmosis (RO) has demonstrated high removal efficiency toward these two NSAIDs and naproxen metabolite (DMN). Besides, the ODTMA-micelle-clay complex has been found capable of completely removing the heavy metal Cr (VI) from its aqueous solutions at ambient pH and temperature.



The efficiency of filters is based on the use of a micelle-clay complex to polish the tertiary treated wastewater that is generated from ultrafiltration plants by using hollow fiber membranes with 100 kD cutoff filters. Solutions of UF-hollow fiber permeate were passed through the column filter performed with 100/1 or 50/1 (w/w) mixtures of quartz sand and ODTMA-clay complex with two flow rate modes at 1.2 mL min^{-1} and 50 mL min^{-1} [37].

The filtration experiment was performed by using a laboratory column (18 × 4 cm) prepared by mixing 3.0 g of micelle-clay complex and 147 g sand. Elution rate was 2 mL min^{-1}, and eluted volume used to investigate the removal efficiency of naproxen was 1,000 mL.

The summary of low flow rate (1.2 mL min^{-1}) indicates that filtration of tertiary treated water obtained from HF ultrafiltration by micelle-clay complex with excess sand reduced significantly the FC, TC, BOD, EC, turbidity, and COD of effluent.

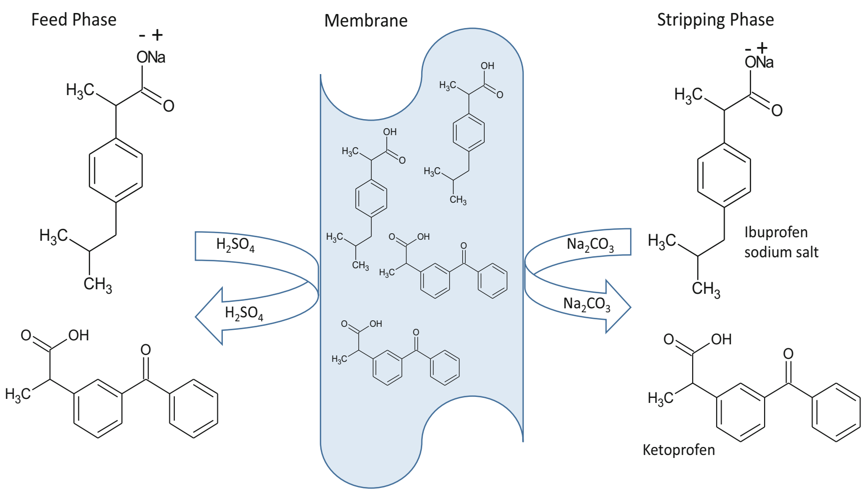
In this study, the effectiveness of ODTMA-micelle-clay complex for the removal of Cr(VI) anion from aqueous solutions has been investigated using either clay (montmorillonite) or micelle-clay complex. Batch experiments have showed the effects of contact time, adsorbent dosage, and pH on the removal efficiency of Cr (VI) from aqueous solutions. Filtration experiments, using columns filled with micelle-clay complex mixed with sand, were performed to assess Cr(VI) removal efficiency under continuous flow at different pH values.

Column experiments were performed using glass columns (18 × 4 cm) prepared by mixing 3.0 g of ODTMA-micelle-clay complex and 147 g sand. The results indicate that complete removal of chromium was achieved at all studied pH values. However, at pH 1 and 2, the breakthrough point was greater than 1,000 mL, whereas at pH 3, 4, and 6, the saturation point was significantly lower with a value of about 500 mL. These results are consistent with those obtained from batch experiments, indicating that the elution volume plays an important role during the adsorption process at pH values higher than 2 complete removal of Cr(VI) with possible reduction to Cr(III) after the breakthrough points.

The removal of the two NSAIDs, naproxen metabolite (DMN) and Cr (VI) using ODTMA-micelle-clay complex, was studied and compared with that of activated charcoal. The adsorption results revealed that ODTMA-micelle-clay complex was more efficient in removing these pollutants than activated carbon as judged by the calculated Qmax and k for both adsorbents.

5 Emulsion Liquid Membrane

Recently, emulsion liquid membrane or surfactant liquid membrane has gained attention as an advanced extraction process for the removal of emerging contaminants present in wastewater. The transport mechanisms of liquid membranes are not only an important technique for concentration, separation, and recovery but also are fundamental importance from an environmental engineering point of view. The emulsion liquid membrane process is carried out by combining extraction and stripping steps in one stage, which leads simultaneous purification and concentration of the solute. Emulsion liquid membrane treatment process represents a very interesting advanced separation process for the removal of nonsteroidal anti-inflammatory drugs from complex matrices such as natural water and seawater [38].



The extraction of IBP and KTP using liquid emulsion membrane involves three steps: preparation of liquid membrane emulsion, removal of the solute from the feed by contacting the emulsion, and separation of liquid emulsion from the external phase.

Volume ratio of internal phase to the membrane phase plays an important role in determining the effectiveness of ELM system. The effect of volume ratios of the internal solution to membrane phase varied between 1:2 and 2:1, by maintaining membrane volume constant on the removal of IBP.

An emulsion liquid membrane was developed to remove NSAIDs ibuprofen and ketoprofen from water. The optimum experimental conditions for the extraction of IBP were summarized as follows: emulsion volume, 60 mL; external phase volume, 600 mL; volume ratio of internal phase to organic phase, 1:1; emulsification time, 3 min; stirring speed, 250 rpm; concentration of span 80, 3% (w/w); volume ratio of W/O emulsion to external phase, 60:600; internal phase concentration (Na_2CO_3), 0.1 N; diluent, hexane; and concentration of H_2SO_4 in the external phase, 0.1 N. Under the best operating parameters, it was possible to extract nearly all of IBP molecules from the feed solution even in the presence of high concentration of salt. At the optimum experimental conditions, about 97.4% KTP was removed in less than 20 min of contact time. This study demonstrates that ELM treatment in comparison with other techniques that are hindered by the presence of salts is a promising process for the elimination of NSAIDs IBP and KTP from complex matrices such as natural water and seawater.

6 Membrane Bioreactor

Membrane bioreactor (MBR) has become a technically and economically feasible alternative for remotion of emerging contaminant. The upgrading of wastewater treatment plants and implementation of sustainable technologies impose as possible solutions for the safe reclamation of high-quality treated effluent. The MBR technology integrates biological degradation of organic matter present in wastewater with membrane filtration, thus passing the limitations of the conventional activated sludge treatment. Membrane bioreactor has become a technically and economically feasible alternative for water and wastewater treatment [20].

For most of the investigated PhACs, membrane bioreactor effluent concentrations were usually significantly lower than in the effluent of a conventional treatment.

The membrane treatment is a promising process to be able to remove negative-charged NSAIDs from wastewater effluent in source waters due to the negative-charged membrane surface.

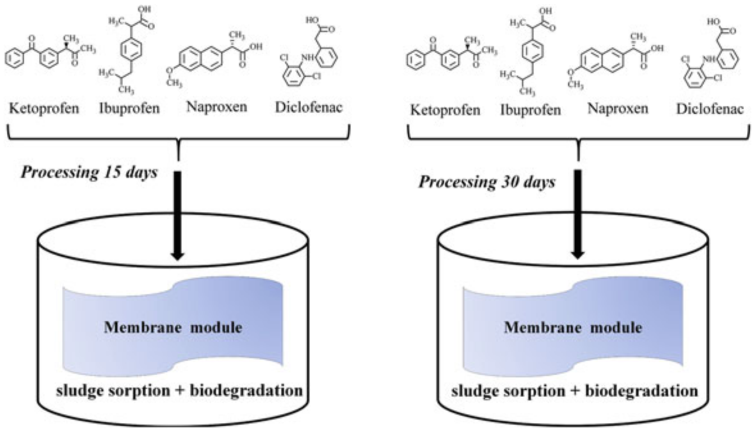
Different materials were compared in terms of rejection of ibuprofen and removal of effluent organic matter from membrane bioreactor (MBR). The membranes used in study by Park et al. [39] were polyethersulfone, polyamide TFC, and titanium oxide, because pharmaceutical compounds contain a potential risk and effluent organic matter is the precursor of carcinogenic disinfection by-products when reusing for drinking water source.

Membrane	NMW (datons)
Polyethersulfone	10,000
Polyamide	8,000
Titanium oxide	1 k, 3 k, 5 k,8 k

Note: NMW, nominal molecular weight

Filtration membrane with a molecular weight cut off of 8,000 Da exhibited 25 ~ 95% removal efficiencies of ibuprofen with a molecular weight of 206 with and without presence of effluent organic matter from membrane bioreactor. The membranes with different nominal molecular weight cut-offs a tight-Ultra. UF membrane could successfully remove ibuprofen at lower J0/k ratio range ($\leq$1) in organic free water.

The sludge retention time (SRT), sludge concentration (SC), and hydraulic retention time (HRT), in the treatment the waste water to scale of the pilot-plants were evaluated by Schröder et al. [24]. The membranes were evaluated during 15 days to 12 g/L and 9 h, and 30 days to 12 g/L and 13 h for. Both MBRs used in this study were equipped with 1.43 m^2 of hollow-fiber ultrafiltration (UF) membranes. To estimate the dilution factor in pharmaceutical compound removal, sodium chloride (NaCl) was aggregated on the tank containing wastewater and membrane. The sludge retention time was performed in separate tanks, for the membranes evaluated during 15 and 30 days.

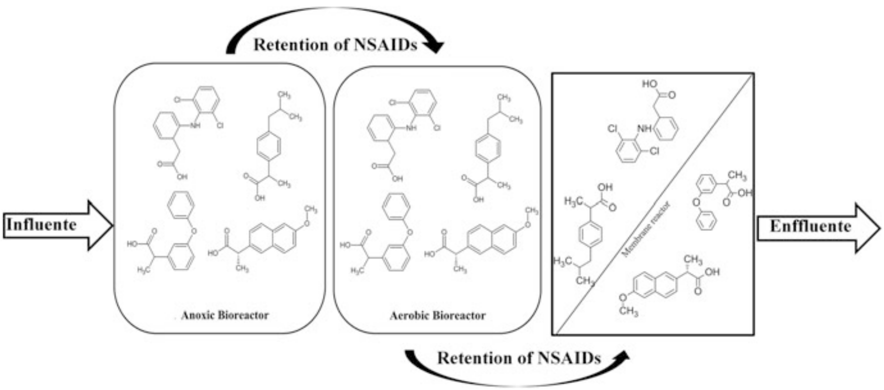


The remotion of each pollutant was the combination between the sludge sorption + biodegradation + membrane retentión. The order of remotion of NSAIDs and antibiotics on both times of treatment, 15 and 30 days, was acetaminophen > ketoprofen > trimethoprim > naproxen > roxithromycin > sulfamethoxazole. The elimination of pharmaceutical compounds can occur in various ways. Sorption onto sludge is one of the mechanisms that take into account the absorption and adsorption factors. The absorption refers to the hydrophobic interactions of the aliphatic and aromatic groups of a compound, while adsorption refers to the electrostatic interactions of positively charged groups of dissolved chemicals with the negatively charged surfaces of the microorganisms.

The elimination of pharmaceutical compounds can occur in two ways. By absorption because of the hydrophobic interactions of the aliphatic and aromatic groups of a compound, and by adsorption through the electrostatic interactions of positively charged groups of dissolved chemicals with the negatively charged surfaces of the microorganisms.

Another mechanism responsible for the removal of pharmaceutical compounds in MBRs is the physical retention by the membranes. The retention of the pharmaceutical depends on the molecular weight cutoff (MWCO) of MBR membranes. Sorption onto the membranes is also limited by the available membrane surface area. Pharmaceutical compounds which are nonpolar will sorb onto the biomass and will therefore be removed indirectly during the retention of the solids by the membranes. Polar pharmaceuticals, with a low tendency to adsorb to the lipophilic sludge surface, will be eliminated neither by adsorption nor by biodegradation because the interaction with the wastewater biocoenosis essential for the biodegradation process will be too short [4, 11]. A better performance in the treatment of wastewater contaminated by drugs could be achieved by the application of additional treatments, e.g., activated carbon adsorption, ozone oxidation, advanced oxidation processes (AOP), nanofiltration (NF), or reverse osmosis (RO).

González-Pérez et al. [16] report a system of wastewater treatment composed of an anoxic bioreactor (3.6 m^3), aerobic bioreactor (8.8 m^3), and membrane reactor (3.5 m^3). The membrane reactor was equipped with hydrophilicized microfiltration flat-sheet membranes (0.4 μm nominal pore size) made of chlorine polyethylene.



All NSAIDs studied by Gonzalez-Pérez (ibuprofen, diclofenac, ketoprofen, and naproxen) were eliminated from the contaminated water inflow. The ibuprofen was almost eliminated (98%) with removal. Naproxen removal efficiency was similar or slightly higher than the best removal efficiency values previously reported in MBR systems. The average removal of ketoprofen for the experimental MBR was at least between 80 and 95% depending on the influent concentration. Thus, the removal efficiency was consistently high compared with the effectiveness found for other MBR treatment. Diclofenac, as opposed to the previous substances, was resistant to MBR treatment, demonstrating that DCF was only partially removed by the MBR (21%).

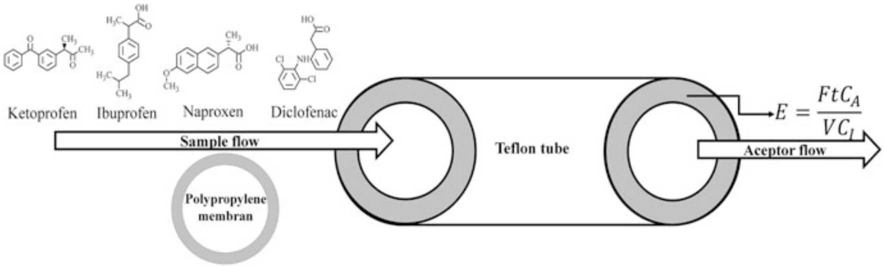
IBU, NPX, and KTP are hydrophilic compounds, so their removal by adsorption to biomass can be considered negligible [11, 40]. Several studies have attributed the high removal effectiveness in MBR of these compounds to biodegradation. The high biodegradability of these compounds causes the greater or lesser effectiveness in elimination to depend on the operational variables of the biological treatment, one of the most influential being sludge retention time.

7 Hollow Fiber Membrane

The hollow fiber membrane liquid-phase microextraction could be a good alternative to extract nonsteroidal anti-inflammatory drugs from aqueous samples. It has been reported that a supported liquid membrane in the pores in the wall of a small porous hollow fiber can be used on bioanalytical and environmental chemistry, where analytes are extracted through the supported liquid membrane by the application of electrical potentials [41].

Liquid-phase membrane extraction is based on passive diffusion, and the flux of analyte across the support liquid membrane is basically controlled by distribution ratios. Recently, LPME was reported with a direct-current electrical potential difference across the SLM as the driving force for extraction based on electrokinetic migration [42]. This technique was termed electromembrane extraction. For the extraction of basic drugs, pH in the sample (300 L) and in the acceptor solution (30 L) was adjusted to 2.0 with HCl to ensure full ionization of the target analytes.

Larsson et al. [33] developed a continuous flow system for the elimination of NSAIDs by liquid-phase microextraction (SPME). In a Teflon tube, polypropylene membranes placed 30 mm wall thickness, 240 mm id, and 0.1 mm by size. The tube was fed by a flow of stock solution of each sample (ibuprofen, ketoprofen, naproxen, and diclofenac) to 10 mgL^{-1} and mixes of the four analytes diluted in water. Ionizable analytes in neutral form were extracted through the membrane, and the extraction was selectively tuned, depending mainly on pH in sample and extract.



In their experiments, Larsson et al. [33] measured the enrichment (E) of each drug in the membrane, as a variable dependent on the feed flow (F) and the contact time (t) between the solution and the membrane. A flow of 30 mL min^{-1} allowed a longer contact time. However, the enrichment rate (ΔE) during the first 30 or 45 min of each analyte was constant when the concentration in the sample flow (C_A) remained approximately equal to the initial concentration (C_I). Enrichment max time was 45 min for ketoprofen and naproxen and 60 min for diclofenac and ibuprofen. The enrichment (E) for diclofenac and ibuprofen is probably because these analytes have somewhat higher log K_{ow} values and therefore are transferred more slowly from the membrane into the acceptor. Your results show that the method can be applied in sewage treatment plants' effluent matrix with linear extraction in an environmentally relevant concentration range.

8 Conclusion

Numerous studies show the presence of five common nonsteroidal anti-inflammatory drugs: diclofenac, ketoprofen, naproxen, ibuprofen, and acetylsalicylic acid in surface waters. High consumption of these medications and the absence and/or limitations of separating wastewater seem to be the most important causes of contamination. Besides, conventional water treatment processes fail to eliminate pharmaceutical substances.

The combined use of polymeric membranes, emulsion membranes, and/or liquid membranes, with adsorbent compounds such as clay, activated carbon, residual sludge, biomass has demonstrated the high efficiency of elimination toward NSAIDs. But due to the physical and chemical complexity of the compounds, there is no single method that is sufficiently effective against all types of contaminants.

The different variables in the separation processes by membranes also play an essential role in the efficiency of the treatment of wastewater contaminated by NSAIDs. Operating conditions, such as sludge retention time, hydraulic retention time, temperature, pH, ionic strength, or porous characteristics of the adsorbent and aqueous matrix, interfere with the adsorption process.

Drug retention also depends on the molecular weight cutoff (MWCO) of the MBR membranes. The absorption on the membranes is also limited by the surface area available. Nonpolar pharmaceutical compounds are absorbed in the biomass and, therefore, are removed indirectly during the retention of the solids by the membranes.

The results of various investigations show that performance in wastewater treatment could be improved by applying additional treatments, for example, activated carbon adsorption, ozone oxidation, advanced oxidation processes (AOP), nanofiltration (NF), or reverse osmosis (RO), among others.

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