ENHANCED PHARMACEUTICAL ELIMINATION FROM WATER: SUPPORTED LIQUID MEMBRANE TECHNOLOGIES

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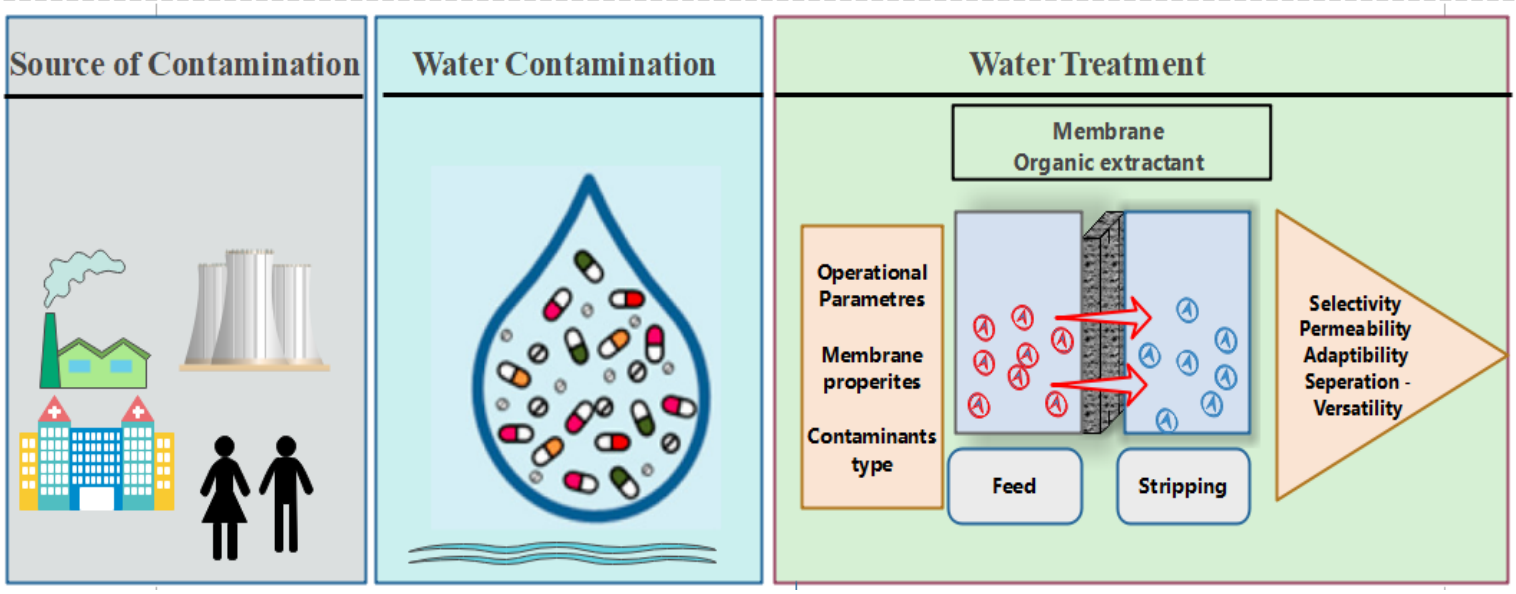

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Enhanced Pharmaceutical Elimination from Water: Supported Liquid Membrane Technologies

DOCTORAL THESIS

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I dedicate this thesis to my parents Tony and Lina

Acknowledgments

¨Never hesitate to go far away, beyond all seas, all frontiers, all countries, all beliefs.¨
Amin Maalouf

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Table of Content

Summary

Quality monitoring of ground and surface water is necessary as these are the major contributors of water for domestic and industrial uses. In the recent time water bodies are being affected by Emerging Contaminants (ECs), can sneak into the ecosystem and cause adverse impact on human health and environment. Pharmaceutical contaminants (PhCs) are one of the major worrying classes of ECs. There has been a massive hike in pharmaceutical production and surge in their consumption over the years. Consequently, these factors have led to a constant and irregulated discharge into the environment. Few studies have thoroughly addressed the detrimental impact of prolonged exposure to pharmaceutical contaminants. Despite their presence in various water sources at minimal levels, it remains crucial to eradicate these contaminants as a preventive measure and enhance their elimination. In this thesis, liquid membrane is proposed as an efficient and alternative extraction technologies to remove different types of pharmaceuticals from aqueous media. Different parameters are investigated that influence the operation with liquid membrane such as the organic extactant, physicochemical properties of the contaminants, the operation conditions (pH, stirring speed, the polymeric support). This combination and interaction of variable influence the process and can present controversial effect; therefore, it was important to investigate the different aspects to optimize the operation with liquid membrane.

Flat sheet liquid membrane is used for batch and optimization experiment to remove Diclofenac, Ibuprofen and Carbamazepine. These pharmaceuticals compounds were tested with various types of extractants (Cyanex 923, TOA, TBP, Versatic acid10 and Aiquat 336) . The optimal extractant and concentration was selected for each contaminant. However, the main drawback of these types of membrane are the instability of extractant within the pores. Methods involving ultrasound and prolonged soaking of the membrane increased relatively the stability and permeability. The integration of SLM in removing pharmaceuticals showcased remarkable results, removing 98% of various pharmaceuticals with minimal organic extractants.

Further research was conducted to investigate the feasibility and the effectiveness of combining supported liquid membrane (SLM) with ozonation as a viable method to eliminate pharmaceutical diclofenac and its by-products. Initially the hybrid process was tested with laboratory-scale flat sheet membrane. Diclofenac was successfully transported through the

liquid membrane using 40% Cy923 at a transfer rate of 10.2 cm/h. The study formulated an equation to predict permeability coefficients based on Cy923 concentration and organic phase viscosity. In addition, Real water matrices did not affect the removal of pharmaceutical contaminants, indicating the membrane's robustness. The integration of ozone was introduced in a separate cell to minimize the adverse effect on the polymeric membrane Ozone treatment significantly mineralized the main contaminants within three hours, generating 9 by-products, that are quantified and including 5-hydroxydiclofenac was identified and its concentration evolution was monitored.

The combination of liquid membrane was tested in hollow fiber liquid membrane to selectively concentrate and remove ibuprofen and diclofenac at low concentration. A simple analytical model was developed to calculate the permeability of hollow fiber configurations using 40% of neutral extractant Cyanex 923. Incorporating a pseudo emulsion in the stripping notably improved system stability and extraction effectiveness of these pharmaceuticals. In this study, ozone was introduced as well as post step to enhance the reduction of diclofenac and ibuprofen, along with their major by-products, 5-hydroxydiclofenac and 4-ethybenzaldehyde. This method achieved substantial mineralization rates of 72% for diclofenac and 52% for ibuprofen by the end of the experiment. The concept of separation with liquid membrane depends on different factors and mainly on the mass transfer resistance. Mathematical modelling is a keystone in comprehending and predicting mass transfer dynamics within liquid membrane systems, particularly concerning the exchange of substances between aqueous and organic phases. Penncilin-G was tested in both flat sheet and hollow fiber membrane using the ionic liquid Aliquat 336. Mathematical models were developed and tested in Matlab 2021B to forecast the efficiency of extraction processes and to provide intricate insights into the factors influencing transfer rates, selectivity, and overall system performance. By enabling the optimization of operational parameters. The objective was to understand the mechanisms involved in mass transfer, shedding light on extraction coefficient and to determine value of the mass transfer the aqueous feed and the membrane.

The last part of this thesis involved collecting data from previous studies with liquid membrane and conducting meta-analysis and statistical assessments to develop a predictive model using a black box for hollow fiber liquid membrane extraction. Assimilating existing data allowed to identify patterns, correlations, and influential factors and eventually forming a foundation for the predictive model. This approach allows for comprehensive comparisons between mechanistic models and empirical data, aiding in the selection and validation of the most accurate and reliable predictive model. Through statistical analyses, relations between various

parameters and extraction efficiency provided insights into the critical factors influencing the process and allow to identify the most impactful methods. . The results obtained were then compared against predictive benchmarks to thoroughly assess their accuracy and reliability. This evaluation aimed to assist researchers in selecting the most appropriate model for real-world applications in hollow fiber liquid membrane extraction.

Chapter 1. Introduction

1. Why Pharmaceuticals Have Emerged as Environmental Contaminants of Concern?

In an era defined by rapid technological advancement global connectivity and massive population growth, an invisible force of new residual substances and contaminants has made their way into our surroundings. These hidden agents, though unseen, have a significant impact on our ecosystems and human well-being.

Emerging contaminants (ECs) encompass a range of diverse chemical compounds that have the potential to cause various environmental challenges. [1]. These chemicals may either occur naturally or be synthesized for several medical, industrial, and daily applications [2][3]. A majority of these contaminants have been in the environment for a while, yet concerns have been raised much more recently. ECs typically exist in trace amounts, often within the micrograms or nomogram's liter range [4]. Traditional instruments and analytical methods were inadequate in detecting such low concentrations, which is why the prevalence and presence of ECs across different settings remained largely unexplored until recent advancements in detection techniques [5].

For instance, pharmaceutical contaminants (PhCs) correspond to a portion of these substances that have actually been present in the ecosystem for a considerable duration however different environmental, social, and economic factors have generated uncertainty and concerns about their potential risk.[6]. Pharmaceuticals (PhCs) are indispensable products and their elimination from daily life is not feasible. They have played a crucial role in preventing, and treating diseases, and enhancing the health of living beings. Over the past decade, the world population has increased along with a massive hike in pharmaceutical manufacturing and industries. Through all these factors, the treatment of the pharmaceutical contaminants released into the environment has not been able to keep pace with the production and hence they are frequently detected in several parts of the environment. Many studies have confirmed that the constant release of pharmaceutical contaminants to water bodies may result in long-term (chronic) effects on aquatic such as genotoxic, mutagenic, and ecotoxicological effects on plants, animals, and humans [7,8].

It can be inferred that the most suitable classification for pharmaceutical contaminants would be "contaminants of emerging concern (CEC) and should remain classified as "emerging" as long as there is a scarcity of information associated with potential risks that can cause [9].

Despite the growing interest of the scientific community in PhCs, there is still a significant gap in understanding their ecological impact due to the limited number of substances being analyzed across different environmental matrices and their risk and toxicological effects depend on time and location of sampling.[10] Li et al. 2020 , have emphasized that PhCs at

certain levels in biota, sediments, and water can cause unfavourable effects to the imminent environment[11]. In another study, Jukosky et al 2008 have shown that estrogen led to an increase in the mortality rate of fish [12]. In addition, the toxicity of a common pharmaceutical, diclofenac, was assessed using fish collected from a river in Germany. The findings revealed that chronic exposure to diclofenac led to damage in the gills and kidneys of the animal along with notable changes in their immune parameters [8]. Furthermore, a significant concern associated with the widespread presence of PPCPs in the environment is the potential development of antibiotic-resistant strains in native bacterial populations.[11].

All of these factors, including any yet undiscovered effects, can classify pharmaceutical contaminants as contaminants of emerging concern, underscoring the importance of their removal. Furthermore, it's crucial to explore the toxicological effects of pharmaceutical contaminants in water.

2. Occurrence of pharmaceuticals in water and wastewater.

Pharmaceutical contaminant contaminants infiltrate the environment through diverse pathways, such as direct emissions from drug production, human and animal excretion, aquaculture practices, and the mishandling of unused medicines. Figure 1 presents the diverse routes that pharmaceuticals can reach the aqueous ecosystem either from industrial production improper disposal or human exertion.

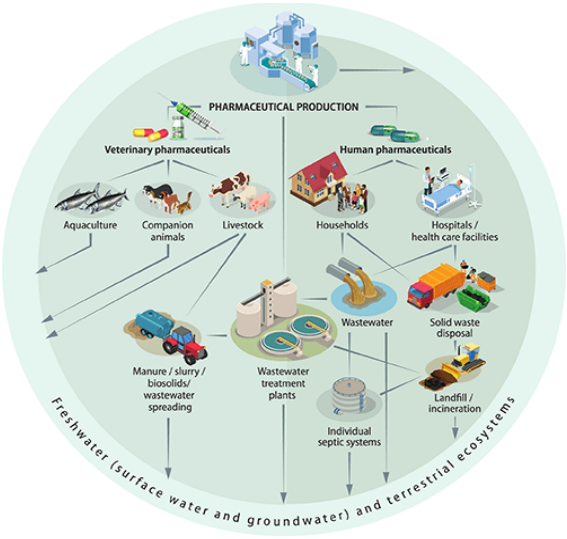


Figure1 Pharmaceutical contaminant pathway (*OECD (2019), Pharmaceutical Residues in Freshwater: Hazards and Policy Responses, OECD Studies on Water, OECD Publishing, Paris*)

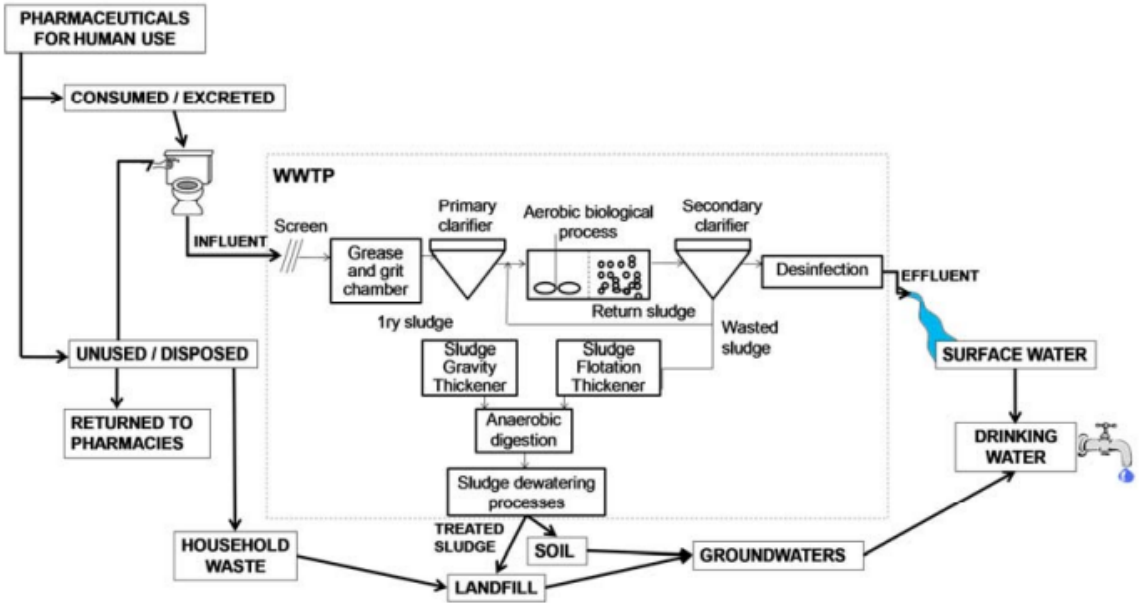


Figure 2. Routes of release of pharmaceutical contaminants for the use of humans into conventional wastewater Treatment

Water bodies can become contaminated with pharmaceutical products through various routes [12]. For instance, following medical usage, PhCs are typically absorbed by the body, eventually excreted and discharged into septic tanks. In addition, cosmetic and personal care products, which linger on the skin, are eventually washed off during bathing or washing. Therefore, after undergoing sewage treatment, wastewater might be repurposed for agricultural irrigation, and treated sludge might be employed as fertilizers on farmlands [13]. In addition, through leaching and soil runoffs, the residues can infiltrate groundwater, contaminating drinking and freshwater sources [14]. This leads to the introduction of pharmaceutical residues into the surface waters like lakes and rivers and even groundwater, as most of contaminants have the potential to migrate downward through back-filtration [15]. Moreover, veterinary pharmaceuticals (When animal waste is employed as fertilizers) can leach into the soil through animal husbandry practices contaminate broader areas, and eventually reach the food chain. [16]. Numerous research studies are consistently affirming that the existence of antibiotics and antimicrobial substances in natural settings can actively increase the emergence of widespread microbial resistance. This situation poses formidable obstacles in the efforts to control and combat infections and diseases [17][18].

Another significant source of pharmaceutical contamination in the environment arises from the release of wastewater by treatment facilities [19]. As shown in Figure 2, water undergoes

different stages of treatment processes such as primary, secondary, and an optional tertiary or advanced treatment process before being released into the environment. Most wastewater treatment plants (WWTPs) are outdated and are designed to remove easily to moderately degradable substances and microorganisms, including biodegradable carbon, nitrogen, and phosphorus compounds [20], as well as nutrients and pathogens [19,20]. However, these plants are not designed to remove persistent micropollutants such as pharmaceuticals.

As a result, WWTPs are regarded as the primary source for the release of pharmaceuticals into various environmental compartments, including surface water, groundwater, and, subsequently, soil. This is because the accumulated sludge from these facilities can be utilized as agricultural fertilizers without undergoing additional treatment. [21,22].

In addition, one of the main issues associated with pharmaceuticals, is their low concentrations, ranging from ng/L to µg/L in different water compartments [22]. In this sense, the physicochemical properties of pharmaceuticals, such as high polarity, volatility, high lipophilicity, persistence, and adsorption can affect their removal rate during the treatment processes in WWTPs [19]. Table 1 summarized the different pharmaceuticals and their related concentration found in different water matrices in different countries the variations in the concentration levels of pharmaceuticals could be attributed to several reasons, such as the consumption rate and pattern, sampling and analysis methods, seasonal variations, and population size and density [23]. Pharmaceutical compounds are characterized by their limits of elimination by volatilization because of their low vapor pressure and pKa values between 3 and 10. Some drugs, such as ibuprofen, diclofenac, and carbamazepine, include extremities vulnerable to biodegradation and sorption. According to the review of Petrie et al. (2013) diclofenac is removed by ≤50%, however carbamazepine removal is low [24]. From the study carried out by Tauxe-Wuersch et al. (2005) in Switzerland, they noted the difficulties faced in the removal of different drugs such as ibuprofen, mefenamic acid, and diclofenac with biological and physico-chemical treatments [25]. Additionally, this work reported that there was a difference in the elimination rates within wet and dry seasons. The removal of ibuprofen and ketoprofen was inhibited during winter in comparison to that during the dry period. This can be explained by the difference in the residence time of treated water in treatment plants depending on the rainfall. In fact, the flow rate was three times higher in winter than in the dry period. In addition, Lindqvist et al. (2005) found ibuprofen, naproxen, ketoprofen, diclofenac, and bezafibrate in seven different sewage water treatment plants in Finland. Despite their effort to remove these pharmaceutical products, they detected them again in the rivers of discharge of sewage water treatment.[26].

Table 1 .Occurrence of pharmaceuticals in water

Contaminant	Country	Concentration (ug/L)	Source	Reference
Carbamazepine, Naproxen, Ibuprofen	Greece	8.02–132	Wastewater	[27]
Propranolol, Paracetamol	Italy	0.001 -284	River Water	[28]
Diclofenac, Sulfamethoxazole, Carbamazepine, Lamivudine, Caffeine, Acetaminophen	South Africa	0.010–0.034	Seawater	[29]
Ketoprofen, Naproxen, Fluoxetine	Spain	0.3–324.7	Wastewater treatment plants discharge	[30]
Carbamazepine, Erythromycin	Netherland	0.91-0.9	Sewage Treatment Plant effluents, surface water	[31].
Ibuprofen, Diclofenac	France	100	Sewage Treatment Plants effluents,	[32]

The detection of pharmaceutical remnants in aquatic ecosystems has triggered extensive global environmental examination in recent times. All studies have concurred that the presence of pharmaceuticals in water differs from one country to another, influenced by various factors like prescription practices, population, and the treatment applied before discharge. For instance, France Switzerland, and Germany are considered the highest consumers of pharmaceuticals. Specifically in Germany, millions of non-steroidal anti-inflammatory drugs (NSAIDS) such as

aspirin, paracetamol, ibuprofen, and diclofenac were produced during 2000 and 2001 corresponding to 86 tonnes [32]. In Italy, Ferrari et al. (2011) investigated the accumulation of pharmaceuticals in surface water and sediments in the largest Italian River Po and the concentration of paracetamol was in the range of 284 µg/L [28]. Ncube et al (2020) found a concentration of 19.2 µg/L [18] of Ibuprofen in surface water, and 1.38 µg/L in wastewater [31]. Diclofenac was detected at a concentration of 0.034 µgL-1 in the sea water in South Africa and 1.51 µgL-1 in surface water [29]]. The concentrations of ibuprofen and diclofenac were near to 100 µg/L were detected in the French municipal influents [32].

By definition, NSAIDs are a common class that compromise analgesic (painkilling) and antipyretic (fever-reducing). Including, ibuprofen, and diclofenac. As shown in the monitored data of Table 1these investigated compounds are frequently detected in high concentrations up to nearly one hundred micrograms per liter in the influents and effluents of WWTPs in different geographical regions.

3. Treatment processes for pharmaceutical contaminants.

Numerous water treatment and new approaches are being developed to limit the accumulation of pharmaceuticals in water and wastewater [32,33,34]. While many of these environmental solutions have proven effective, they often come with significant operational expenses and face challenges regarding feasibility and scalability. The persistence of these pollutants emphasizes the need for effective and developed methods that can tackle the problem not only in the effluent of wastewater but also in the generation of hazardous sludge as well [35]. This underscores the need for treatment of water at the tertiary stage before distribution to various recipients. Table 2 below provides a summary of various studies conducted to attain acceptable concentrations of the specific pharmaceutical contaminants under investigation in this study: Diclofenac, Ibuprofen, Carbamazepine, and Penicillin G, within aqueous matrices. These investigations have examined diverse techniques, such as adsorption [36,37], membrane separation [338,39], and advanced oxidation processes [40].

3.1 Adsorption

Table 2. Studies using different materials for adsorption of pharmaceuticals.

Contaminant	Treatment process	Efficiency (%)	References
Diclofenac	Activated Sludge	98	[41]
	Graphene oxide-based nanocomposite	89	[42].
	Mesoporous silica nanoparticles	99	[43]
Ibuprofen	Powdered AC	88	[44]
	Hydroxyl amine-functionalised MWCNT	97	[45]
	Ultrasound modified AC	92	[46]
Carbamazepine	Coconut shell-activated carbon	52	[47]
	Biochar BC700 Pine sawdust	66	[48].
Penicillin G	Multi-walled carbon nanotubes	56.4	[49]
	Activated carbon	64.4	[50]

The application of the adsorption technique has been widely employed in studies aimed at removing various contaminants, especially pharmaceuticals and personal care products. This method is favoured due to its simplicity, high removal rate, ease of operation and implementation, cost-effectiveness, and lack of sludge formation [38]. Among the targeted pharmaceutical products, such as diclofenac, can generate metabolites when exposed to sunlight, and some of these by-products may even be more toxic than pure diclofenac [36]. In this context, the removal of diclofenac and other products from aqueous media through adsorption represents a promising alternative. This approach avoids the transformation of emerging contaminants into other by-products or the generation of genotoxic compounds.

The application of adsorption technique for wastewater treatment requires several crucial steps in choosing, developing, and characterizing the adsorbent materials. These adsorbent materials should possess desirable characteristics, including low cost, widespread availability, chemical, mechanical, and thermal stability, high adsorption capacity, rapid adsorption kinetics, high

selectivity, favourable physicochemical and textural properties, and the potential for reuse and regeneration [42].

Activated carbon adsorption is one of the most commonly used techniques worldwide for removing water contaminants and in most of cases, the carbon precursors are altered to enhance the adsorption capacity. A study by Fröhlich et al. (2018), demonstrated that 92% of ibuprofen in an aqueous solution was adsorbed when exposed to ultrasound using activated carbon [46]. The adsorption efficiency of penicillin was investigated using single and multi-walled carbon nanotubes, resulting in removal efficiencies of 68.25% and 56.37% for an initial concentration of 50 mg/L, pH of 5, an adsorption dose of 0.8 g/L, a duration of 105 minutes at 300 rpm, and a temperature of 10°C. Yu et al. (2009) illustrated that enhancing the textural properties of activated carbon, obtained from coconut shells, and improved its adsorption capacity. Additionally, carbamazepine was removed using biochar BC700 from pine sawdust, employing hydrothermal carbonization (HTC) of waste biomass, such as agricultural residues, as a substitute for commercial activated carbon [44] Adsorbents with low acquisition costs and widespread availability are typically derived from natural sources, including biomass from nature or industrial and agro-industrial processes. Ultimately, the physiochemical properties of the contaminants play a pivotal role in selecting the most suitable adsorbent, as well as determining the optimal isotherm and kinetic parameters.

3.2 Membrane separation

Membranes used in various applications come in different forms such as tubular, spiral, and hollow fiber [33]. These membranes can be fabricated from various materials, including polymers, ceramics, or mixed matrix compounds and comes in different forms such as tubular, spiral and hollow fiber. They can have diverse shapes, morphologies, porosity levels, and electrical charges, and they can exist in solid or liquid forms [47]. When selecting the membrane material, it's crucial to consider cost-effective raw materials while ensuring the desired properties like corrosion resistance, mechanical strength, driven force, and filtration efficiency [48]. They are categorized into Reverse osmosis (RO) nanofiltration (NF), ultrafiltration (UF), and microfiltration (MF) based on the membrane's pore size based on the pore size of the membrane as shown in Figure 3. It's imperative to assess the entire process, considering the membrane's intended purpose and the contaminants to be eliminated, to determine its feasibility and suitability for use. For instance, reverse osmosis membranes

exhibit high rejection rates but incur higher operational costs due to the need for high operating pressure to overcome lower permeability. However, they excel in removal efficiency by having smaller pore sizes compared to other membrane separation methods. In addition, membrane separation is usually adapted to remove pharmaceutical due to their capability to remove contaminants at low concentration. Many studies have been conducted using membrane separation to remove pharmaceuticals. Table 3 presents some studies that used membranes to remove the targeted pharmaceuticals the removal efficiencies obtained. When employing microfiltration, it was necessary to employ other pre- or post-treatment techniques to achieve higher removal rates, since the molecular sizes of pharmaceuticals are generally smaller. Plakas et al (2019) achieved a maximum of 65.5 % removal efficiency when combining microfiltration with Fenton oxidation. A simple Nanofiltration was used to remove antibiotics such as penicillin G from real effluent in Spain [51]. On the other hand, ibuprofen was removed by an efficiency of 88% by a polysulfone nanofiltration coated with graphene oxide [52]. When using forward osmosis combined with a membrane bioreactor, a high rejection efficiency (88%) was obtained for carbamazepine. The removal mechanism was attributed to the combination of the rejection and biodegradation [53].

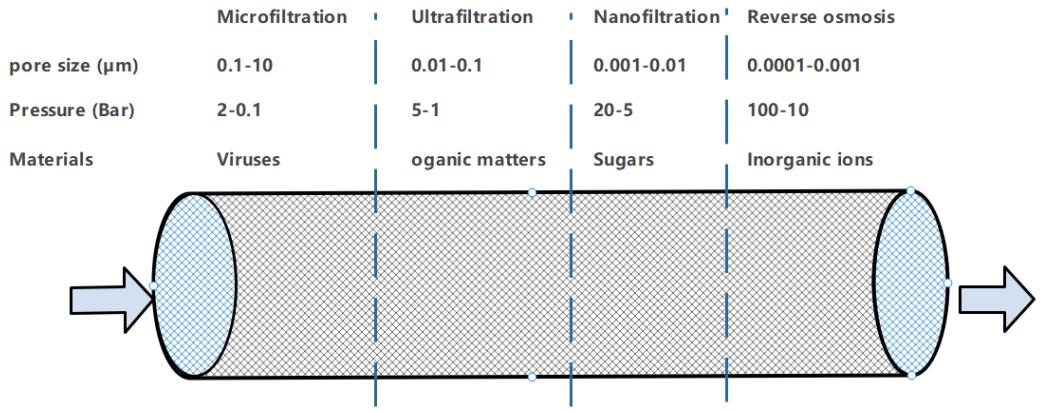


Figure 3 Classification of membranes according to pore size, driven force and removed materials.

Table 3. Studies using different membrane processes for pharmaceuticals removal.

Filtration	Contaminant	Removal efficiency (%)	References

Microfiltration/ Heterogeneous Fenton oxidation	Diclofenac	65.5	[51]
Graphene Oxide Coated Polysulfone Nanofiltration Membranes	Ibuprofen	88	[52]
Forward osmotic membrane bioreactor	Carbamazepine	88.20	[53]
Nanofiltration	Penicillin G	70	[54]

3.3 Advanced oxidation

Advanced oxidation processes (AOPs) represent a tertiary approach for eliminating emerging contaminants. These processes encompass chemical, electrochemical, or photochemical methods that produce highly reactive oxygen free radicals, primarily hydroxyl radicals ($^{\cdot}OH$), that facilitate the degradation or combustion of organic compounds through hydroxylation or dehydroxylation reactions, to produce smaller molecules and eventually carbon dioxide, water and inorganic ions, [35,38,55]. AOPs can have different sources of oxidizing species such as including ozone, hydrogen peroxide, photolysis, electrochemical oxidation, sonochemical oxidation, and heterogeneous photocatalysis [55,56]. The following Table 4 gives a summary of the removal efficiency along with the time needed to oxidize the targeted pollutant. It is noteworthy, that the elimination of the main compound- does not signify total mineralization, therefore combinations of oxidation methods are more favourable to enhance mineralization efficiency. Studies have shown 76% of diclofenac (10mg/L) was removed from synthetic water with the combination of ozonation and after 3 min of treatment [55]. Ozonation can enhance its potential for generating hydroxyl radicals when combined with hydrogen peroxide (H_2O_2). In this context, a study by Huber et al. (2003) demonstrated that the addition of peroxide to the ozonation process for ibuprofen resulted in an impressive removal efficiency of 98% [56]. Conversely, using ozone alone achieved a 98% removal rate for carbamazepine. However, it's important to note that various operational factors, including temperature, flow rate, mass transfer of ozone, type of diffuser, and reactor configuration, can influence the oxidation

reaction when utilizing ozone [57]. In addition, different potent oxidant SO_4 can be generated through the decomposition of oxidants like persulfate ($S_2O_8^{-2}$). Norzee et al (2017) assessed the use of activated persulfate to effectively eliminate penicillin-G from water and the highest removal was 98.7% after 90 minutes of operation [58].

Table 4. Advanced oxidation processes for different pharmaceuticals.

Advanced oxidation processes	Contaminant	Removal time (mins)	Removal efficiency (%)	References
Ozonation /UV	Diclofenac	3	76	[56]
Ozonation / Peroxone ($O3/H_2O2$)	Ibuprofen	10	97	[57]
Ozonation	Carbamazepine	10	98	[57
Persulfate UV activation	Penicillin G	90	98.7	[58]

3.4 Comparison between all technologies

Different degrees of treatment; preliminary, primary, secondary, and tertiary are used in wastewater. Tertiary treatment is the highest level of treatment in the conventional wastewater treatment process and focuses on further improving the quality of treated wastewater before it is discharged into the environment or reused [38,59]. Table 5 offers a comprehensive overview of the advantages and drawbacks associated with the chosen treatment method tailored specifically for addressing the targeted contaminant.

Adsorption involves the use of adsorbent materials, such as activated carbon or other specialized adsorbents, to remove specific contaminants from wastewater. These adsorbent materials have a high surface area and can attract and capture pollutants through physical and chemical interactions. Adsorption is particularly effective in removing organic compounds, including certain chemicals, pharmaceuticals, and dissolved organic matter. Adsorption has advantages over other methods because of its simple design that can involve low investment in terms of both initial cost and space required. Yet, this technique is more suitability for batch processing with a mild operation condition, and the ability requires an additional step to treat regenerate adsorbents. On the other hand, with advanced oxidation process, it is possible to

treat large volumes of wastewater. Despite that advanced oxidation process can lead to a high degradation of pharmaceuticals, it is difficult to apply on a wide scale of WWTPs due to the oxidative by-products and high operation cost. In addition, a common problem for all AOPs is their high cost, mainly because of the high demand for electrical energy [59]. Membrane separation is a versatile technology widely used in both industrial and environmental applications [35,51]. It offers significant advantages, including reduced energy consumption and the replacement of conventional methods like filtration, distillation, ion exchange, and chemical treatments. Although membrane separation and treatment technologies is associated with different drawbacks, such as concentration polarization, membrane fouling, limited membrane lifetime, and challenges with selectivity and flux. To address these issues, various membrane morphologies can be designed, incorporating biological and chemical enhancements.

Table 5. Comparison between treatment technologies

Treatment Method	Advantages	Disadvantages
Adsorption	• Low energy consumption • Removal of specific contaminants	• Saturation and further treatment for adsorbent. • pH and Temperature control. • Limited specific area for adsorbent
Membrane filtration	• Effective for various types • Continuous operation • Impossibility of using the membranes in all types of waters	• Impossibility of using the membranes in all types of waters • Initial installation and operation cost • Membrane fouling
Advanced oxidation	• Effective for treating persistent pollutants. - • - improve water quality and reduce color, odor, and taste. • Effective for complex organic compound	• Generation of transformation products • May require the addition of chemicals. • Energy intensive • High operational cost

4. Liquid membrane

4.1 Liquid Membrane General

Liquid membrane (LM) is a relatively new and prospective separation system consisting of a liquid film through which selective mass transfers of gases, ions, or molecules occur via permeation and transport processes [60]. Owing to its advantages over solid membranes and solvent extraction [60, 61]. Liquid membrane separation combines the solvent extraction and stripping processes (re-extraction) in a single step. The significant potential for conserving energy, along with low capital and operational expenses, as well as the opportunity to employ cost-effective extractants due to the limited quantity of the membrane phase, highlights the importance of giving special consideration to liquid membrane technology [62]. They can be broadly classified into three different types: bulk, emulsion, and supported liquid membrane (SLM)[61]. SLMs are thought to be the most investigated and BLMs and ELMs belong to the group of non-supported liquid membranes as they contain only liquid phases without involving polymeric support. [62,63]. This part of the thesis gives a closer look at the basics of supported liquid membrane technology, with emphasis on the facilitated transport that governs the separation SLM systems.

4.2 Bulk Liquid membrane

Bulk liquid membranes usually consist of an aqueous feed and stripping phase, separated by a water-immiscible liquid membrane phase in a U-tube. They are often used to study the transport properties of novel carriers and a small membrane surface area of BLM makes them technologically not very attractive LM is the simplest form of LM without support which consists of an aqueous bulk feed and receiving solution separated by an organic bulk, water-immiscible liquid solution [64,65].

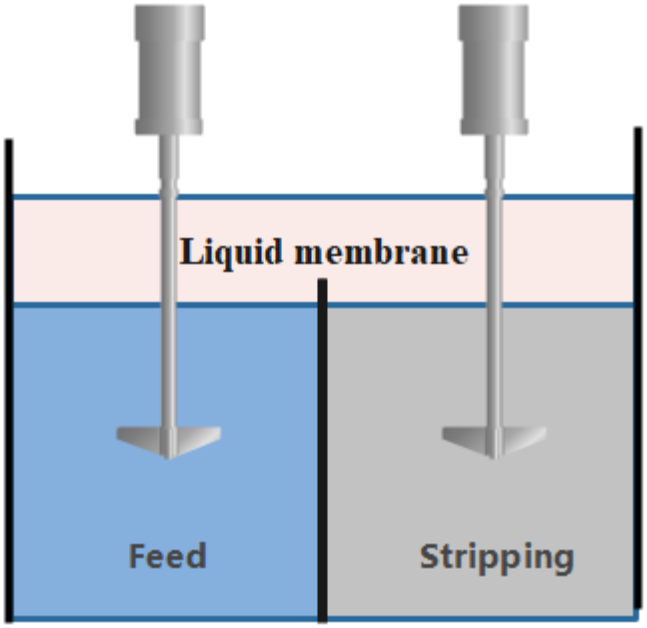


Figure 4. Bulk Liquid membrane

The membrane phase is usually mixed so the diffusion path is limited to the distance of the boundary layer as seen in Figure 4. Although it is one of the simplest types of liquid membranes that shows superior membrane stability, inferior solute fluxes, low selectivity, and high operating costs are obtained [64]. Thus, this LM configuration is mostly used in laboratory measurements for evaluation of the metal mass transfer, but this membrane configuration has no relevance for large-scale separation processes due to their large thickness. [64-65].

4.3 Emulsion Liquid Membrane

It is defined by the use of a liquid membrane dispersed as tiny droplets within a continuous phase, forming an emulsion. The principle behind ELM is to transport specific solutes or contaminants from one phase (usually an aqueous solution) to another phase (usually an organic solvent) through the liquid membrane [66]. The benefit from low solvent inventory and energy needs. However, a better understanding of the process and factors influencing the operating conditions and the emulsion stability of the extraction/stripping process is crucial to enhancing ELM's performance. Emulsion stability always has been the main concern in their application. Factors that need to be controlled to overcome this problem involve ionic strengths, pH, temperature, or any factors that disrupt the membrane stability during the separation [66,67]. Generally, the ELM process consists of four main steps, which are emulsification,

permeation or extraction process, settling, and demulsification (breaking of the emulsion) as shown in Figure 5. ELM has been used extensively to treat and remove various emerging contaminants from water. The existing studies that elucidate briefly the application of ELM are listed in Table 6.

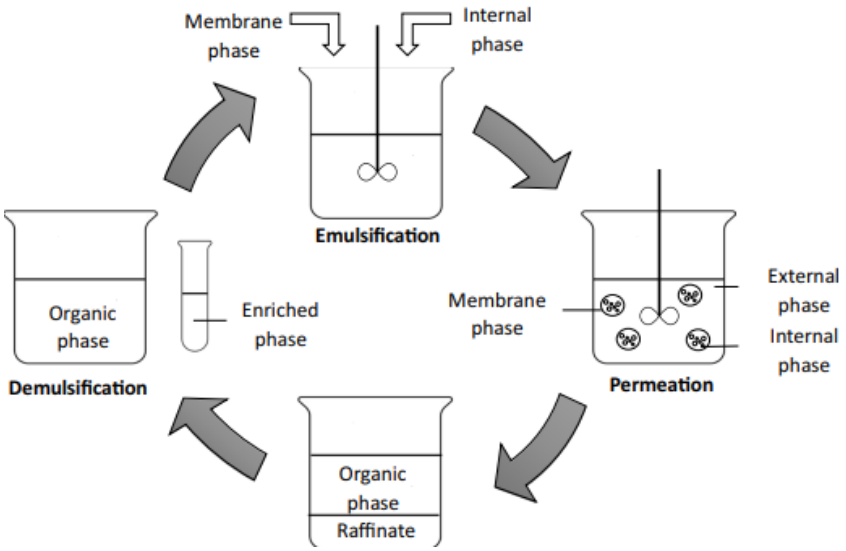


Figure 5. Preparation of emulsion liquid membrane

Table 6. Summary of application of ELM for pharmaceutical compounds.

Contaminant	Concentration (mg/L)	Extractant	Diluent	Surfactant	Efficiency (%)	Reference
Diclofenac	20-100	tetrabutylammonium bromide (TBAB) /	Dichloromethane	Span 80	99.65	[68]
Ibuprofen	10	trioctylamine,(TOA (	kerosene	Span 80	≤85	[69]
Ciprofloxacin	100	Tributyl phosphate (TBP)	n-Heptane	Nano-Fe2O3 particles	98	[70]
penicillin G,	50	Amberlite LA2 Kerosene	Kerosene	Span 80	95	[71]
Acetaminophen	100	TOMAC/Aliquat 336	Hexane	Span 80	99	[72]

4.4 Supported Liquid membrane.

SLM is a nondispersive type of LM, in which membrane phase is immobilized in the pores of a polymer. The main components are the polymeric support, extractant and stripping agent [62]. The polymeric support is a microporous hydrophobic that provides a structural support for the membrane phase (organic extractants) which is the active component in the separation [62,63]. Permeation occurs as a result of the chemical potential gradient between the phases, which is essentially driven by the difference in compound concentrations. The permeants from liquid feed (donor solution) are transported through a nonporous, polymeric, or liquid membrane phase and stripped into another liquid phase (stripping phase). Schlosser et al (1985) called this process pertraction, by analogy to the term extraction, which can be seen as a combination of extraction and solvent stripping carried out simultaneously [73]. Additionally, to its to its high selectivity, SLM acts on nonequilibrium mass-transfer characteristics where the separation is not limited by the conditions of equilibrium [74]. Hence, the quantity of transported compounds does not follow a direct proportion to the quantity of the organic membrane phase, as is observed in traditional extraction processes [75]. This eliminates certain constraints associated with parameters such as the aqueous-to-organic phase ratio, emulsification, flooding, loading limits, phase separation, and substantial solvent inventory [74,75]. Supported liquid membranes (SLMs) have diverse applications in both industrial and analytical domains, separation, preconcentration, extraction, and wastewater treatment [73,74,75]. These membranes come in various forms, such as flat, cylindrical, and hollow fiber. However, it's worth noting that only a limited selection of these configurations can be readily upscaled. The primary hindrance to scalability is the membrane stability. Supported liquid membranes can be broadly categorized into two primary groups based on their dimensions, shape, surface area, and application support [76]. These groups primarily encompass flat sheet-supported liquid membranes (FSSLM) and hollow fiber-supported liquid membranes (HFSLM).

4.4.1 Flat sheet supported liquid membrane.

This represents the most straightforward design for Supported Liquid Membranes (SLM), typically employed in preliminary laboratory-scale experiments [63]. It involves microporous solid support with its pores saturated by an organic liquid forming the liquid membrane. The impregnated membrane is positioned between two mechanically stirred compartments. One compartment corresponds to the he feed solution, while the other is designated for the strip solution represented in Figure 6.

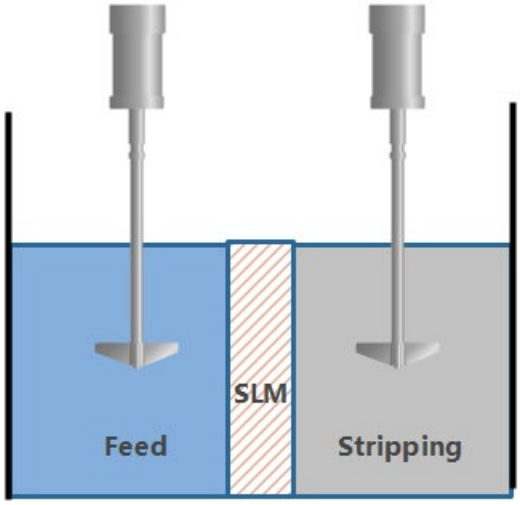


Figure 6. Flat sheet supported liquid membrane.

4.4.2 Hollow fiber

The design of the hollow-fiber SLM module presented in Figure 7. It consists of an outer nonporous shell that prevents the transport of materials in and out. Inside this shell, a specific number of hydrophobic microporous fibers are densely packed. These porous fibers are filled with an organic extractant. Usually, the feed is flow through the shell and stripping phase is passed through the lumen side (inside the tube) using mechanical pumps. Liquid flow operation can be carried out in both a counter-current and concurrent mode [63,76]. The application of hollow fiber configuration offers several benefits, making it an optimal choice for industrial implementation. These advantages include a notably high surface area-to-volume ratio compared to the flat sheet module, minimal membrane thickness, and continuous operation [76]. Consequently, these factors lead to highly efficient mass transfer rates and enhanced overall effectiveness. This particular setup can be customized for diverse uses in both industrial and analytical domains, serving a broad spectrum of industries [62,63].

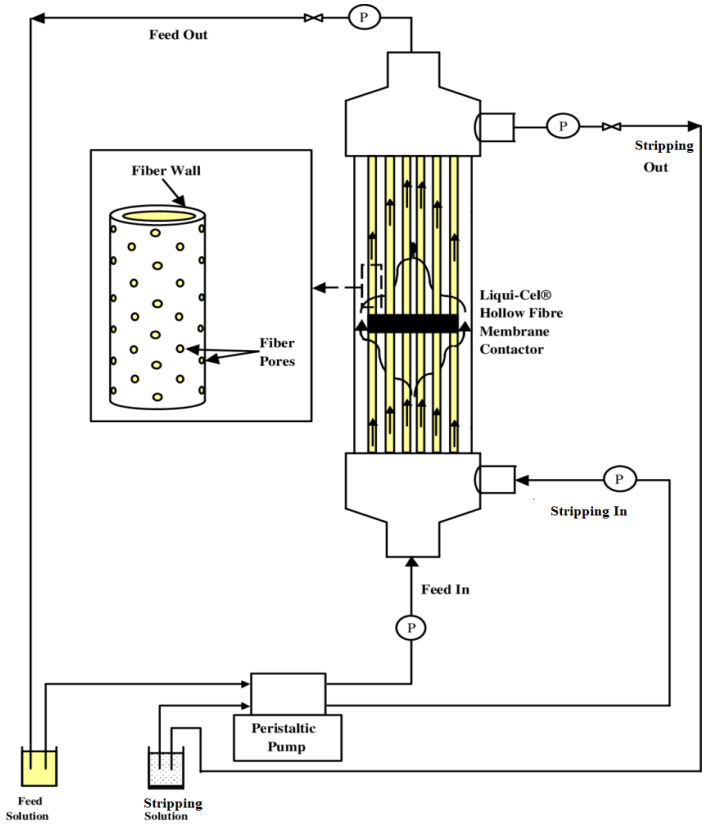


Figure 7. Hollow fiber liquid membrane operating in concurrent flow.

4.5 Transport Mechanism and driving force with SLM

The primary concept of SLM involves the separation of mixtures and the extraction or concentration (enrichment) of one or more components. This process is built upon a three-phase system that facilitates mass transfer between these phases. The feed and stripping phases are separated by a membrane, which contains an organic extractant that is entirely immiscible in both of these phases [61,63 ,76].

As previously mentioned, the transport process operates as a dynamic non-equilibrium process. The effectiveness of membrane transport for a specific compound relies on its partition coefficient within the various components of the membrane system [77]. It signifies that only selective compounds according to physicochemical properties can be transported from the feed phase into the membrane and simultaneously re-extracted from the membrane into the strip phase. Consequently, the separation of different compounds follows a similar concept as liquid extraction followed by back extraction. This entails establishing a difference in the chemical potentials of the mixture components on opposing sides of the membrane to sustain continuous separation or concentration.

The two critical properties of SLM separation are high diffusion coefficient and solubility of solute in liquids [78]. The transport of the substances from the feed solution to the strip side can be divided into the following steps depending on the concentration gradient [79]. The concentration profile in the SLM system is schematically shown in Figure 8.

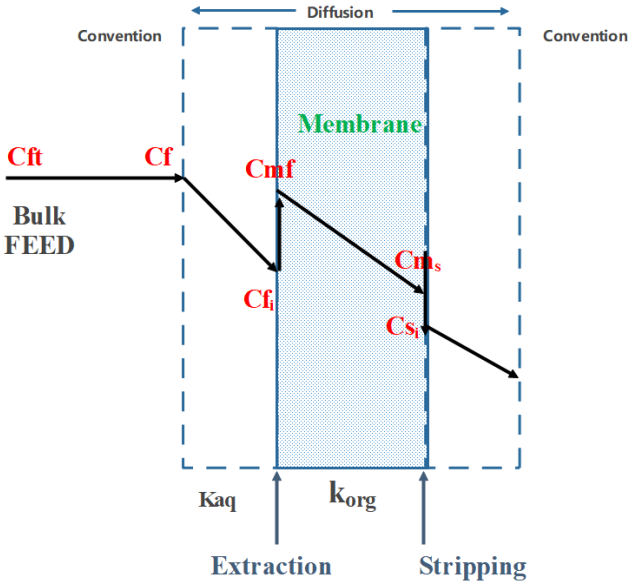


Figure 8. Concentration profile in SLM

- Solute convention in the feed solution.
- Solute diffusion across the boundary aqueous layer in the feed phase.
- extraction of solute on the feed/membrane phase interface.
- Diffusion of solute in the membrane phase.
- Stripping of solute on membrane/stripping interface.
- Diffusion across the boundary layer on the stripping.
- Solute convention (desorption) in the stripping solution.

Every diffusion step is governed by the resistance to transport, usually, assumptions are made to simplify mass transfer calculations [78, 79,80]. Initially, resistance on the feed and stripping sides can be disregarded due to the mechanical stirring minimizing the thickness of the boundary layers. Additionally, it is often considered that chemical reactions (extraction and stripping) are instantaneous making temporal resistances negligible [81,82]. Given these considerations, diffusion through the liquid membrane is taken as the primary limiting step in the transport of contaminants. Consequently, various mathematical models, such as solution-diffusion or simple network models, along with numerical models have been employed to describe mass transfer in liquid membrane systems [79,82].

The specific component can be transported across the membrane according to two distinct transport mechanisms: simple permeation, also known as (passive diffusion) and carrier-mediated transport [82,83]. Their occurrence is determined by the type and properties of the transported components.

4.5.1 Simple Permeation

In simple permeation mechanism, the diffusion is ensured by the solubility the component of interest in the organic phase [79]. The transported compound exists in the same form (uncharged) in both the feed and strip phases, and the transport ends when an equilibrium concentration is reached. Therefore, concentrating the transported compound becomes impossible in this scenario. An example of this type of process is the separation of aliphatic and aromatic hydrocarbons [80,84]. In several cases, components such as organics, metals and emerging contaminants have low solubility in the organic phase and require the means of carriers. In other words, the selectivity of separation and/or the pertraction capacity can be enhanced if the solute undergoes a chemical reaction in the stripping phase [62,63]. In this way, the concentration gradient can be maintained across the membrane, hence facilitating the transport. By employing facilitated transport, the choices of carriers and reaction windows are tailored hence the selectively and the efficiency can be further enhanced.

4.5.2 Facilitated transport.

Facilitated transport through an SLM is based on the reversible chemical reaction between compounds with the carrier at the membrane surface and the two liquid phases and the diffusion process [84]. Therefore, the permeability and selectivity of SLM transport can then be increased by several orders of magnitude. The carrier should reversibly react with the compound and form a complex that can be transported through the organic membrane phase. In this situation, it is important that the carrier and its complex formed with the transported compound are soluble in the membrane but not in the feed and strip aqueous [85]. The possibility of using various compounds as a membrane carrier defers the facilitated transport mechanism from the simple permeation and the mechanism can be divided into:

1) Simple carrier transport

   In simple carrier transport, the carrier, selectively and reversibly reacts with the component found in the feed, forming extractable complexes. These complexes then diffuse through the liquid membrane to reach the membrane-stripping interface, where they are subsequently released into the stripping solution. This transport process occurs when the

components in the feed are in a neutral form (uncharged). The reactions with the carrier exclusively occur at the surface of the membrane, as the carrier is highly hydrophobic and remains within the pores of the membrane support [73, 80]. This type of liquid membrane transport is termed "simple" because only the solute to be extracted is involved.

2) Coupled carrier cotransport.

This mechanism is preferred when the substances present in the feed are ionic species. If the carrier used in the membrane phase is in an uncharged form, the transported ionic substance can only be extracted as an ion pair by introducing a counterion into the feed phase. The carrier interacts with this neutral ion pair, forming a complex that is transported through the membrane. In this type of transport, the concentration gradient of the co-transported compound acts as the driving force. Tertiary amines are commonly used as carriers for this process. Consequently, ionic substances and their counterions are transported in the same direction, and their fluxes are stoichiometrically coupled [84].

3) Coupled carrier counter transport.

The coupled carrier counter transport mechanism involves the simultaneous movement of two positively charged species in opposite directions. To illustrate, species A^+ migrates from the feed phase to the stripping phase, while species B+ travels from the stripping phase to the feed phase. Species A^+ associates with carrier C, forming AC complexes that traverse the membrane phase and are discharged at the membrane-strip interface. Meanwhile, the unbound carrier C interacts with species B^+ and conveys it through the membrane phase as BC complexes, releasing it at the feed-membrane interface. In these cases, a gradient of counterions from the strip (receiving) phase to the feed (source) phase provides the driving force for the transport. This mechanism is commonly observed with cationic extractants that react with cationic species from the feed phase, form extractable neutral complexes in the organic phase, and release hydrogen ions into the feed solution [85,86].

A SLM process with facilitated transport is very effective for the removal of trace contaminants to very low levels due to their high selectivity, particularly when dealing with low concentration driving forces. Secondly, they can achieve high permeability even when the concentration driving force is minimal. Lastly, these membranes have the capability to simultaneously maintain both high permeability and high selectivity. These attributes make

them highly promising for applications involving the removal of contaminants from water and especially pharmaceutical compounds [77,85.].

4.6 Application of SLM to remove pharmaceuticals.

Supported Liquid Membranes (SLMs) offer a versatile approach for diverse separation purposes, combining simplicity with adaptability. They enable the separation of a wide range of chemical compounds from gases or inorganic ions to various organic compounds (charged or uncharged, hydrophobic to hydrophilic) and even large molecules like peptides or proteins.[81]. This has led to significant interest in SLMs across various fields, including analytical and organic chemistry, hydrometallurgy, chemical engineering, biotechnology, and biomedical engineering[63]. The specific separation requirements depend on the compound, matrix composition, and research objectives. In the context of wastewater treatment and pharmaceutical contaminant removal, SLMs, both flat sheet and hollow fiber modules, offer promising applications. They can effectively address the challenge of separating pharmaceutical contaminants from wastewater, contributing to cleaner and safer water sources. The following table summarizes the applications of SLM to remove pharmaceutical contaminants with Flat sheet-supported liquid membrane (FLSLM) and hollow fiber-supported liquid membrane (HFSLM).

Table 7. Summary of SLM application for pharmaceutical removal

Compound	Application	Membrane	configuration	References
Diclofenac	Removal from Synthetic water	TBP in n-decane	FSLM	[87]
Ibuprofen	Removal from Synthetic water	TOA in dodecane	FLSLM	[88]
Sulfamethoxazole	Removal from Synthetic water	decanol	FLSLM	[89]
Carbamazepine	Removal from Synthetic water	decanol	FLSLM	[89]

acetaminophen	Removal from Synthetic water	Aliquat in octanol	FLSM	[90]
Pen-G	Removal from buffer solution	TOMAC	FSSLM	[91]
Salysilic acid	Removal from synthetic water	Tetrabutylammonium chloride in octainic acid	FSSLM	[92]
Lctic acid	Removal from synthetic water	TOA in xylene	FSSLM	[93]
Gemfibrozil	Removal from synthetic water	TBP in ndecane	FSSLM in loop circulation	[94]
Ibuprofen	Sample preparation	Octanol	HF	[95]
Diclofenac	Removal from synthetic water	D2EHPA In n-heptabe	HF	[96]
Pen-G	Removal from fermentation broth	di-*n*-octylamine in iso-octanol and kerosene	HF	[97]
Ketoprofen, naproxen	Sample preparation from wastewater	1-octanol	HF	[98]

In the realm of pharmaceutical extraction from different matrices, pre-concentration, and sample preparation, hollow fiber liquid membrane emerges as a highly promising and advantageous technology over ion exchange and solvent extraction processes [98,99]. Conventionally, hollow fiber configurations are widely used as microextraction techniques for isolation and pre-Concentration of Pharmaceuticals (HFL-PME) [99]. The extraction efficiency involves the transfer of analytes from a sample solution (the donor phase) across a supported liquid membrane (SLM) into an acceptor phase inside the lumen of the hollow fibre.

The SLM consists of a water-immiscible organic solvent embedded in the pores of a hollow fibre and acts as a clean-up barrier between the donor phase and the acceptor phase to avoid mixing of the two phases [99,100]. The Table 7 summarizes some literature results of employing both FSSLM and HFSLM with a combination of organic extractant. Diclofenac was extracted with TBP in dodecane in flat sheet membrane [87], Alternatively, D2EHPA dissolved in heptane was selected to extract the same pharmaceutical using hollow fiber liquid membrane [96]. In fact, the choice of extractant is crucial and it is defined by the physical properties of the compound of interest (pka), the operational condition (pH, stripping agent). In addition to the properties of the organic extractant (concentration, viscosity) finally it is essential to select a combination of organic extractant that are efficient and cheap.

4.7 Future consideration and gaps

In conclusion, to face the water shortage, new water treatment technique needs to be elaborated and the need of water treatment guarantee the availability of water. However, improvements in wastewater treatment processes are necessary in order to make treated wastewater re-usable for industrial, agricultural, and domestic purposes. Membrane technology has emerged as a favourite choice for reclaiming water from different wastewater streams for re-use. Membrane technology is gradually updating water and wastewater treatment. Much work has been done in this area over the years. There is however still room for improvement in many areas. As fouling and high energy demand remain a major issue in non-equilibrium pressure driven processes, continuous research is needed to find a lasting solution to them, either through introduction of rigorous but cheap pre-treatment processes or through development of fouling resistant membranes. Further research for solute recovery processes should prioritize membrane advancement and energy efficiency. Combining diverse membrane technologies or integration with other treatments could leverage their respective advantages, mitigate limitations, and enhance overall efficiency.

5. Objectives

Due to rapid population growth and the surge in pharmaceutical industry innovation and medical research, society is increasingly exposed to new contaminants. Significant changes are imperative to address this influx of contaminants into the ecosystem, especially in the water sources. While pharmaceuticals have become an integral part of our daily lives, it is essential

to consider the consequences of their overuse, discharge in natural resources, and their chronic and acute effects.

Dealing with these contaminants in water is particularly challenging, as they often exist in soluble amounts that are difficult to measure. The diversity of these contaminants, even within specific groups like pharmaceuticals, makes it clear that there is no one-size-fits-all method for their removal from water. Numerous reviews have explored methods for removing these emerging contaminants (ECs), but they often reach similar conclusions: "The method was found to be quite effective, but...". Since wastewater, treatment plants are unable to eliminate ECs, significant efforts are being invested in finding appropriate technologies. In the context of promoting a circular economy, this thesis has been developed based on the application of supported liquid membrane, as follows:

In this work, supported liquid membrane technologies based on facilitated transport were assessed for the removal of different type of pharmaceuticals with different organic extractant.

1. Assessment of Flat sheet supported liquid membrane to remove a certain pharmaceuticals such Diclofenac, Ibuprofen, carbamazepine, from synthetic water by investigating different extractant.
2. Combination of Supported liquid membrane and ozonation to remove diclofenac and ibuprofen.
3. Application of Hollow fiber liquid membrane to remove Ibuprofen and diclofenac with Cyanex 923
4. Development of the mathematical models for each of them that describe the extraction/transport, what leads to the determination of the unknown equilibrium/kinetic parameters, to give a better understanding of industrial application.
5. Removal of penicillin G by SLM and HFM and determination of their mass transfer coefficient.

6. Thesis Outline

Chapter 1 presents the comprehensive assessment of supported liquid membrane (SLM) technologies, focusing on facilitated transport, for the removal of various pharmaceutical compounds. Firstly, we investigated the effectiveness of flat sheet supported liquid membranes in eliminating pharmaceuticals like Diclofenac, Ibuprofen, and Carbamazepine from synthetic water, employing different organic extractants.

Chapter 2. The feasibility of integrating of supported liquid membrane with oznation , Diclofenac was selected for the experiments. Two processes were tested and the ozone concentration was varied. Finally, the by-products obtained with ozonation were identified and the most abundant compounds were quantified.

Chapter 3 includes the application of hollow fiber liquid membranes to target Ibuprofen and Diclofenac removal, utilizing Cyanex 923 as the extractant. In addition, the stability was enhanced by pseudo emulsion, and the performance of hollow fiber membrane was tested to pre-concentrate the stream. A simplified permeability model was developed to determine the permeability in hollow fiber liquid membranes and explored the synergistic potential of combining supported liquid membranes with ozonation techniques to enhance the removal of Diclofenac and Ibuprofen

Chapter 4 To gain a deeper understanding of potential industrial applications, developed mathematical models for each configuration (Flat sheet and hollow fiber) for the removal of penicillin G with ionic liquid Aliquat 336. Several parameters were tested to obtain the optimized parameter. The mass transfer coefficient was also obtained by elucidating the pharmaceutical extraction and transport processes and enabling the determination of previously unknown equilibrium and kinetic parameters. This multifaceted approach aimed to provide valuable insights into the practical applications of these technologies for pharmaceutical contaminant removal.

Chapter 6 provides a general conclusion and future recommendations.

7. References

[1] Samal, K., Mahapatra, S., Hibzur Ali, M. (2022). Pharmaceutical wastewater as emerging contaminants (EC): Treatment technologies, impact on environment and human health. Energy Nexus, 6, 100076. https://doi.org/10.1016/j.nexus.2022.100076

[2] Afonso-Olivares, C., Sosa-Ferrera, Z., Santana-Rodríguez, J.J., 2017. Occurrence and environmental impact of pharmaceutical residues from conventional and natural wastewater treatment plants in Gran Canaria (Spain). Sci. Total Environ. 599–600, 934–943, http://dx.doi.org/10.1016/J.SCITOTENV.2017.05.058.

[3] Patel, M., Kumar, R., Kishor,K., Mlsna,M., Pharmaceuticals of Emerging Concern in Aquatic Systems: Chemistry, Occurrence, Effects, and Removal Methods, Chem. Rev. 119 (2019) 3510–3673.

[4] Rasheed, T., Bilal, M., Nabeel, F., Adeel, M., Iqbal, H. M. N. (2019). Environmentally related contaminants of high concern: Potential sources and analytical modalities for detection, quantification, and treatment. Environment International, 122, 52–66. https://doi.org/10.1016/j.envint.2018.11.038

[5] Couto, C. F., Lange, L. C., Amaral, M. C. S. (2019). Occurrence, fate and removal of pharmaceutically active compounds (phacs) in water and wastewater treatment plants—a review. Journal of Water Process Engineering, 32, 100927. https://doi.org/10.1016/j.jwpe.2019.100927

[6] Anjali, R., Shanthakumar, S., (2019). Insights on the current status of occurrence and removal of antibiotics in wastewater by advanced oxidation processes. J. Environ. Manage. 246, 51–62, http://dx.doi.org/10.1016/J.JENVMAN.2019.05.090.

[7] Osuoha, J. O., Anyanwu, B. O., Ejileugha, C. (2023). Pharmaceuticals and personal care products as emerging contaminants: Need for combined treatment strategy. Journal of Hazardous Materials Advances, 9, 100206. https://doi.org/10.1016/j.hazadv.2022.100206

[8] Hoeger, B., Köllner, B., Dietrich, D. R., Hitzfeld, B. (2005). Water-borne diclofenac affects kidney and Gill integrity and selected immune parameters in brown trout (Salmo trutta F. Fario). Aquatic Toxicology, 75(1), 53–64. https://doi.org/10.1016/j.aquatox.2005.07.006

[9] Mimeault, C., Woodhouse, A. J., Miao, X.-S., Metcalfe, C. D., Moon, T. W., Trudeau, V. L. (2005). The human lipid regulator, gemfibrozil concentrates and reduces testosterone in the goldfish, carassius auratus. Aquatic Toxicology, 73(1), 44–54. https://doi.org/10.1016/j.aquatox.2005.01.009

[10] Jiménez-Bambague, E. M., Madera-Parra, C. A., Ortiz-Escobar, A. C., Morales-Acosta, P. A., Peña-Salamanca, E. J., Machuca-Martínez, F. (2020). High-rate algal pond for removal of pharmaceutical compounds from urban domestic wastewater under tropical conditions. case study: Santiago de Cali, Colombia. Water Science and Technology, 82(6), 1031–1043. https://doi.org/10.2166/wst.2020.362

[11] Li, Xiaolin, Bin Wang, Feng Liu, and Gang Yu. (2023). "Occurrence and Removal of Pharmaceutical Contaminants in Urine: A Review" *Water* 15, no. 8: 1517. https://doi.org/10.3390/w15081517

[12] de Ilurdoz, M. S., Sadhwani, J. J., Reboso, J. V. (2022). Antibiotic removal processes from water & wastewater for the protection of the aquatic environment - A Review. Journal of Water Process Engineering, 45, 102474. https://doi.org/10.1016/j.jwpe.2021.102474

[13] Yu, G.Q.; Zhang, C.X.; Zhang, D.D.; Xu, Y.; Yang, B.; Wei, X.C.; Zheng, X.Q.(2022). Prospects and problems in the agricultural utilization of source-separated urine as a substitute for chemical fertilizers.Journal of Agriculture Resources39, 256–265

[14] Fick, J., Söderström, H., Lindberg, R. H., Phan, C., Tysklind, M., & Larsson, D. G. J. (2009). Contamination of surface, ground, and drinking water from pharmaceutical production. Environmental Toxicology and Chemistry, 28(12), 2522. https://doi.org/10.1897/09-073.1

[15] Morin-Crini, N., Lichtfouse, E., Liu, G., Balaram, V., Ribeiro, A. R., Lu, Z., Stock, F., Carmona, E., Teixeira, M. R., Picos-Corrales, L. A., Moreno-Piraján, J. C., Giraldo, L., Li, C., Pandey, A., Hocquet, D., Torri, G., Crini, G. (2021). Emerging contaminants: Analysis, aquatic compartments and water pollution. Emerging Contaminants Vol. 1, 1–111. https://doi.org/10.1007/978-3-030-69079-3_1

[16] Ferrari, F., Gallipoli, A., Balderacchi, M., Ulaszewska, M. M., Capri, E., Trevisan, M. (2011). Exposure of the main Italian River Basin to pharmaceuticals. Journal of Toxicology, 2011, 1–11. https://doi.org/10.1155/2011/989270

[17] O. S. Santos, G., A. Goulart, L., J. M. Cordeiro-Junior, P., Sánchez-Montes, I., R. V. Lanza, M. (2022). Pharmaceutical contaminants: Ecotoxicological aspects and recent advances in oxidation technologies for their removal in aqueous matrices. Journal of Environmental Chemical Engineering, 10(6), 108932. https://doi.org/10.1016/j.jece.2022.108932

[18] McArdell, C. S., Molnar, E., Suter, M. J.-F., & Giger, W. (2003). Occurrence and fate of macrolide antibiotics in wastewater treatment plants and in the Glatt Valley watershed, Switzerland. *Environmental Science & Technology*, *37*(24), 5479–5486. https://doi.org/10.1021/es034368i

[19] Mompelat, S., Le Bot, B., & Thomas, O. (2009). Occurrence and fate of pharmaceutical products and by-products, from resource to drinking water. *Environment International*, *35*(5), 803–814. https://doi.org/10.1016/j.envint.2008.10.008

[20] Madikizela, L. M., Ncube, S., Chimuka, L. (2020). Analysis, occurrence and removal of pharmaceuticals in African Water Resources: A current status. *Journal of Environmental Management*, *253*, 109741. https://doi.org/10.1016/j.jenvman.2019.109741

[21] Margot, J., Rossi, L., Barry, D. A., Holliger, C. (2015). A review of the fate of micropollutants in wastewater treatment plants. *WIREs Water*, *2*(5), 457–487. https://doi.org/10.1002/wat2.1090

[22] Okoya, A. A., Ogunfowokan, A. O., Asubiojo, O. I., Torto, N. (2013). Organochlorine pesticide residues in sediments and waters from cocoa producing areas of Ondo State, southwestern Nigeria. *ISRN Soil Science*, *2013*, 1–12. https://doi.org/10.1155/2013/131647

[23] Goossens, h., Ferech, M., Vanderstichele, R.(2005). Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. *The Lancet*, *365*(9459), 579–587. https://doi.org/10.1016/s0140-6736(05)70799-6

[24] Petrie, B., McAdam, E. J., Scrimshaw, M. D., Lester, J. N., Cartmell, E. (2013). Fate of drugs during wastewater treatment. *TrAC Trends in Analytical Chemistry*, *49*, 145–159. https://doi.org/10.1016/j.trac.2013.05.007 .

[25] Tauxe-Wuersch, A., De Alencastro, L. F., Grandjean, D., & Tarradellas, J. (2005). Occurrence of several acidic drugs in sewage treatment plants in Switzerland and risk assessment. *Water Research*, *39*(9), 1761–1772. https://doi.org/10.1016/j.watres.2005.03.003

[26] Lindqvist, N., Tuhkanen, T., & Kronberg, L. (2005a). Occurrence of acidic pharmaceuticals in raw and treated sewages and in receiving waters. *Water Research*, *39*(11), 2219–2228. https://doi.org/10.1016/j.watres.2005.04.003

[27] Kyzas, G. Z., Koltsakidou, A., Nanaki, S. G., Bikiaris, D. N., Lambropoulou, D. A. (2015). Removal of beta-blockers from aqueous media by adsorption onto graphene

oxide. *Science of The Total Environment*, *537*, 411–420. https://doi.org/10.1016/j.scitotenv.2015.07.144

[28] Ferrari, F., Gallipoli, A., Balderacchi, M., Ulaszewska, M. M., Capri, E., Trevisan, M. (2011). Exposure of the main Italian River Basin to pharmaceuticals. Journal of Toxicology, 2011, 1–11. https://doi.org/10.1155/2011/989270

[29] Oluwole, A. O., Omotola, E. O., & Olatunji, O. S. (2020). Pharmaceuticals and personal care products in water and wastewater: A review of treatment processes and use of photocatalyst immobilized on functionalized carbon in AOP Degradation. *BMC Chemistry*, *14*(1). https://doi.org/10.1186/s13065-020-00714-1

[30] Eslamian, L., Borzabadi-Farahani, A., & Gholami, H. (2016). The effect of benzocaine and ketoprofen gels on pain during fixed orthodontic appliance treatment: A randomised, double-blind, crossover trial. *Australasian Orthodontic Journal*, *32*(1), 64–72. https://doi.org/10.21307/aoj-2020-114

[31] Sauter, D., Dąbrowska, A., Bloch, R., Stapf, M., Miehe, U., Sperlich, A., Gnirss, R., Wintgens, T. (2021). Deep-bed filters as post-treatment for ozonation in tertiary municipal wastewater treatment: Impact of design and operation on treatment goals. *Environmental Science: Water Research & Technology*, *7*(1), 197–211. https://doi.org/10.1039/d0ew00684j

[32] Thiebault, T., Chassiot, L., Fougère, L., Destandau, E., Simonneau, A., Van Beek, P., Souhaut, M., & Chapron, E. (2017). Record of pharmaceutical products in river sediments: A powerful tool to assess the environmental impact of urban management? *Anthropocene*, *18*, 47–56. https://doi.org/10.1016/j.ancene.2017.05.006

[33] Kosma, C. I., Lambropoulou, D. A., Albanis, T. A. (2014). Investigation of ppcps in wastewater treatment plants in Greece: Occurrence, removal and environmental risk assessment. *Science of The Total Environment*, *466–467*, 421–438. https://doi.org/10.1016/j.scitotenv.2013.07.044

[34] Kaur, H., Hippargi, G., Pophali, G. R., Bansiwal, A. K. (2019). Treatment methods for removal of pharmaceuticals and personal care products from domestic wastewater. *Pharmaceuticals and Personal Care Products: Waste Management and Treatment Technology*, 129–150. https://doi.org/10.1016/b978-0-12-816189-0.00006-8

[35] Loganathan, P., Vigneswaran, S., Kandasamy, J., Cuprys, A. K., Maletskyi, Z., Ratnaweera, H. (2023). Treatment trends and combined methods in removing pharmaceuticals and personal care products from wastewater—a review. *Membranes*, *13*(2), 158. https://doi.org/10.3390/membranes13020158

[36] Neha, R., Adithya, S., Jayaraman, R. S., Gopinath, K. P., M, P., L, P., Arun, J. (2021). Nano-adsorbents an effective candidate for removal of toxic pharmaceutical compounds from aqueous environment: A critical review on emerging trends. *Chemosphere*, *272*, 129852. https://doi.org/10.1016/j.chemosphere.2021.129852

[37] Sophia A., C., Lima, E. C. (2018). Removal of emerging contaminants from the environment by adsorption. *Ecotoxicology and Environmental Safety*, *150*, 1–17. https://doi.org/10.1016/j.ecoenv.2017.12.026

[38] Fonseca Couto, C., Lange, L. C., Santos Amaral, M. C. (2018). A critical review on membrane separation processes applied to remove pharmaceutically active compounds from water and wastewater. *Journal of Water Process Engineering*, *26*, 156–175. https://doi.org/10.1016/j.jwpe.2018.10.010

[39] Heo, J., Kim, S., Her, N., Park, C. M., Yu, M., Yoon, Y. (2020). Removal of contaminants of emerging concern by FO, Ro, and UF membranes in water and wastewater. *Contaminants of Emerging Concern in Water and Wastewater*, 139–176. https://doi.org/10.1016/b978-0-12-813561-7.00005-5

[40] Fatta-Kassinos, D., Meric, S., & Nikolaou, A. (2010). Pharmaceutical residues in environmental waters and wastewater: Current State of Knowledge and future research. *Analytical and Bioanalytical Chemistry*, *399*(1), 251–275. https://doi.org/10.1007/s00216-010-4300-9

[41] Elshikh, M. S., Hussein, D. S., Al-khattaf, F. S., Rasheed El-Naggar, R. A., & Almaary, K. S. (2022). Diclofenac removal from the wastewater using activated sludge and analysis of multidrug resistant bacteria from the sludge. *Environmental Research*, *208*, 112723. https://doi.org/10.1016/j.envres.2022.112723

[42] Tran, T. V., Nguyen, D. T., Le, H. T. N., Vo, D.-V. N., Nanda, S., & Nguyen, T. D. (2020). Optimization, equilibrium, adsorption behavior and role of surface functional groups on graphene oxide-based nanocomposite towards Diclofenac Drug. *Journal of Environmental Sciences*, *93*, 137–150. https://doi.org/10.1016/j.jes.2020.02.007

[43] Yehia, A. M., Elbalkiny, H. T., Riad, S. M., & Elsaharty, Y. S. (2019). Monitoring and optimization of diclofenac removal by adsorption technique using in-line potentiometric analyzer. *Microchemical Journal*, *148*, 521–530. https://doi.org/10.1016/j.microc.2019.05.005.

[44] Mestre, A. S., Pires, J., Nogueira, J. M. F., Carvalho, A. P. (2007). Activated carbons for the adsorption of Ibuprofen. *Carbon*, *45*(10), 1979–1988. https://doi.org/10.1016/j.carbon.2007.06.005

[45] Hanbali, G., Jodeh, S., Hamed, O., Bol, R., Khalaf, B., Qdemat, A., & Samhan, S. (2020). Enhanced ibuprofen adsorption and desorption on synthesized functionalized magnetic multiwall carbon nanotubes from aqueous solution. *Materials*, *13*(15), 3329. https://doi.org/10.3390/ma13153329

[46] Fröhlich, A. C., Ocampo-Pérez, R., Diaz-Blancas, V., Salau, N. P. G., Dotto, G. L. (2018). Three-dimensional mass transfer modeling of ibuprofen adsorption on activated carbon prepared by sonication. *Chemical Engineering Journal*, *341*, 65–74. https://doi.org/10.1016/j.cej.2018.02.020

[47] Yu, Z., Peldszus, S., Huck, P. M. (2008). Adsorption characteristics of selected pharmaceuticals and an endocrine disrupting compound—naproxen, carbamazepine and nonylphenol—on activated carbon. *Water Research*, *42*(12), 2873–2882. https://doi.org/10.1016/j.watres.2008.02.020

[48] Chu, G., Zhao, J., Liu, Y., Lang, D., Wu, M., Pan, B., Steinberg, C. E. W. (2019). The relative importance of different carbon structures in biochars to carbamazepine and bisphenol A sorption. *Journal of Hazardous Materials*, *373*, 106–114. https://doi.org/10.1016/j.jhazmat.2019.03.078

[49] Chavoshan, S., Khodadadi, M., Nasseh, N., Hossein Panahi, A., Hosseinnejad, A. (2018). Investigating the efficiency of single-walled and multi-walled carbon nanotubes in removal of penicillin G from aqueous solutions. *Environmental Health Engineering and Management*, *5*(4), 187–196. https://doi.org/10.15171/ehem.2018.26

[50] Aksu, Z., & Tunç, Ö. (2005). Application of biosorption for penicillin G removal: Comparison with activated carbon. *Process Biochemistry*, *40*(2), 831–847. https://doi.org/10.1016/j.procbio.2004.02.014

[51] Plakas, K. V., Mantza, A., Sklari, S. D., Zaspalis, V. T., & Karabelas, A. J. (2019). Heterogeneous fenton-like oxidation of pharmaceutical diclofenac by a catalytic iron-oxide ceramic microfiltration membrane. *Chemical Engineering Journal*, *373*, 700–708. https://doi.org/10.1016/j.cej.2019.05.092

[52] . Hidalgo, A. M., Gómez, M., Murcia, M. D., León, G., Miguel, B., Gago, I., & Martínez, P. M. (2022). Ibuprofen removal by graphene oxide and reduced graphene oxide coated polysulfone nanofiltration membranes. *Membranes*, *12*(6), 562. https://doi.org/10.3390/membranes12060562

[53] Yao, M., Duan, L., Wei, J., Qian, F., & Hermanowicz, S. W. (2020). Carbamazepine removal from wastewater and the degradation mechanism in a submerged forward osmotic membrane bioreactor. *Bioresource Technology*, *314*, 123732. https://doi.org/10.1016/j.biortech.2020.123732

[54] Egea-Corbacho, A., Gutiérrez Ruiz, S., & Quiroga Alonso, J. M. (2019). Removal of emerging contaminants from wastewater using nanofiltration for its subsequent reuse: Full–scale pilot plant. *Journal of Cleaner Production*, *214*, 514–523. https://doi.org/10.1016/j.jclepro.2018.12.297

[55] Jankunaite, D., Tichonovas, M., Buivydiene, D., Radziuniene, I., Racys, V., & Krugly, E. (2017). Removal of diclofenac, ketoprofen, and carbamazepine from simulated drinking water by Advanced Oxidation in a model reactor. *Water, Air, & Soil Pollution*, *228*(9). https://doi.org/10.1007/s11270-017-3517-z

[56] Huber, M. M., Canonica, S., Park, G.-Y., & von Gunten, U. (2003). Oxidation of pharmaceuticals during ozonation and advanced oxidation processes. *Environmental Science & Technology*, *37*(5), 1016–1024. https://doi.org/10.1021/es025896h

[57] Aguilar, C. M., Vazquez-Arenas, J., Castillo-Araiza, O. O., Rodríguez, J. L., Chairez, I., Salinas, E., Poznyak, T. (2020). Improving ozonation to remove carbamazepine through ozone-assisted catalysis using different NIO concentrations. *Environmental Science and Pollution Research*, *27*(18), 22184–22194. https://doi.org/10.1007/s11356-020-07883-5

[58] Norzaee, S., Bazrafshan, E., Djahed, B., Kord Mostafapour, F., & Khaksefidi, R. (2017). UV activation of persulfate for removal of penicillin G antibiotics in aqueous solution. *The Scientific World Journal*, *2017*, 1–6. https://doi.org/10.1155/2017/3519487

[59] Alfonso-Muniozguren, P., Serna-Galvis, E. A., Bussemaker, M., Torres-Palma, R. A., Lee, J. (2021). A review on pharmaceuticals removal from waters by single and combined biological, membrane filtration and ultrasound systems. *Ultrasonics Sonochemistry*, *76*, 105656. https://doi.org/10.1016/j.ultsonch.2021.105656

[60] Li, N. N. (1968). Separating hydrocarbons with liquid membrane. US Patent 3,410,794

[61] Kostanyan, Artak E., Andrey A. Voshkin, Vera V. Belova, and Yulia A. Zakhodyaeva. 2023. "Modelling and Comparative Analysis of Different Methods of Liquid Membrane Separations" *Membranes* 13, no. 6: 554. https://doi.org/10.3390/membranes13060554

[62] Dżygiel, P., & Wieczorek, P. P. (2010). Supported liquid membranes and their modifications. Liquid Membranes, 73–140. https://doi.org/10.1016/b978-0-444-53218-3.00003-9

[63] Tandlich, R. (2010). Application of liquid membranes in wastewater treatment. Liquid Membranes, 357–400. https://doi.org/10.1016/b978-0-444-53218-3.00008-8

[64] Soniya, M., & Muthuraman, G. (2015). Comparative study between liquid–liquid extraction and bulk liquid membrane for the removal and recovery of methylene blue from wastewater. Journal of Industrial and Engineering Chemistry, 30, 266–273. https://doi.org/10.1016/j.jiec.2015.05.032

[65] Madaeni, S. S., Jamali, Z., Islami, N. (2011). Highly efficient and selective transport of methylene blue through a bulk liquid membrane containing cyanex 301 as carrier. Separation and Purification Technology, 81(2), 116–123. https://doi.org/10.1016/j.seppur.2011.07.004

[66] Zaulkiflee, N.D., Ahmad, A.L., Che Lah, (2022),Removal of emerging contaminants by emulsion liquid membrane: perspective and challenges. Environ Sci Pollut Res 29, 12997–13023 https://doi.org/10.1007/s11356-021-16658-5

[67] Patnaik, P. R. (1995). Liquid emulsion membranes: Principles, problems and applications in fermentation processes. Biotechnology Advances, 13(2), 175–208. https://doi.org/10.1016/0734-9750(95)00001-7

[68] Seifollahi Z, Rahbar-Kelishami A (2017) Diclofenac extraction from aqueous solution by an emulsion liquid membrane: parameter study and optimization using the response surface methodology. Journal of Molecular Liquids 231:1–10. https://doi.org/10.1016/j.molliq.2017.01.081

[69] Ahmad AL, Mohd Harun MHZ, Akmal Jasni MK, Zaulkiflee ND. Removal of Ibuprofen at Low Concentration Using a Newly Formulated Emulsion Liquid Membrane. Membranes (Basel). 2021 Sep 28;11(10):740. doi:10.3390/membranes11100740. PMID: 34677506; PMCID: PMC8538757.

[70] Mohammed AA, Atiya MA, Hussein MA (2020a) Studies on membrane stability and extraction of ciprofloxacin from aqueous solution using Pickering emulsion liquid membrane stabilized by magnetic nano-Fe2O3. Colloids and Surfaces A: Physicochemical and Engineering Aspects 585:124044. https://doi.org/10.1016/j.colsurfa.2019.124044

[71] Lee SC (2000) Continuous extraction of penicillin G by emulsion liquid membranes with optimal surfactant compositions. Chemical Engineering Journal 79(1):61–67

[72] Chaouchi S, Hamdaoui O (2014a) Acetaminophen extraction by emulsion liquid membrane using Aliquat 336 as extractant. Separation and Purification Technology 129:32–40. https://doi.org/10.1016/j.seppur.2014.03.021

[73] Schlosser, Kossaczký, E. (1980). Comparison of pertraction through liquid membranes and double liquid-liquid extraction. Journal of Membrane Science, 6, 83–105. https://doi.org/10.1016/s0376-7388(00)82152-3

[74] Pabby, A. K., Swain, B., Sastre, A. M. (2017). Recent advances in smart integrated membrane assisted liquid extraction technology. Chemical Engineering and Processing - Process Intensification, 120, 27–56. https://doi.org/10.1016/j.cep.2017.06.006

[75] Parhi, P. K., Behera, S. S., Mandal, D., Das, D., & Mohapatra, R. K. (2020). Fundamental principle and practices of solvent extraction (SX) and supported liquid membrane (SLM) process for extraction and separation of rare earth metal(s). Rare-Earth Metal Recovery for Green Technologies, 57–85. https://doi.org/10.1007/978-3-030-38106-6_4

[76] Klaassen R. and Jansen A.E.. (2001) The membrane contactors: environmental applications and possibilities, Environmental Progress 20(1) 37-43.

[77] Kocherginsky N.M., Qian Yang, Lalitha Seelem (2007). Recent advances in supported liquid membrane technology, Separation and Purification Technology 53 171-17

[78] Alguacil, F. J., Robla, J. I. (2023). Transport of chromium(vi) across a supported liquid membrane containing Cyanex 921 or Cyanex 923 dissolved in Solvesso 100 as

carrier phase: Estimation of diffusional parameters. Membranes, 13(2), 177. https://doi.org/10.3390/membranes13020177

[79] Kostanyan, A. E., Voshkin, A. A., Belova, V. V., Zakhodyaeva, Y. A. (2023). Modelling and comparative analysis of different methods of liquid membrane separations. Membranes, 13(6), 554. https://doi.org/10.3390/membranes13060554

[80] Rathore, N. S., Leopold, A., Pabby, A. K., Fortuny, A., Coll, M. T., Sastre, A. M. (2009). Extraction and permeation studies of CD(II) in acidic and neutral chloride media using Cyanex 923 on supported liquid membrane. Hydrometallurgy, 96(1–2), 81–87. https://doi.org/10.1016/j.hydromet.2008.08.009

[81] Pavón, S., Fortuny, A., Coll, M. T., Bertau, M., Sastre, A. M. (2020). Permeability dependencies on the carrier concentration and membrane viscosity for y(iii) and eu(iii) transport by using liquid membranes. Separation and Purification Technology, 239, 116573. https://doi.org/10.1016/j.seppur.2020.116573

[82] Benzal, G., Kumar, A., Delshams, A., Sastre, A. M. (2004). Mathematical modelling and simulation of cotransport phenomena through flat sheet-supported liquid membranes. Hydrometallurgy, 74(1–2), 117–130. https://doi.org/10.1016/j.hydromet.2004.01.005

[83] Bringas, E., San Román, M. F., Ortiz, I. (2006). Separation and recovery of anionic pollutants by the emulsion pertraction technology. remediation of polluted groundwaters with cr(vi). Industrial & Engineering Chemistry Research, 45(12), 4295–4303. https://doi.org/10.1021/ie051418e .

[84] Kislik V.S.(2010). Liquid membranes. Principles & Applications in Chemical Separations &Wastewater Treatment, 2010 Elsevier.

[85] Yang, X., Duan, H., Shi, D., Yang, R., Wang, S., Guo, H. (2015). Facilitated transport of phenol through supported liquid membrane containing bis(2-Ethylhexyl) sulfoxide (BESO) as the carrier. Chemical Engineering and Processing: Process Intensification, 93, 79–86. https://doi.org/10.1016/j.cep.2015.05.003.

[86] Bartsch, R. A., Way, J. D. (1996). Chemical separations with Liquid Membranes: An overview. ACS Symposium Series, 1–10. https://doi.org/10.1021/bk-1996-0642.ch001 .

[87] Molinari, R., Argurio, P., Poerio, T., Caruso, A. (2006). Stagnant sandwich and supported liquid membrane systems for removal of pharmaceuticals in water. Desalination, 199(1-3), 529–531. https://doi.org/10.1016/j.desal.2006.03.188.

[88] Razo-Lazcano, T. A., Stambouli, M., González-Muñoz, M. del, Pareau, D., Ávila-Rodríguez, M. (2014). Emulsion liquid membranes for recovery of ibuprofen from Aqueous Solutions. Journal of Chemical Technology & Biotechnology, 89(6), 890–898. https://doi.org/10.1002/jctb.4329

[89] Grote M, Haciosmanoglu B, Bataineh M, Nolte J. (2004). Separation of drug traces from water with particular membrane systems. J Environ Sci Health A Tox Hazard Subst Environ Eng; 39(4):1039-53. doi: 10.1081/ese-120028412. PMID: 15137718.

[90] Kouki, N., Tayeb, R. Dhahbi, M. Recovery of acetaminophen from aqueous solutions using a supported liquid membrane based on a quaternary ammonium salt as ionophore. Chem. Pap. 68, 457–464 (2014). https://doi.org/10.2478/s11696-013-0479-5

[91] Matsumoto, M., Ohtani, T., Kondo, K. (2007). Comparison of solvent extraction and supported liquid membrane permeation using an ionic liquid for concentrating penicillin G. Journal of Membrane Science, 289(1–2), 92–96. https://doi.org/10.1016/j.memsci.2006.11.046

[92] López-Porfiri, P., González-Miquel, M., Gorgojo, P. (2022). Green supported liquid membranes: The permeability activity-based linear operation (Pablo) method. Chemical Engineering Journal, 446, 137253. https://doi.org/10.1016/j.cej.2022.137253

[93] Rastogi, N., Chanukya, B. S. (2015). Supported liquid membrane composed of tertiary or/and quaternary amine for the extraction of lactic acid. International Journal of Membrane Science and Technology, 2(2), 19–28. https://doi.org/10.15379/2410-1869.2015.02.02.03

[94] Molinari, R., Argurio, P., Poerio, T. (2009). Flux enhancement of stagnant sandwich compared to supported liquid membrane systems in the removal of gemfibrozil from waters. Journal of Membrane Science, 340(1–2), 26–34. https://doi.org/10.1016/j.memsci.2009.05.012

[95] Williams, N. S., Ray, M. B., Gomaa, H. G. (2012). Removal of ibuprofen and 4-isobutylacetophenone by non-dispersive solvent extraction using a hollow fibre membrane contactor. Separation and Purification Technology, 88, 61–69. https://doi.org/10.1016/j.seppur.2011.11.022

[96] Kohli, H. P., Gupta, S., Chakraborty, M. (2019). Separation of diclofenac using pseudo-emulsion hollow fiber membrane: Optimization by box-behnken response surface design. Journal of Water Process Engineering, 32, 100880. https://doi.org/10.1016/j.jwpe.2019.100880

[97] He, L., Li, L., Sun, W., Zhang, W., Zhou, Z., Ren, Z. (2016). Extraction and recovery of penicillin G from solution by cascade process of hollow fiber renewal liquid membrane. Biochemical Engineering Journal, 110, 8–16. https://doi.org/10.1016/j.bej.2016.02.002

[98] Sagristà E, Larsson E, Ezoddin M, Hidalgo M, Salvadó V, Jönsson JA. Determination of non-steroidal anti-inflammatory drugs in sewage sludge by direct hollow fiber supported liquid membrane extraction and liquid chromatography-mass spectrometry. J Chromatogr A. 2010 Oct 1;1217(40):6153-8. doi: 10.1016/j.chroma.2010.08.005. Epub 2010 Aug 11. PMID: 20810117.

[99] Khan, W. A., Arain, M. B., Yamini, Y., Shah, N., Kazi, T. G., Pedersen-Bjergaard, S., Tajik, M. (2020). Hollow fiber-based liquid phase microextraction followed by analytical instrumental techniques for quantitative analysis of heavy metal ions and pharmaceuticals. Journal of Pharmaceutical Analysis, 10(2), 109–122. https://doi.org/10.1016/j.jpha.2019.12.003

[100] Fernández, E., Vidal, L. (2014). Liquid-phase extraction and microextraction. Ionic Liquids in Separation Technology, 107–152. https://doi.org/10.1016/b978-0-444-63257-9.00003-1

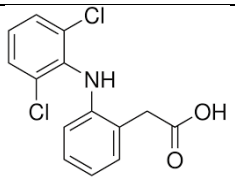
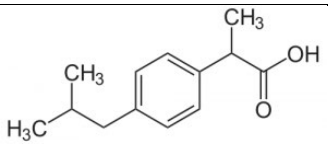
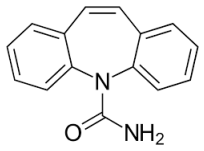
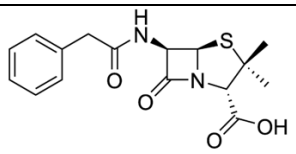
Chapter 2 Materials and Chemicals

1. Materials

This chapter, it gives a brief summary of all the chemicals and materials adapted in the development of this thesis.

1.1.Pharmaceuticals components

Table 1. The physicochemical properties of the pharmaceutical used are listed in Table 1

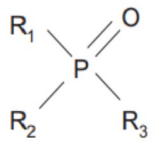
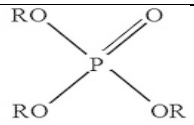
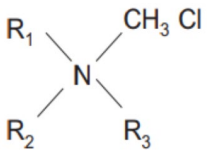
Compound	ClaSS	Chemical structure	Molecular weight (g/mol)	Density (g/cm)	pka
Diclofenac	Nonsteroidal anti-inflammatory drug (NSAID		296.74	1.42	4.15
Ibuprofen	Nonsteroidal anti-inflammatory drug (NSAID		206.28	0.91	4.4
Carbamazepine	Anticonvulsant/antiepileptic		236.27	1.29	2,3-13.9
Penicillin- G	Antibiotic		334.39	1.4	2.8

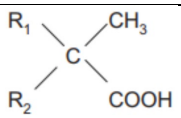
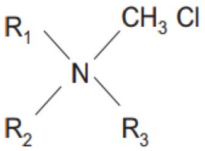
A stock solution with a known concentration of the target compounds was prepared using deionized water. Subsequently, each working solution was analyzed using an HPLC system to determine the limit of detection, limit of quantification, and linearity. It's important to note that the concentrations used in these solutions were significantly higher than those typically found in wastewater treatment, allowing for more effective system monitoring. All solutions were stored at a temperature of 2 °C.

1.2.Extractant used

Several types of extractant were used in the following thesis the properties of all extractants are listed in Table 2. They have been mainly diluted in kerosene expect for aliquat was diluted with kerosene containing 10% of decanol.Organic extractants are often diluted in a diluent when used in supported liquid membranes for several reasons:

- Enhance the solubility of the extractant since some organic extractants may have limited solubility in their pure form.
- Decrease the viscosity of Pure organic extractants that can be quite viscous, making it challenging to diffusion of the target solute.
- Reduce the interfacial tension: Dilution can also help reduce the interfacial tension between the extractant and the surrounding phases, such as the aqueous phase. This can promote better contact and mixing at the interface, improving extraction efficiency.
- Minimizing toxicity and environmental impact some organic extractants can be toxic or environmentally harmful in their concentrated form. Diluting them can reduce their toxicity and environmental impact, making the process safer and more environmentally friendly.
- Cost-Efficiency: Diluting expensive organic extractants allows for the use of smaller quantities of the costly extractant while maintaining extraction efficiency.

Organic extractant	Type	Chemical structure	Molecular weight (g/mol)	Density (25°C (g/cm
bis(2,4,4-trimethylpentyl) phosphinic acid (Cyanex 923)	Neutral		348.6	0.88
Tributylphosphate (TBP)	Neutral		266.32	0.97
Trioctylamine(TOA)	Acidic/Neutral		353.67	0.80

Neodecanoic acid (Versatic acid 10)	Acidic/Neutral		172.26	0.9
Trioctylmethylammonium chloride (Aliquat 336)	Cationic		404.4	0.88

1.3.Stripping solution

A stripping solution in a supported liquid membrane (SLM) system is essential for the efficient separation and recovery of target compounds. It serves to recover selectively extracted compounds from the liquid membrane, enabling their reuse and continuous operation. In most scenarios, a deionized water solution with an alkaline pH is chosen as the stripping solution. In the case of Aliquat 336, a concentrated solution of NaCl/KCl is employed to provide chloride ions, which facilitate the process of ionic exchange.

Chapter 3 Supported Liquid Membranes for the Removal of Pharmaceuticals from Aqueous Solutions

Abstract

In the following study, the extraction of three pharmaceutical compounds: Diclofenac (DCF), Ibuprofen (IBP), and Carbamazepine (CBZ) by liquid-liquid extraction and their transport by supported liquid membrane (SLM) using Cyanex 923 (Cy923), Trioctylamine (TOA), Tributylphosphate (TBP), methyl(trioctyl/decyl) ammonium chloride quaternary amine (Aliquat 336) and a Neodecanoic acid (Versatic acid 10) diluted in kerosene have been evaluated. Different pH conditions affecting the transport of these pharmaceuticals were analyzed and the permeability was calculated. Cy923 was demonstrated to be an efficient extractant for Diclofenac and Ibuprofen transport through a facilitated transport mechanism from the aqueous feed phase to the aqueous stripping phase using hydroxide ions as counterions. Among the organic extractants, Verstaic Acid 10 was the single solvent able to transport carbamazepine through SLM. Furthermore, the transport of DCF across the flat sheet supported membrane was tested with different concentrations of Cy923. The stability and efficiency of SLM with two polymeric supports (PVDF and PTFE) were compared for three consecutive runs of 3 hours each. Finally, the lifetime of the membrane was extended by soaking the polymeric material in the organic solution at atmospheric pressure for 24 h and compared with the membrane prepared with an ultrasound-assisted method.

Keywords: Supported liquid membrane, Cyanex 923, Pharmaceutical contaminant, Permeability, Stability, Solvent Extraction.

1. Introduction

Among the large number of pollutants that occur in the environment, the presence of pharmaceutical contaminants is recognized as an issue of major concern. The escalation in medication use is associated with the continuous growth of population, life span, new diseases, climate change, and pharmaceutical industry expansion. In fact, pharmaceutical usage in Germany is projected to increase by 43 to 67% by the year 2045 [1]. Despite being essential for human and animal health, pharmaceutical residues and their active compounds are detected in the aquatic environment, surface water, groundwater, and drinking water. One of the major reasons, that these contaminants are gaining great attention, is their ability to interact with a living system and produce a pharmacological response even at low doses. For instance, the excessive use of antibiotics can cause antimicrobial resistance as well as psychiatric drugs residue can alter fish behaviour and endocrine-disrupting pharmaceuticals can cause reproduction toxicity in fish and increase the risk of breast or prostate cancer in humans. [2]
Many pharmaceutical residues are non-biodegradable and resistant to conventional wastewater treatments. The impacts of pharmaceuticals in the environment depend on a combination of variables, including the toxicity, degradation, persistence, and properties of the drugs [3]. Therefore, it is necessary to upgrade the existing conventional wastewater treatment technologies to be able to cope with new emerging contaminants and their metabolites even at low concentrations, taking into account the potential of energy savings. A study by Jones et al. proves that up to 90% of pharmaceutical residues metabolised and unmetabolised bio recalcitrant fragments were found in final effluents of water and wastewater treatment plants (WWTPs). [4, 5]
Various methods have been proposed to remove pharmaceuticals from the aquatic solutions such as adsorption [6, 7], advanced oxidation processes (AOPs) [8], biological treatment [9], membrane filtration [10] and were intensively investigated for industrial applications and abatement of various organic pollutants. Notwithstanding their wide range of applications, these techniques are limited by their low efficiency at low dose contaminants, sensitive operating costs, production of secondary sludge, and disposal requirements. Consequently, the potential of energy savings and the concerns about environmental problems have drawn attention to the membrane processes [4]. Membrane technologies namely reverse osmosis, microfiltration, ultrafiltration, electrodialysis are used successfully in the separation, recovery, and removal of various organics and inorganics from wastewater plants [11, 12]. When the concentration is relatively low (ng/L–μg/L) (pharmaceutical active compounds, endocrine

disrupting compounds, and artificial sweeteners), liquid membranes are considered the optimum alternative solution for their removal. Liquid membranes combine extraction and stripping in a single unit which is separated by a thin film of the organic phase, permitting selective mass transfers of gases, ions, or molecules to occur via permeation and transport processes. Characterized by high selectivity, operational simplicity, low solvent inventory, and low energy consumption, liquid membranes present pronounced advantages over the traditional separation methods [13]. Henceforward, they have been given considerable attention all over the world ever since they were discovered by Li and co-workers in 1960, they have been used for various purposes such as the recovery of metal ions from aqueous solutions, the removal of contaminants from industrial effluents, and the recovery of fermentation products. To this end, three different types of liquid membranes: emulsion liquid membranes (ELM), bulk liquid membranes (BLM) and supported liquid membranes (SLM) were used for separation studies. They differ by the mode in which the carrier is retained in the membrane [14]. Basically, the concept of all liquid membranes consists of an extractant agent (carrier) in the organic solvent that binds with high selectivity to one or a class of components in the aqueous feed phase and transports it to the aqueous receiving phase (stripping) through the membrane. Supported liquid membranes (SLMs) are the non-dispersive liquid membranes where the organic solvent is immobilized in the pores of a hydrophobic polymer. These varieties of liquid membrane do not depend on the conditions of equilibrium and aqueous /organic phase ratio which are the main setbacks of membrane processes. They can be categorized as flat sheets or cylindrical types based on the size, shape, surface area, and applications.

Recently, SLMs systems have been used in both industrial and analytical fields for separation, preconcentration and wastewater treatment. It exists a significant review describing many experimental papers dealing with SLMs from 1970 to this day. SLMs have been extensively used for the recovery of metals from industrial process streams. Several authors have reported the recovery of metal and anions such as Copper, Zinc Nickel, Cr (VI), Hg and Cd through liquid membrane contactors [15].

During the last years, more studies were conducted on the SLMs for the separation of fine chemicals and even drugs from wastewater. Evidently, their ability to extract products in relatively small volumes makes SLM technology even more attractive for the chemical and pharmaceutical industry as an alternative solution for distillation, crystallization, solvent extraction, and precipitation. On this basis, the rising concerns around these resistive contaminants in urban wastewater have demanded alternative methods to ensure their efficient

and effective removal without major contribution to the overall cost. Membrane techniques and more specifically supported liquid membranes are the optimal choices that check all the requirements for an efficient treatment to remove pharmaceutical contaminants from water [16]. Lately, the drugs most frequently detected in wastewater are anti-inflammatories, antibiotics, hormones, lipid regulators, anticonvulsants, anti-ulcer agents, diuretics, antidiabetics, and bronchodilators[17,18]. Diclofenac ([2-(2,6-Dichloroanilino) phenyl] acetic acid) and Ibuprofen (methylpropyl)phenyl)propanoic acid)are typical representatives of analgesic non-steroidal anti-inflammatory pharmaceutical compounds (NSAIDs). Diclofenac is found in the effluent of water and was listed in the European first watch substances list [17] and as for Ibuprofen, it is one of the over-prescribed drugs and sold easily over the counter [19]. Therefore, due to its high human consumption, it can be found in sewage treatment plants effluents and surface water at concentrations ranging from 600 – 85000 ng/L in parts of Europe, Canada, and USA [9, 13-17]. In addition to anti-inflammatory, the emergence of psychiatric drugs in drinking water has garnered a lot of scientific interest, particularly with regard to the effects of long-term exposure. Carbamazepine (5H-dibenzo[b,f]azepine-5-carboxamide) is a common pharmaceutical prescribed for antiepileptic and the treatment of neurotic pain seizure disorders and several psychological disorders [17].

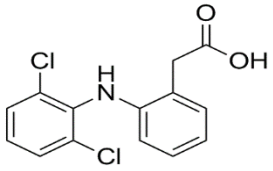
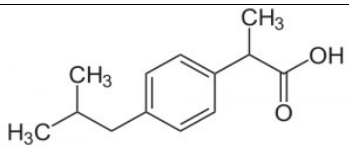
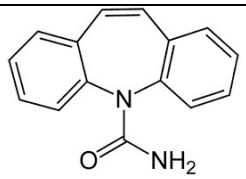
In the following study, flat sheet supported liquid membranes (SLM) are investigated for the separation of drugs (Diclofenac, Ibuprofen, and Carbamazepine) from aqueous solution in laboratory-scale chambers. Different operational parameters, types of extractants, time transfer, and polymeric support were analysed in order to select the optimum conditions for the transport of different pharmaceutical contaminants from water streams. Finally, the stability of the supported liquid membranes is tested.

2. Material and method

2.1 Reagents

Diclofenac Sodium salt (D6899-10G) Ibuprofen Sodium salt (ref. I1892) and Carbamazepine (ref. C4024) were purchased from Sigma Aldrich. The chemical structure of each pharmaceutical is shown in Table 1. Stock solutions of drugs (30 mg/L) were prepared in deionized water.

Table 2. Pharmaceutical compounds chemical structure

Compound	Molecular Structure	MW (g/mol)	pKa
Diclofenac		296.14	4.15
Ibuprofen		228.26	4.9
Carbamazepine		236.37	pka

2.2 Supported Liquid Membrane

The components of the SLM system, namely support, extractants and diluent has been made for the laboratory grade. The solid support in a liquid membrane is a hydrophobic polymer that can retain the organic solvent in the membrane pores by capillary action. Two different types of polymer were studied: A microporous hydrophobic Polyvinylidene fluoride PVDF (Millipore Durapore GVHP 10), with the following specifications: effective area 11.4 cm^2, porosity of 75%, pore diameter of 0.45 □m and thickness 125 □m; and a porous membrane of polytetrafluoroethylene film PTFE (Merk): effective area 11.4 cm^2, pore size 0.45 □m, porosity 85%, and thickness 125 □m. The pores of the membrane are filled with an organic solvent, which has been chosen based on the selectivity of the components present in the feed phase: Cyanex 923 (Cy923, 91%), Trioctylamine (TOA, 98%), Tributylphosphate (TBP, 99%, Merk), Methyl (trioctyl/decyl) ammonium chloride quaternary amine (Aliquat 336, 90.9%) and a Neodecanoic acid (Versatic acid 10, 98%). Various concentrations of organic extractants were prepared in adequate diluents. The nature of the diluents preferred is the same as it is for the solvent extraction process. It is favourable to have low viscosity, solubility, and price. Decanol and kerosene were selected as the diluents in this study.

2.3 Extraction Test Procedure.

The liquid-liquid extractions for all three pharmaceuticals were carried out in a small beaker where 5 mL of the aqueous solution containing 30 mg/L of contaminants is mixed with 5 mL

of organic phase at room temperature 23 ± 3 Cº. The two phases were stirred at 200 rpm for 1 hour. After extraction, the solution was put to rest in a separatory funnel for 10 minutes to reach equilibrium. The aqueous phase was separated and the concentration of the drug remaining was analysed by high-performance liquid chromatography (HPLC, Agilent 1100 infinity series) with a diode array detector at 280 nm, 230 nm, and 285 nm for diclofenac, ibuprofen, and carbamazepine respectively. The column used was Hypersil C18 (4x25 mm) and the mobile phase consisted of a mixture of formic acid (25 mM) in water and Acetonitrile at 60:40 (v/v) with a flow rate of 1.0 mL/min. The concentration of pharmaceuticals in the loaded organic phase was determined by the mass balance of the pharmaceutical before and after extraction. The main purpose of conducting L-L is to select the optimum conditions of extraction and stripping for the transport studies. Different parameters such as equilibrium pH (from 3 to 14), the presence of extractants at different concentrations dissolved in diluents are tested and summarized in **Table 2**

Table 2. Range of concentration of extractants used

Extractant	**% v/v**
Kerosene with no extractant	-
Decanol without extractant	-
Cyanex 923 in kerosene	10, 20, 30, 40, 60
TBP in kerosene	20, 40, 80
TOA in kerosene	5; 10, 20
Aliquat 336 in 10% decanol/kerosene	10
Versatic Acid 10 in kerosene	10

2.4 Supported liquid membrane preparation and transport experiment.

The supported liquid membrane was prepared by dipping the solid support into the organic liquid for a few minutes. It was then removed, wiped with a soft paper to eliminate the excess solution, and inserted into the device used for SLM experiments shown in Figure 1. The permeation cell consists of two chambers (feed cell and stripping cell) of 220 cm^3 communicated with a circular window where the impregnated membrane is placed. The effective area for PTFE and PVDF membranes were 11.4 cm^2. The stripping and the feed

phase were added respectively in each cell and stirred mechanically at 1000 rpm at room temperature (23±2 ºC).

Batch experiments were carried out for pharmaceutical transport (Diclofenac, Ibuprofen Carbamazepine) with the different organic solvents. At established time intervals, aliquots were withdrawn from the feed and stripping cells, and the concentration of pharmaceuticals was measured. The pH for feed and stripping phase were continuously monitored during the experiment and was adjusted when needed to the operating value by adding some drops of 1 M HCl in the feed and 1 M NaOH in the stripping cell.

The rate of transport and the quantity of transported solute through a specific area of the membrane into a given unit time for different operational parameters is usually defined by the permeability coefficient P. The Permeability is derived from the mass balance of solute in the feed cell and the Fick's law of diffusion (Equation 1).

$$ln\frac{C_t}{C_0} = -\frac{P \cdot A}{V}t \qquad (1)$$

(Where P is the SLM permeability ($cm \cdot h^{-1}$), C_t and C_0 are the concentration of the studied pharmaceutical at time t and at time 0 respectively, A is the SLM area (cm^2), V is the volume of feed phase (cm^3) and t is the time in hours.

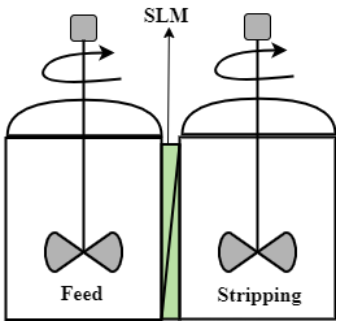


Figure1. Schematic representation of the experimental setup

2.5 Stability Studies

The main characterisation of SLM is their simple application, yet they are rarely applied for industrial use due to their short lifetime and their instability. This very much depends on different factors such as the nature of solvent used, the type of polymeric support and the pore size. Firstly, the stability of both PVDF and PTFE polymer supports were tested by conducting transport experiment for diclofenac for three consecutive runs of 4 hours. The liquid membrane phase was drenched with a 40% solution of Cyanex 972 in commercial kerosene. Secondly, to improve the efficiency, the pores of the polymeric support PTFE were

filled with the organic solution of Cy923 40 % (v/v) in two ways: At atmospheric pressure for 24 h and at atmospheric pressure but assisted by ultrasound (50 kHz, 150 μm) for 30 min. by means of ultrasonic Lab homogeniser UP200S M (Hieltcher). The active layer of the polymeric support was positioned perpendicularly to the direction of the ultrasound and at a distance of 10 mm from the ultrasound probe. Transport studies were carried out for 4 hours by monitoring the concentration of diclofenac in the feed phase.

3. Results and discussion

3.1 Extraction tests

Liquid-Liquid extraction experiments were studied primarily to define the best operating conditions to be used in the transport studies. The effects of pH in the extraction extension for the different extractants used were investigated for each pharmaceutical.

3.1.1 Effect of aqueous pH and different extractant

Samples with 30 mg/L of Diclofenac (DCF), Ibuprofen (IBU) and Carbamazepine (CBZ) were prepared in a range of pH between 2 and 13. 10% (v/v) of Cy923, 10% (v/v) Aliquat 336, 20% (v/v) TBP and 10% (v/v) TOA diluted in kerosene were used to estimate the distribution coefficient and the extraction efficiency with $V_{aqueous}./V_{Org}$ =1. All extractants were diluted in kerosene since it is easily available with low toxicity and lower viscosity than decanol.

The extraction results corresponding to the type of extractant obtained at equilibrium pH are shown in **Figures 2 (a, b, c and d)**. As expected for both carboxylic acid compounds (DCF and IBU), they are extracted simultaneously and completely at acidic pH with Cy923, TOA, and TBP. Upon analysis of the diclofenac, it was noticed then for a pH less than 4, the initial concentration of diclofenac exhibited a decrease (the measured concentration obtained was 20 mg/L lower than the concentration at neutral pH 30 mg/L). This is due to the formation of insoluble diclofenac. Nonetheless, this behaviour did not cause any problem since diclofenac presented a high extraction for pH range between 4-7 for all the extractant used (10 % of each Cy923, Aliquat 336, TOA, and 20 % of TBP).

As for Ibuprofen with a pKa of 4.9, a higher extraction is achieved for a pH less than 6. For this value of pH, ibuprofen is protonated hence easily removed from the aqueous solution. On the other hand, as expected for Ibuprofen and diclofenac as the pH increased, the extraction efficiency decreased since both molecules are deprotonated. These results are in accordance with a study by Razo-Lazcano et al. [19] for the extraction of ibuprofen with TOA at pH 2. For instance, results depicted in **Figure 2** show that at low pH (pH 2), high IBU extraction is

reached, while at pH higher than 6.5 the IBU concentration in the organic phase is null. In addition, it was noticed that high extraction of 95 % of IBU was obtained at pH 5. Therefore, a high acidic medium is not required. Alternatively, Carbamazepine is characterized by two pKa values:3.9 and 15.9. This pharmaceutical was only partially extracted with all of the following extractants Cy923, Aliquat 336, and TBP. As for TOA, it was ineffective to extract the pharmaceutical at a different range of pH. Consequently, 10% of Versatic acid 10 (Neodecanoic acid) was tested as a potential extractant for carbamazepine. The purpose was to ensure a back extraction for CBZ when applying SLM. As a result, Carbamazepine was poorly extracted at basic pH = 13 and for a lesser pH range, the extraction percentage tends to increase as shown in **Figure 2d**. The highest value was obtained for acidic pH 2 and the only low extraction was achieved at a pH 14, therefore Versatic acid 10 was selected for the SLM experiment for the amino-functional group.

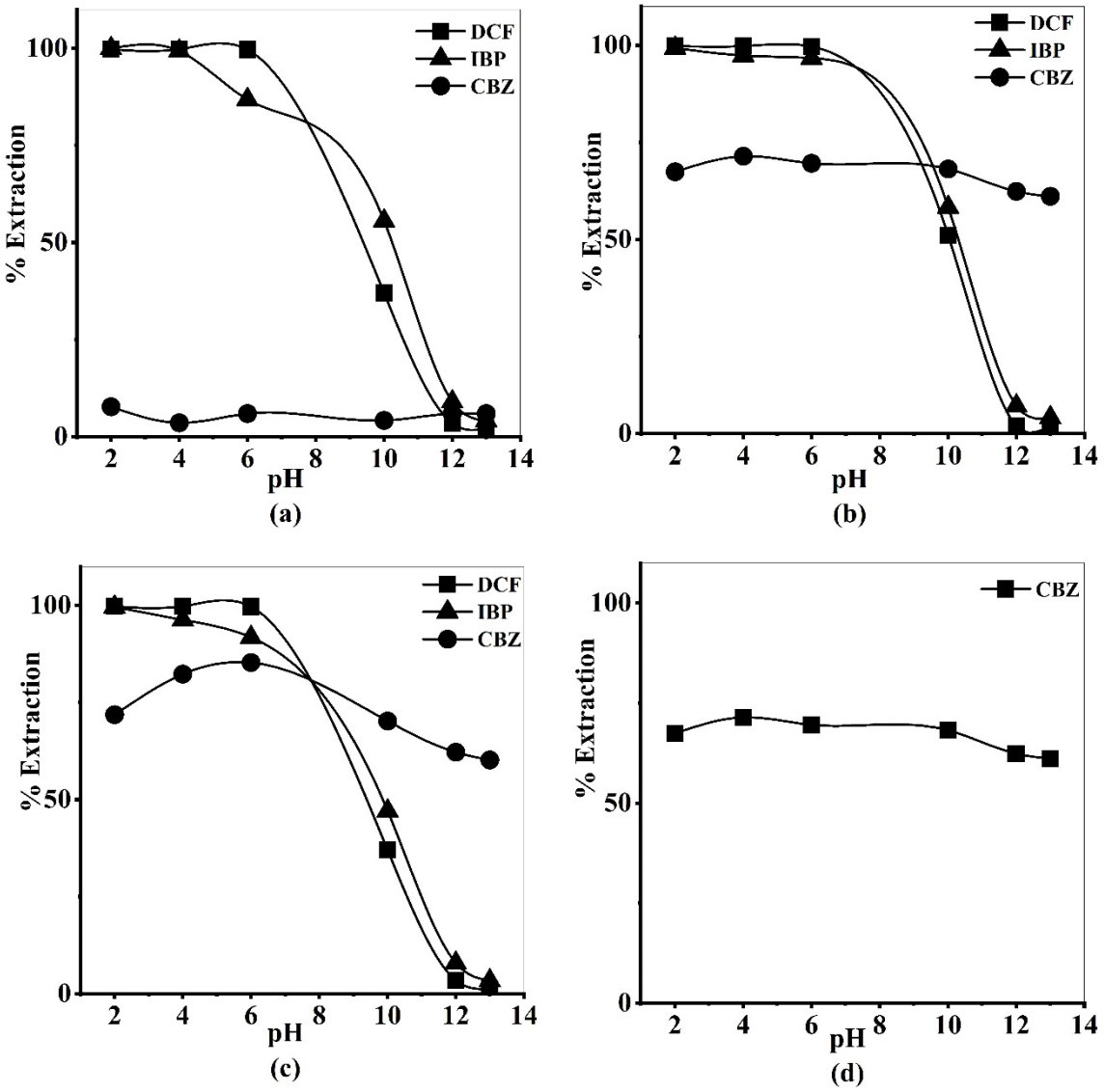


Figure 2. Effect of the $pH_{equilibruim}$ on the extraction of Pharmaceuticals with different extractants: **(a)** 10 % Cy923; **(b)** 20% TBP; **(c)** 10% TOA; **(d)** 10% Versatic Acid 10

3.2 Transport studies through SLM

Transport through SLM tests were performed for Diclofenac, Ibuprofen and Carbamazepine using different extractant, 10 % volume ratio of Cy923, TOA, Aliquat 336, and 20% of TBP diluted in kerosene.

Considering the acid-base properties of the pharmaceutical used, Diclofenac and Ibuprofen contain a carboxylic group in their structure. Hence, their dissociation reaction in aqueous media is the following:

$$HA \leftrightarrow A^- + H^+$$

Taking into account that Cy923, TBP, and TOA extract neutral species, the extraction process was carried out at neutral pH 6 and 5 for Diclofenac and Ibuprofen respectively. Diffusion occurs from the bulk phase of the feed to the inner surface of the membrane. The molecules of the organic carrier (E) can solvate the non-charged form of the drug HA permitting the extraction of this molecule to the organic phase, and the reaction equation for the extraction step is the following:

$$HA + n\ \bar{E} \leftrightharpoons \overline{E_n \cdot HA}$$

The pharmaceutical organic complex diffuses through the membrane phase due to the concentration gradient to reach the membrane/product interface where the complex is broken by the hydroxide ion present in the receiving phase and the pharmaceutical is released. The reaction occurring in the stripping phase is the following:

$$\overline{E_n \cdot HA} + OH^- \leftrightharpoons n\,\bar{E} + A^- + H_2O$$

Based on results obtained with liquid-liquid extraction, membrane experiments were carried out using the optimized parameters for initial pH in the feed phase (pH 6 for Diclofenac and pH 5 for Ibuprofen), drug concentration (30mg/L). The permeability coefficient for each organic solvent is calculated using equation (1) as well as the evaluation of concentration in the feed and the stripping is shown in **Figure 3**.

For Diclofenac, although the three carriers Cy923, TBP, and TOA were able to extract Diclofenac from the feed to the receiving phase, the rate of transport was higher using Cy923. More than 80% of Diclofenac was transported after 3 h using 10% Cy923 (**Figure 4**.) The transport was examined by determining the permeability coefficient (P) with all three extractants, and the highest value was 6.3 cm/h when using 10% (v/v) Cy923.. The complex formed with Cy923 is transported faster than TBP and TOA complex. Therefore, Cy923 diluted in kerosene was selected to extract diclofenac. Cy923 is considered a cheaper extractant with better stability compared to tributyl phosphate and has better stability [23].

For ibuprofen, maintaining the pH gradient between the two phases was a major key for extraction and back extraction with the three organic solvents. During the experiment, the pH in the feed phase increases to a value of 7 as ibuprofen is extracted, thereafter, all the experiments with ibuprofen were carried out at a pH of approximately 5. Based on the results plotted in **Figure 5,** the transfer is faster with Cy923 and the permeability coefficient was found to be 6.7 cm/h. Another difference is that less than two hours is needed for 50 % of the concentration in feed to be transported to the stripping phase. This means that the IBP does not

accumulate on the SLM and all the ibuprofen is transferred to the stripping phase. Therefore, Cy923 is selected for the SLM experiment of ibuprofen. Whereas for Aliquat (336), the stripping conditions evaluated in L-L extraction did not allow back extraction for diclofenac and ibuprofen. These pharmaceuticals were accumulated on the membrane surface, therefore the ionic extractant was discarded.

SLM experiment for Carbamazepine in the feed phase was tested with Versatic Acid 10. 1 M of NaOH was used to ensure a back-extraction in the stripping phase. The Permeability coefficient was calculated a found to be 4.2 cm/h and the evolution of drug concentration are shown in **Figures 3**. The results of the graph show that the transport rate of carbamazepine increased gradually compared to other drugs in which 50 % of the drug was transported after 3 hour of experiment .

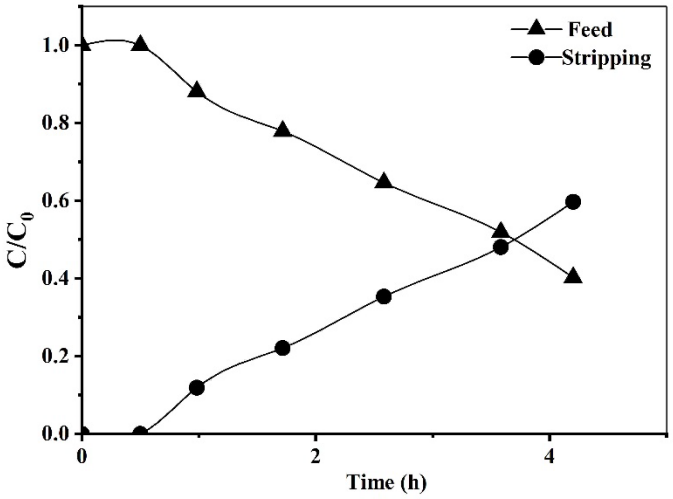


Figure 3. Evaluation CBZ concentration vs time in the feed phase with 10% Vesatic acid (C_0 = 30 mg/L, pH=4), and stripping phase (pH stripping=13.5).

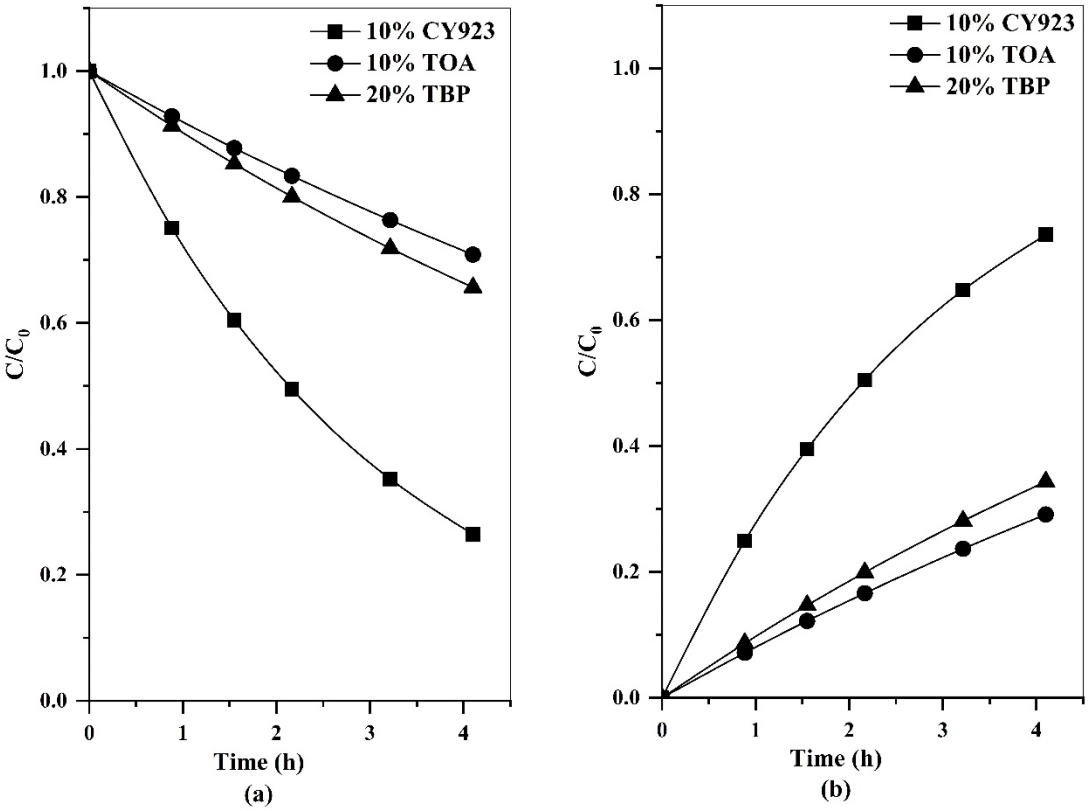


Figure 4: (a) Evolution of DCF concentration in the feed phase vs time for different extractants (C_0 = 30 mg/L; pH 6.0) and (b) Evolution of DCF concentration in the stripping phase vs time with different extractants (pH=10**)**.

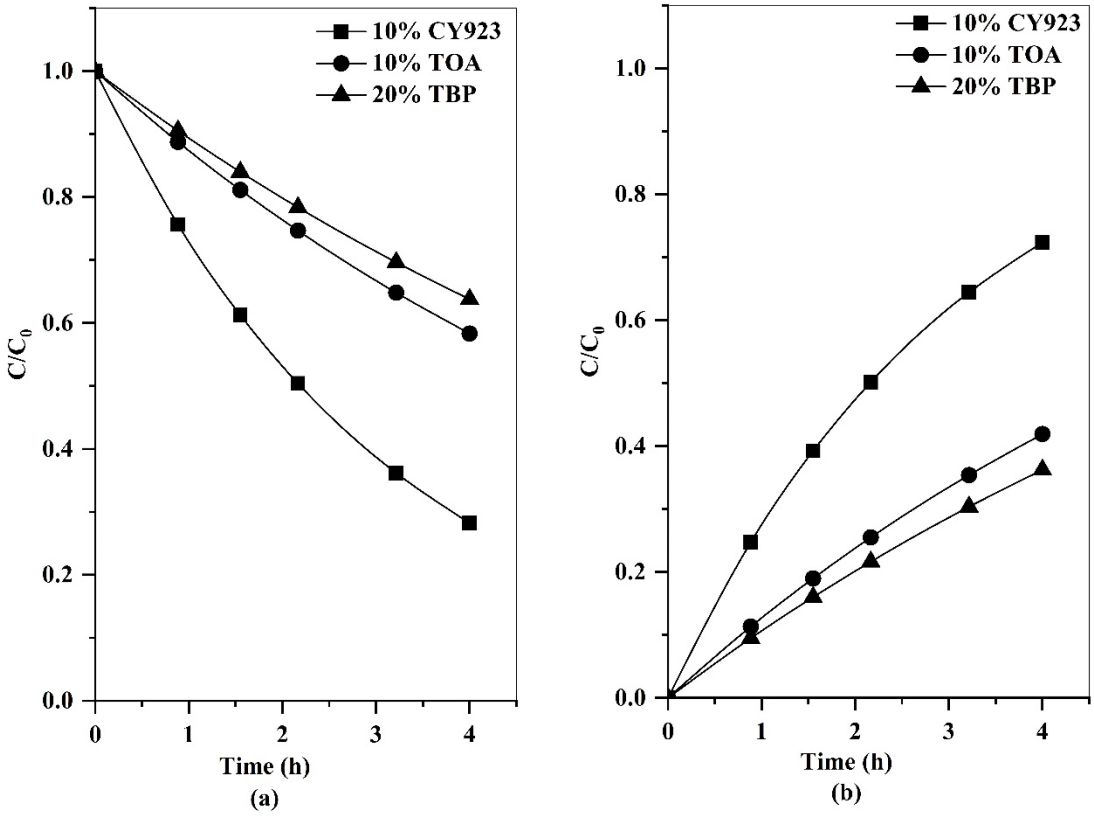


Figure 5: (a) Evaluation of IBU concentration in the feed phase vs time for different extractants (C_0 = 30 mg/L;; pH = 5.0) and (b) Evolution of IBU concentration in the stripping phase vs time with different extractants (pH = 11).

3.1 Effect of extractant concentration

The influence of Cy923, TOA and TBP concentration in the transport process for DCF and IBU through the SLM was evaluated. The SLM impregnated with a higher concentration of TBP did not have any effect on the transfer of both drugs when varying the extractant concentration from 10% up to 50%. This reverse effect is attributed to the increase of viscosity of the organic phase. Therefore, when the concentration of extractant is high, the transport flux decreases due to the higher viscosity of the organic phase. Previous studies proved that this complex species formation between the contaminant and the organic extractant does not only depend on the equilibrium constant of the reaction mechanisms, but also on the viscosity effect of the organic extractants. An extractant with high viscosity can present a counter effect on the transport during the SLM experiments [21].

On the other hand, the permeability coefficient when using Cy923 increased for Diclofenac and Ibuprofen, obtaining a linear dependence of extractant concentration and permeability coefficient as shown in **Figure 6**. This linear proportionality was not observed when using TOA with both drugs where the permeability coefficient increased slightly with the concentration. In addition, as shown in the transport studies the complex formed with TOA is transported at a slower rate compared to the one formed with Cy923.

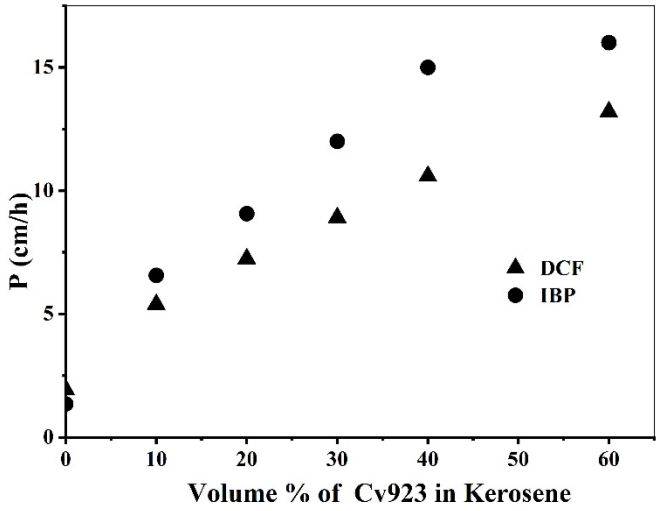


Figure 6 .Effect of Cy923 concentration on Diclofenac and Ibuprofen permeability coefficient.

The transport process was controlled by the diffusion with less than 60% (v/v) for Cy923. According to the principle of chemical equilibrium, increasing the concentration of extractant favoured the formation of complexes therefore the removal rate of contaminants increased rapidly; but when the extractant concentration reached 60%, the permeability coefficient did not follow the linear trend as shown in Figure 6. Increasing the organic extractant concentration leads to higher viscosity of the organic phase which can reduce the diffusion coefficient due to the effect of the shear stress [21]. Thus, a concentration of 40% (v/v) is selected as the optimum concentration of Cy923. In addition, it was noticed, that for this value the organic liquid formed was not easily displaced to the aqueous phase and was maintained in the pores of the polymeric support.

3.3 Effect of membrane support

As described in the previous section, the polymeric support of the membrane consists of microporous hydrophobic polymers that does not play an active role in the separation but provide structural support for the membrane phase, which is the active component in the separation [17]. Two types of polymeric flat sheet membrane (PTFE and PVDF) were studied and Diclofenac was selected as a case study.to investigate the effects. The characteristics of both membranes are mentioned in the previous section.

The membranes were impregnated at the same conditions tested in the transport studies (10% of Cy923, concentration of DCF in the feed 30 mg/L and concentration of NaOH in the stripping 0.1 mM). In the case of polyvinylidene fluoride (PVDF), the rate of transport of pharmaceutical was lower than the one obtained with PTFE membrane, the permeability coefficient determined was P = 3.9 cm/h less than 6.3 cm/h . The transport rate of contaminants through the membrane varies with the porosity. According to the supplier specifications, the two polymeric support differs by the percentage of porosity. In fact, the main challenge of SLM is to retain the organic solvent and several factors should be evaluated when selecting a support: high hydrophobicity, high porosity, adequate pore size, and low tortuosity. Additionally to the difference in porosity, the surface structure of the membrane plays an important role in the stability of the organic solvent, therefore stability studies were conducted to select the most efficient polymeric support in the transport of pharmaceutical contaminants using SLM.

3.4 **Stability of the membrane**

Instability of the membrane can occur when the organic extractant fails to be retained inside the membrane pore during the process. SLM membranes present several advantages, such as high selectivity, operational simplicity, low solvent inventory, and low energy consumption however they can fall back on their stability and lifetime [11].

For the stability studies, the pores of the microporous support were filled with the organic solution of 40% Cy923. The stability of both PVDF and PTFE polymer support was tested by conducting transport experiments for Diclofenac for three consecutive runs of 4 hours and the permeability coefficient determined with equation (1) for each run is shown in **Table 3**.

It is essential to take into account the structure of the polymer material. The PTFE membrane exhibits a porous top surface compared to PVDF membrane which presents no obvious pores and a smoother surface. The comparison between the coefficient of permeability for the first

run and the subsequent two for both polymeric support shows that PVDF is more stable after 3 consecutive operations. Although PTFE membranes are characterized by higher porosity and exhibit a faster transfer rate for both Diclofenac and Ibuprofen, however, the liquid membrane had a tendency to leach out during the SLM process. Moreover, it was noted for both polymeric support, the permeability of the membrane shows a variation between the first two runs, but maintains a similar value for the following two. To investigate this behaviour and whether water molecules affect the organic extractant, the organic solvent solution was washed with water for 20 minutes then was used to impregnate the membrane. The test was conducted with 30 mg/L of Diclofenac at the same operating condition as the transport studies with PTFE membrane. The permeability decreased by 60 % (data not shown). The decrease in permeability after contacting the organic solution with water confirms that water can alter the organic molecule, hence decreasing the permeability in SLM transport. It is important to ensure a longtime run of SLM while maintaining a high permeability coefficient.

Table 3. Permeability coefficient (cm/h) for three consecutive runs.

	PTFE support	**PVDF support**
1st Run	10.1	5.5
2nd Run	4.1	2.3
3rd Run	4.1	2.3

Different studies have analysed the influence of these factors but many have discarded the importance of the method applied to fill the pores of the polymeric support [11]. Leon et al. evaluated three different techniques to increase the stability and transport efficiency of supported liquid membranes for cobalt (II) removal by proposing ultrasounds for the preparation of the support [22]. The study found that applying ultrasounds on the membrane support while soaking the membrane in the organic solvent for 30 minutes, increased the stability of the membrane for 3 consecutive runs compared to the one prepared by only soaking the polymeric support for 24 hours. To increase the long term runs of SLM, the pores of the polymeric support PTFE was filled with the organic solution of Cy923 40% (v/v) in two different ways: At atmospheric pressure for 24 h, and at atmospheric pressure but assisted by ultrasounds. The results after three consecutive runs are shown in **Figure 7.**

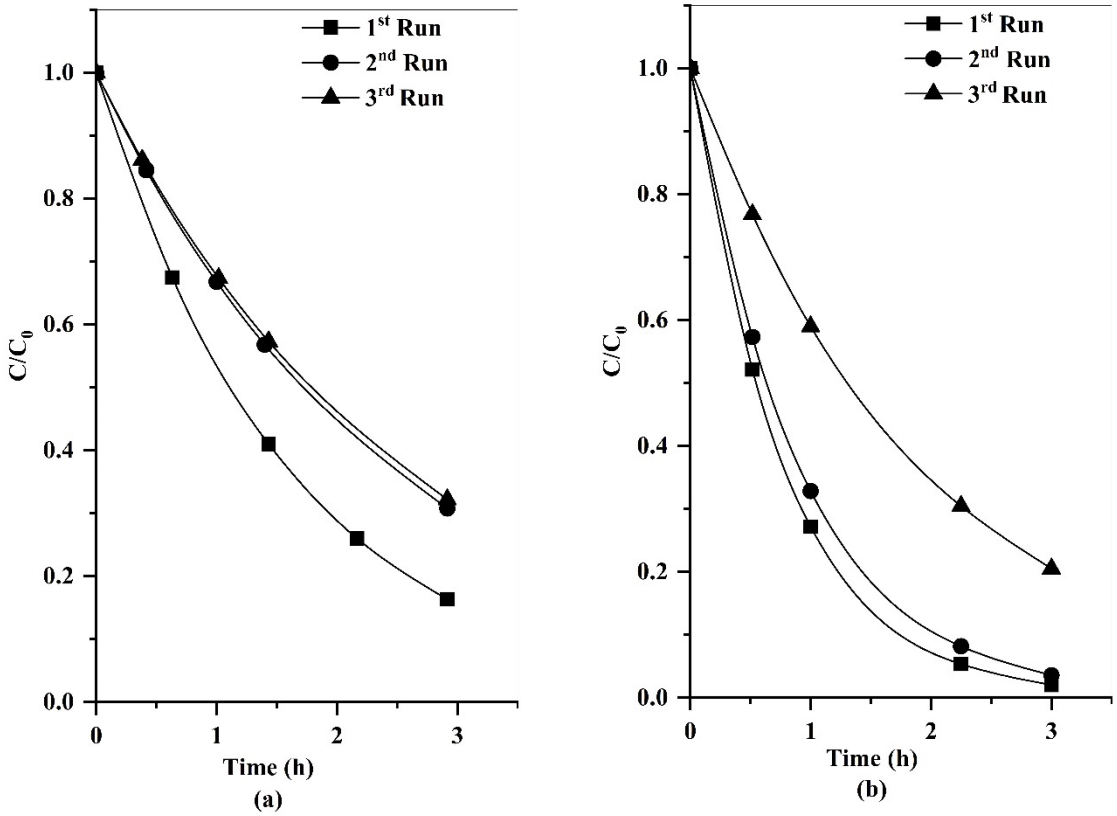


Figure 7. Effect of ultrasounds on the transport of DCF for PTFE support with (a) Ultrasound for 30 min at 50 kHz and 40% Cy923 of organic solvent (b) PTFE membrane left for 24 h in contact with 40% Cy923.

Acoustical streaming and cavitation produced when ultrasounds pass through a liquid medium can increase pore filling. A study done by Killomen (2005) suggested that this enhancement of performance is due to the increase in pore radius and pore density [23]. In fact, the highest transport rate for the first run was obtained when the membrane was kept in contact with organic for 24 h, where more than 50 % of pharmaceutical was transported from the feed phase to the organic phase in less than 2 hours. In addition, the efficiency of the membrane was maintained for subsequent experiments. While proving that ultrasound can enhance the stability of the membrane, it usually adds additional cost to the treatment, thus it is favourable to have the polymeric support in contract with the organic solvent to optimize the transfer of pharmaceuticals through SLM.

4. Conclusion

Upgrading wastewater treatment with new technologies will not solely solve the problem of pharmaceuticals in water. They are limited by their removal efficiencies, high capital investment and operation costs and excessive energy consumption. In this study, SLMs were evaluated as an alternative effective method for the removal of different types of pharmaceuticals. The removal of Diclofenac, Ibuprofen, and Carbamazepine from aqueous solutions has been performed through a flat sheet supported liquid membrane composed by Cy923, tri-octylamine (TOA), tributylphosphate (TBP), Aliquat 336 and Versatic acid 10 as extractant, and kerosene as diluent. In the case of diclofenac and ibuprofen, SLM with 10% Cy923 was more efficient for the transport from the feed phase to the stripping phase. The optimum conditions for the IBU removal are when the pH in the feed phase was regulated to 5, whereas neutral pH (pH=6) was efficient for Diclofenac transport. Versatic acid 10 was the single option for the extraction of Carbamazepine through SLM experiments.

An efficient transfer was reached without accumulation on the SLM when the concentration of Cy923 increased to 40% (v/v). Moreover, two different polymeric support were tested and the permeability obtained with PTFE support with higher porosity (85%) was greater than PVDF support. The stability and efficiency of the supported liquid membrane are tested for the removal of Diclofenac through a facilitated transport mechanism using 40% Cy923 as an extractant and hydroxide ions as counter ions. Comparisons of stability of two polymeric support showed that PVDF was more efficient after three consecutive runs.

Two methods were tested to enhance the efficiency of the supported liquid membrane by optimizing the contact of organic extractant and the membrane support. Ultrasound-assisted methods were able to increase the permeability by 20% but higher values of permeability coefficient and stability are obtained by the membrane soaked with the organic solvent for 24h at atmospheric pressure. Hence the stability of SLM is increased by enhancing pore filling to ensure long-term applications. The integration of SLM in the abatement of persisting pharmaceutical contaminants shows promising results since 98% of different pharmaceuticals were removed with a minimal amount of organic extractants.

The purpose of this study is to investigate SLM in the removal of pharmaceutical contaminants efficiently and effectively. Further studies are recommended to investigate the possibility to combine this technique with different established wastewater technologies to increase the efficiency of the treatment and lower the cost and energy consumption.

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6. References

[1] Civity (2017), *Pharmaceutical usage in the context of demographic change: The significance of growing medication consumption in Germany for raw water resources*, Civity Management Consultants.

[2] Peeling, R. W., Boeras, D., Nkengasong, J. (2020). Ensuring innovation for diagnostics for bacterial infection to combat antimicrobial resistance. *Challenges to Tackling Antimicrobial Resistance*, 155–180. https://doi.org/10.1017/9781108864121.008.

[3] Kümmerer, K. (2009). The presence of pharmaceuticals in the environment due to human use – present knowledge and future challenges. Journal of Environmental Management, 90(8), 2354–2366. https://doi.org/10.1016/j.jenvman.2009.01.023.

[4] Jones, O., Voulvoulis, N., Lester, J. (2002). Aquatic Environmental Assessment of the top 25 English prescription pharmaceuticals. Water Research, 36(20), 5013–5022. https://doi.org/10.1016/s0043-1354(02)00227-0 .

[5] Verlicchi, P., Zambello, E., Al Aukidy, M. (2013). Removal of pharmaceuticals by conventional wastewater treatment plants. Analysis, Removal, Effects and Risk of Pharmaceuticals in the Water Cycle - Occurrence and Transformation in the Environment, 231–286. https://doi.org/10.1016/b978-0-444-62657-8.00008-2.

[6] Akhtar, J., Amin, N. A., Shahzad, K. (2015). A review on removal of pharmaceuticals from water by adsorption. Desalination and Water Treatment, 57(27), 12842–12860. https://doi.org/10.1080/19443994.2015.1051121.

[7] Mansouri, F., Chouchene, K., Roche, N., Ksibi, M. (2021). Removal of pharmaceuticals from water by adsorption and advanced oxidation processes: State of the art and trends. Applied Sciences, 11(14), 6659.

[8] Tungudomwongsa, H., Leckie, J., Mill, T. (2006). Photocatalytic oxidation of emerging contaminants: Kinetics and pathways for photocatalytic oxidation of pharmaceutical compounds. Journal of Advanced Oxidation Technologies, 9(1). https://doi.org/10.1515/jaots-2006-0109
.

[9] Park, J., Yamashita, N., Park, C., Shimono, T., Takeuchi, D. M., Tanaka, H. (2017). Removal characteristics of pharmaceuticals and personal care products: Comparison

between membrane bioreactor and various biological treatment processes. Chemosphere, 179, 347–358. https://doi.org/10.1016/j.chemosphere.2017.03.135.

[10] Li, X., Shen, S., Xu, Y., Guo, T., Dai, H., Lu, X. (2021). Application of membrane separation processes in phosphorus recovery: A Review. Science of The Total Environment, 767, 144346. https://doi.org/10.1016/j.scitotenv.2020.144346

[11] San Roman, M. F., Bringas, E., IbaÃ±ez, R., Ortiz, I. (2010). Liquid Membrane Technology: Fundamentals and review of its applications. Journal of Chemical Technology & Biotechnology, 85(1), 2–10. https://doi.org/10.1002/jctb.2252.

[12] Balasubramanian, A., Venkatesan, S. (2012). Removal of phenolic compounds from aqueous solutions by emulsion liquid membrane containing ionic liquid [bmim]+[pf6]− in tributyl phosphate. Desalination, 289, 27–34. https://doi.org/10.1016/j.desal.2011.12.027

[13] Santiago-Santiago, L. A., Reyes-Aguilera, J. A., Gonzalez, M. P., Cholico-Gonzalez, D., Avila-Rodríguez, M. (2012). Separation of bi(iii) and SB(III) from cu(ii) hcl/H2SO4 mixed media by supported liquid membranes using Cyanex 921 as carrier. Industrial & Engineering Chemistry Research, 51(46), 15184–15192. https://doi.org/10.1021/ie301447x.

[14] Molinari, R., Argurio, P., Poerio, T., Caruso, A. (2006). Stagnant sandwich and supported liquid membrane systems for removal of pharmaceuticals in water. Desalination, 199(1-3), 529–531. https://doi.org/10.1016/j.desal.2006.03.188.

[15] Parhi, P. K. (2013). Supported liquid membrane principle and its practices: A short review. Journal of Chemistry, 2013, 1–11. https://doi.org/10.1155/2013/618236.

[16] Kocherginsky, N. M., Yang, Q., Seelam, L. (2007). Recent advances in supported liquid membrane technology. Separation and Purification Technology, 53(2), 171–177. https://doi.org/10.1016/j.seppur.2006.06.022.

[17] Schröder, P., Helmreich, B., Škrbić, B., Carballa, M., Papa, M., Pastore, C., Emre, Z., Oehmen, A., Langenhoff, A., Molinos, M., Dvarioniene, J., Huber, C., Tsagarakis, K. P., Martinez-Lopez, E., Pagano, S. M., Vogelsang, C., Mascolo, G. (2016). Status of hormones and painkillers in wastewater effluents across several European states—considerations for the EU Watch List concerning estradiols and diclofenac. Environmental Science and Pollution Research, 23(13), 12835–12866. https://doi.org/10.1007/s11356-016-6503-x

[18] Mestre, A. S., Pires, J., Nogueira, J. M. F., Parra, J. B., Carvalho, A. P., Ania, C. O. (2009). Waste-derived activated carbons for removal of ibuprofen from solution: Role of Surface Chemistry and pore structure. Bioresource Technology, 100(5), 1720–1726. https://doi.org/10.1016/j.biortech.2008.09.039

[19] Razo-Lazcano, T. A., Stambouli, M., González-Muñoz, M. del, Pareau, D., Ávila-Rodríguez, M. (2014). Emulsion liquid membranes for recovery of ibuprofen

from Aqueous Solutions. Journal of Chemical Technology & Biotechnology, 89(6), 890–898. https://doi.org/10.1002/jctb.4329

[20] Li, Z., Binnemans, K. (2021). Opposite selectivities of tri- n -butyl phosphate and Cyanex 923 in solvent extraction of lithium and magnesium. AIChE Journal, 67(7). https://doi.org/10.1002/aic.17219

[21] Pavón, S., Fortuny, A., Coll, M. T., Bertau, M., & Sastre, A. M. (2020). Permeability dependencies on the carrier concentration and membrane viscosity for Y(III) and Eu(III) transport by using liquid membranes. *Separation and Purification Technology*, *239*, 116573. https://doi.org/10.1016/j.seppur.2020.116573

[22] León, G., Martínez, G., Guzmán, M. A., Moreno, J. I., Miguel, B., Fernández-López, J. A. (2013). Increasing stability and transport efficiency of supported liquid membranes through a novel ultrasound-assisted preparation method. its application to cobalt(II) removal. Ultrasonics Sonochemistry, 20(2), 650–654. https://doi.org/10.1016/j.ultsonch.2012.10.002

[23] Kyllönen, H. M., Pirkonen, P., & Nyström, M. (2005). Membrane filtration enhanced by ultrasound: A Review. *Desalination*, *181*(1-3), 319–335. https://doi.org/10.1016/j.desal.2005.06.003

Chapter 4. Intensification of Diclofenac Removal through Supported liquid membrane and Ozonation

Abstract

Pharmaceutical contaminants are frequently encountered at trace concentrations in various environmental ecosystems. This study introduces a significant approach to water treatment and environmental remediation by combining liquid membrane and ozonation. Initially, diclofenac is transported across the supported liquid membrane using a neutral organic extractant Cyanex 923. The highest removal efficiency was achieved with a 40 % concentration of Cyanex923 dissolved in kerosene, resulting in a permeability of 10.2 cm/h. Additionally, diclofenac is extracted from different environmental matrices such as tap water and real effluent of wastewater, and the effect of ions species was studied. The post-ozonation in the stripping phase resulted in removal of pharmaceuticals and 72 % reduction of total organic carbon at pH = 10 and 45.3 g/Nm^3 initial ozone concentration. The study also investigates the identification and tracking of the most prevalent by-product of diclofenac over time.

1 Introduction

Pharmaceuticals have been extensively used to prevent, cure, and treat diseases, and to increase life expectancy. However, the identification of pharmaceuticals in various environmental contexts has sparked significant health concerns. Numerous pharmaceutical agents are introduced into water sources, and their remnants are consistently identified in surface water, groundwater, wastewater, and even drinking water [1]. As these pharmaceutical substances remain essential to daily life, it becomes imperative to manage their consumption and discharge due to the potential risks they pose to both human well-being and aquatic ecosystems. Some pharmaceuticals, like antibiotics, can have detrimental effects on microbial genomes, leading to the development of bacterial resistance. One noteworthy pharmaceutical in this category is diclofenac, a nonsteroidal anti-inflammatory drug (NSAID) commonly used to alleviate pain and reduce inflammation. Diclofenac is considered one of the top-selling anti-inflammatory drugs and its oral global consumption was estimated at around 940 tons per year according to a trend analysis from, 2020–2027 for the consumption of pharmaceuticals [2]. Furthermore, diclofenac can easily reach surface and wastewater through various means, such as improper disposal as solid waste, discharge through human and veterinary excretion, and effluents from industrial and urban wastewater treatment plants (WWTPs and UWWTPs). Conventional treatment methods have proven insufficient in removing diclofenac from water [3,4]. Recently, diclofenac has been detected in effluent water at concentrations up to 1.2 µg/L in various parts of Europe. Water undergoes conventional physical, chemical, and biological processes such as coagulation, flocculation, filtration, and disinfection [5]. Yet several studies have addressed the low biodegradability of diclofenac and its high persistence in wastewater treatment plants, leading to its accumulation in surface waters, sediments, and sludge . The partial or low elimination of diclofenac by conventional treatment has been reported by several studies: conventional coagulation and sedimentation (25 %) [6] membrane bioreactor 40 % [7] conventional activated sludge (66 %) [8] In addition, the separation technique was studied to reduce the pharmaceutical environmental loading of pharmaceutical into the environment. The selective separation of diclofenac from urine was investigated with a strong-base anion exchange resin [9]. However, over time, as the resin interacts with pharmaceutical compounds, it may become fouled or saturated, diminishing its capacity to effectively remove the target substances. Consequently, frequent resin regeneration or replacement might be necessary, resulting in increased operational costs and maintenance efforts. In addition, Ansarimehr et al. (2022) utilized solvent extraction with tetra-n-butyl ammonium bromide (TBAB) to extract

diclofenac from water. Yet, compared to different separation techniques, solvent extraction techniques lack selectivity and can require additional separation steps [10]. Therefore, it is imperative to eliminate diclofenac from aqueous matrices to meet the required concentration levels. Various tertiary techniques have been developed for the removal of emerging contaminants, including adsorption, membrane separation, and advanced oxidation processes.New advancements in membrane technology have significantly transformed wastewater treatment by improving pollutant filtration and extraction processes. The integration of membrane technologies in various applications, such as water treatment and desalination, has gained widespread popularity [11]. In contrast to conventional methods such as coagulation, flocculation, and biochemical treatments, membrane processes emerge as a highly efficient and promising approach for wastewater treatment. They not only save on chemicals and space but also provide superior treatment efficiency [12]. Membranes play a pivotal role as selective barriers in the separation and removal of contaminants at low concentrations. In this context, liquid membranes have been gaining widespread interest due to their high selectivity and simple manipulation. Unlike pressure-driven membrane technologies, liquid membranes (LM) operate based on the principles of facilitated transport and selective extraction [13]. By definition, LMs consist of an organic liquid phase immobilized within or supported by a porous material, typically a polymer support. This liquid phase acts as a carrier for specific substances, allowing them to be selectively transported or separated from one phase to another, such as from a feed solution to a stripping solution [13,14]. The driving force for separation does not come primarily from hydraulic pressure, but rather from the chemical interactions between the liquid membrane and the target components. Moreover, they can offer enhanced resistance to fouling and pore blockage compared to traditional solid membranes [15,16]. As a result of these characteristics, liquid membranes have been used across different fields like environmental remediation, pharmaceutical purification, and chemical processing [16]. In particular, supported liquid membranes (SLM) are studied in various fields like analytical, chemical engineering, biotechnology, and biomedical engineering for the removal, pre-concentration, and recovery of targeted compounds [17,18]. They are mainly available in two forms flat sheet membranes (FSSLM) and hollow fiber (HFSLM). Lately, membrane processes, focusing on separation and extraction, can be integrated with advanced oxidation processes (AOPs) in several ways: as a pre-treatment to break down organic compounds in the feed stream, as a post-treatment for complete mineralization of non-rejected micropollutants in the permeate stream, or as a hybrid approach where both separation and degradation of pollutants are carried simultaneously [19]. AOPs are

defined by mainly the formation of hydroxyl radicals($OH^{\cdot}$) with high oxidizing power capable of transforming complex organic compounds to other smaller molecules, carbon dioxide, water, and inorganic ions [20]. Ozonation presents a unique feature that combines selective reaction with ozone molecules and unselective radical pathways with hydroxyl radicals to remove a wide spectrum of contaminants. The elimination of diclofenac by simple ozonation [21] or with the addition of UV/H_2O_2 [22], activated carbon [23], sonolysis [24] catalytic ozone [23] and Fenton-based processes [25] have been widely studied. The listed processes promoted mineralization but are faced with high energy costs, the formation of by-products, and the requirement of adding a disinfection final process [26].

AOPs are widely versatile and highly efficient for the abatement of various types of contaminants, yet they are less effective for the treatment of low-concentration pollutants and generate several toxic intermediates which at times are more harmful than the parent pollutants. AOPs usually request complementary treatments to remove such toxic byproducts that are generated alongside disinfection and oxidation effects. Numerous investigations have highlighted the viability and effectiveness of combining ozonation and membrane filtration to eliminate pharmaceutical and personal care products and their active by-products from water sources and wastewater [27,]. The majority of these studies focused on using ozone-based methods (O_3; O_3/H_2O_2 or O_3/UV) either as a preliminary stage before membrane filtration or as a post-treatment for both the filtrate and residue streams. For instance, Real et al. (2012) conducted a comparative study exploring the effectiveness of combining different chemical oxidation techniques, such as ozone (O_3), chlorine (Cl_2), ozone with hydrogen peroxide (O_3/H_2O_2), ultraviolet (UV) treatment and ultraviolet with hydrogen peroxide (UV/H_2O_2), with membrane filtration methods like ultrafiltration (UF) or nanofiltration (NF) to remove pharmaceutical compounds from water systems. The results confirm that using nanofiltration (NF) as an initial stage followed by ozonation was more effective in removing 97 % of pharmaceuticals from natural waters [28]. Nevertheless, Saquib et al. (2010) found that ultrafiltration (UF) used as a pretreatment with combined ozone and hydrogen peroxide had limited positive effects on removing organics from surface water [29]. Another study by Abdelmelek et al. (2011), examined the removal of diclofenac along with different types of pharmaceuticals RO retentate using ozonation [30]. They monitored the oxidation of organic matter in the retentate using excitation-emission matrix spectroscopy and were able to follow the evaluation of every contaminant used. Conversely, numerous research works have documented the practicality and effectiveness of membrane-catalyzed ozonation [31]

membrane filtration [32], or membrane-contact reactor systems for enhanced ozone dispersion and mass transfer [33]. However, these methods often encounter challenges such as membrane fouling, energy consumption, chemical use, environmental concerns, and scalability issues. To provide an efficient tertiary treatment for the removal and degradation of diclofenac, liquid membrane technology with ozone treatment has been investigated. To the best of our knowledge, the integration of supported liquid membrane separation and ozonation within a single unit has not been explored. The primary objective of this study is to develop an efficient method to remove diclofenac from water with FSSLM coupled with ozonation. The focus is on achieving selective removal of diclofenac from the water stream during transport through the membrane and subsequent application of ozonation in the stripping phase. Initially, FSSLM was selected to gain a thorough understanding of the removal process of diclofenac from the feed to the stripping phase. Various operational parameters, including different organic extractant concentrations, environmental water matrices, and different initial ozone concentrations and the effect of ozone on the polymeric membrane were examined to measure the effectiveness of this process. Additionally, the generated by product during the ozonation were identified. This approach provides a preliminary and in-depth assessment of the potential combination of SLM with ozonation before transitioning to more complex configurations.

2 Materials and Methods

2.1 Reagent and Chemicals

Diclofenac sodium salt (2-[(2,6-dichlorophenyl) amino] phenylacetic acid; CAS No. 15307-79-2) and its properties are listed in Table 1, and 5-hydroxydiclofenac ($C_{14}H_{11}Cl_2NO_3$) (2-[2-(2,6-dichloroanilino)-5-hydroxyphenyl]acetic acid, CAS No. 62248) was supplied by Sigma-Aldrich . Fresh solutions were prepared with adequate concentrations (1, 10, and 30 mg/L) in deionized water at ambient temperature (25 °C). The chosen concentrations were intentionally higher than those typically encountered in actual water samples.to facilitate more accurate monitoring and measurement of the removal efficiency using the available analytical techniques. Acetonitrile, NaOH, KI, HCL and NaCl, were all obtained as high purity reagents from Merck. Potassium Indigo tri-sulfonate and potassium iodide were used for detecting residual ozone in the samples and were obtained from Sigma Aldrich.

Table 3 Pharmaceutical characteristics.

Compound	Diclofenac sodium salt
Molecular weight (g/mol)	318.1
Molecular formula	$C_{14}H_{10}Cl_2NNaO_2$
pk$_a$	4.15
Log $_{kow}$	4.51

2.2 Supported liquid membrane (SLM)

Cyanex 923 (Cy923, 94%, Solvay), in the range of (0.126 to 0.757 mol/L) was selected to transport diclofenac after previously testing different organic extractants. The adequate concentration was diluted in commercial-grade kerosene. The diluent is known for its cost-effectiveness and low viscosity. The polymeric solid support used is Millipore polytetrafluoroethylene (PTFE). Further details regarding the membrane's specifications are provided in Table 2.

Table 4 Specifications of PTFE support (Fluoropore^{TM} FHLP04700).

Parameters	**Value**
Diameter (mm)	47
Pore diameter (µm)	0.45
Porosity (%)	85
Effective area (cm^2)	11.4
Thickness (µm)	150

Transport experiments were conducted using an experimental set-up similar to the one depicted by a previous study [34,35]. Solutions containing a specific concentration of diclofenac (DCF) were prepared using deionized water unless specified otherwise (such as real wastewater effluent or tap water). The permeation cell consists of two chambers (feed and stripping cell) of 220 cm^3 volume separated by the membrane. The PTFE membrane was submerged in a desired concentration of Cy923 in kerosene for a few minutes to effectively saturate the pores

of the membrane with the organic extractant. Following this, the saturated membrane was carefully removed and thoroughly rinsed with distilled water to eliminate any excess Cy923 and placed between the chamber cells. In each cell, the feed, containing diclofenac at a pH of 5, and the stripping phase consisting of distilled water at a pH of 10, were introduced. The feed and stripping cells were mechanically stirred at 1000 rpm to minimize interfacial resistance, and they were maintained at a constant room temperature of 23±2°C. Throughout the experiment, the pH of both aqueous phases was continuously monitored using a Crison GLP21 pH meter and adjusted as necessary with a few drops of 1 M HCl in the feed phase and 1 mol/L of NaOH in the stripping cell. All experiments were conducted in replications for accuracy.

The transport of DCF across the membrane is based on the diffusion mechanism through the liquid membrane. It was assumed that the diffusion resistance on both the feed and stripping sides could be ignored. Additionally, the interfacial chemical reactions involving the formation of the DCF/Cy923 complex within the membrane, as well as its decomposition during the stripping process, were considered instantaneous. Consequently, the permeability coefficient of diclofenac, defined as the rate of transport through the membrane, was determined for various extractant concentrations (as per Eq.4). This calculation was accomplished by combining the fundamental concepts outlined in the first Fick law of diffusion (as represented by Eq. 1) along with the mass balance of diclofenac in the feed (as detailed in Eq. 2)

$$.J = -D\frac{dC}{dx} \approx -D\frac{\Delta C}{\delta * \tau} \qquad \text{(Eq.1)}$$

Where J is the diffusive molar flux of DCF (mol /cm^2 h); D is the diffusion coefficient (cm^2/h); C is the concentration of diclofenac in the internal sides of the membrane (mol/L) and x is the position (m)

In addition, the mass balance of the pharmaceutical in the feed is given by the following equation:

Input + Generation – Output- consumption = Accumulation

Accumulation =-Output

Given there is no consumption, generation, or input, the accumulation is expressed as the rate of change of DCF over time in the feed and the output as the mass flow of transferred DCF to the receiving phase. The mass balance of DCF in the feed is expressed in (Eq.2):

Accumulation = - output

$$\frac{\mathrm{dmi}}{\mathrm{dt}} = \frac{\mathrm{VdC}}{\mathrm{dt}} = -\mathrm{N_{Out}} \qquad \text{(Eq.2)}$$

With the mass flow, N_{out} (mol/h) is equal to the molar flux J (mol/cm^2 h) multiplied by the area of the membrane A (cm^2)

$$\mathrm{Nout} = \mathrm{J} * \mathrm{A} \qquad \text{(Eq.3)}$$

Considering there is no accumulation in the membrane and combining (Eq.3) and (Eq 4), the permeability coefficient is determined:

$$ln\frac{C_t}{\mathrm{C_0}} = -\frac{\mathrm{P{\cdot}A}}{\mathrm{V}}\mathrm{t} \qquad \text{(Eq.4)}$$

Given P is the permeability coefficient (cm/h), V volume of the feed (cm^3), A area of the membrane (cm^2), C_t and C_0 are the concentration of diclofenac at a specific and initial time respectively and t the time (h) of the transport experiment.

2.3 Hybrid system: SLM and Ozonation

Ozone was produced in situ by the Anseros ozone generator (COM-AD-04) at various initial ozone concentrations (10, 28.5, and 45.3g O_3 /Nm^3) using pure oxygen. The flow rate was monitored with a flowmeter mounted on the Ozonator to regulate the feed gas entering the cell. Integrating ozone successively for the removal of pharmaceuticals from aqueous solution was conducted in a separate cell. Initially, ozone was initially introduced directly into the stripping cell of the FSSLM. However, this configuration was abandoned due to encountered issues where ozone diffused into the feed cell and caused undesired alterations of the polymeric support. It was observed that ozone diffused through the polymeric support and across the membrane from the stripping phase into the feed phase. Detailed information regarding the ozone diffusion through the PTFE membrane and the corresponding outcomes can be found in the supplementary materials. Alternatively, ozone was introduced in a separate cell as post-treatment to the flat sheet supported liquid membrane. Subsequently, it is applied after FSSLM, in a separate reactor to avoid any direct contact of ozone with the membrane surface. The feed was prepared using 10 mg/L of DCF dissolved in deionized water at pH=5 and a volume of 220 cm^3. O_3 was continuously bubbled at a flow rate of 150 L/h through a diffuser placed at the bottom of the reactor at room temperature (23 ±2 Cº). The stripping phase (with a volume of 220 cm^3 and a pH of 10) was circulated in a closed loop within the ozone reactor using a peristaltic pump. Any excess ozone was removed by passing the solution through absorption

bottles containing a 2% (w/v) potassium iodide solution. The experimental scheme and setup are shown in Figure 1. Samples were withdrawn from the feed and stripping cells at specific time intervals to evaluate the concentration of diclofenac.

2.4 Analytical method

The quantification of diclofenac transported across the membrane and the formation of its by-products was achieved using High-performance Liquid Chromatography (HPLC) on an Agilent 1100 Infinity series system equipped with a diode array detector set at 280 nm. The Zorbax C18 column (4x25 mm) was employed, and the mobile phase comprised a mixture of water and acetonitrile (60:40, v/v) with 25 mM formic acid [32]. Meanwhile, the identification of transformation products was conducted using a Thermo Scientific™ Orbitrap IDXTribrid mass spectrometer with an ESI interface. The Vanquish UHPLC Liquid Chromatograph in line with a C18 column (4 x 25 mm) provided by Agilent was used. Elution was isocratically performed with a mixture of 25 mM formic acid (A) and acetonitrile (B) at a 60/40 (A/B) ratio, and the entire runtime was 15 minutes. The Mass spectrometry detection involved heated electrospray ionization settings in both negative and positive ionization modes. Additionally, pH measurements were taken both from the feed and stripping phase.

Total Organic Carbon (TOC) measurements at initial and final times were carried out utilizing a Shimadzu TOC-L model analyzer both before and after treatment.

The examination of the polymeric support structure before and after contact with ozone was conducted through scanning electron microscopy (SEM) with a field-emission scanning electron microscope (FEGSEM, Quanta 400F).

Finally, the concentration of dissolved ozone transported through the membrane was determined through its reaction with neutral potassium iodide, and the concentration of liberated triiodide was quantified at a wavelength of 352 nm using UV-visible spectrophotometer on a Lovibond XD 700 instrument.

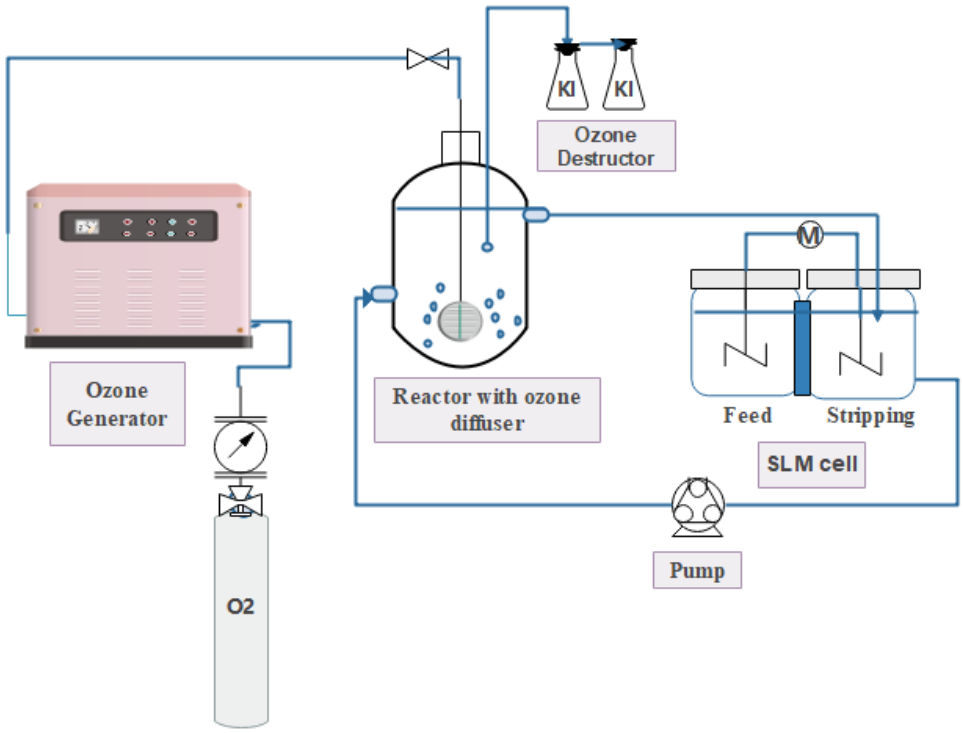


Figure 1 Experimental set up

3 Results and Discussion.

3.1 Diclofenac transfer in the FSSLM

By definition, the dissociation constant (pK_a) is used to determine the relative acidity or basicity of weakly ionizing compounds or their miscibility in aqueous solvent. The pK_a of DCF is 4.15, therefore at a pH lower than 4.15, the predominant species are the undissociated form of the contaminant: HA

$$HA \leftrightarrow A^- + H^+$$

Taking into account that Cy923 extracts neutral species, the pH of the dissolved diclofenac in water was measured to be approximately 5. As a result, the extraction process was conducted without making any adjustments to the pH in the feed solution. The organic carrier can solvate the undissociated form of the drug HA permitting the extraction of this molecule to the organic phase and the reaction equation for the extraction step:

$$\overline{Cy923} + HA \leftrightharpoons \overline{Cy923 \cdot HA}$$

The pharmaceutical substance forms a complex with the organic extractant and then moves through the membrane phase due to a concentration gradient. Eventually, it reaches the interface between the membrane and the product. At this point, the complex breaks apart due to the presence of hydroxide ions in the receiving phase. The reaction that takes place in the stripping phase is as follows:

$$\overline{Cy923 \cdot HA} + OH^- \leftrightharpoons \overline{Cy923} + A^- + H_2O$$

The performance is measured by calculating the permeability coefficient (cm/h) by combining the mass balance of solute in the feed cell and the 1st Fick law of diffusion. The rate of transport of DCF was found to be 7.1 cm/h with 0.47 mol/L of Cy923 diluted in kerosene.

3.2 Effect of organic extractant concentration

To optimize the transport of pharmaceuticals the concentration of extractant was increased and the permeability was calculated. The results depicted in **Figure 2** show that a higher permeability was obtained with a greater concentration of Cy923 (0.975 mol/L). As shown in Figure 2, an additional increase in Cy923 concentration has a noteworthy impact on permeability. This trend has been observed across various research papers that have explored the influence of extractant concentration on transport efficiency. The primary factors governing pharmaceutical transport are the diffusion coefficient and viscosity and they are related by the following expression [35]:

$$\text{Constant} = \mu^{\alpha} * D \qquad \text{(Eq. 5)}$$

Given D is the diffusion coefficient, μ is the viscosity of the mixture used.

Following the same procedure proposed by Pavón et al (2020) and neglecting any extraction of diclofenac by the diluent (kerosene), the exact relationship between the permeability, the extractant concentration, and their related viscosity can be determined [33]:

$$P_{DCF\,(\frac{cm}{h})} = 27.78 * [Cy923] * \mu^{-0.53.} \qquad \text{(Eq.6)}$$

With α ranging between 0.5-1 which is in accordance with several publications [35-36] P is in (cm/h), [Cy923] in (mol/L), and μ in (mPa·s)

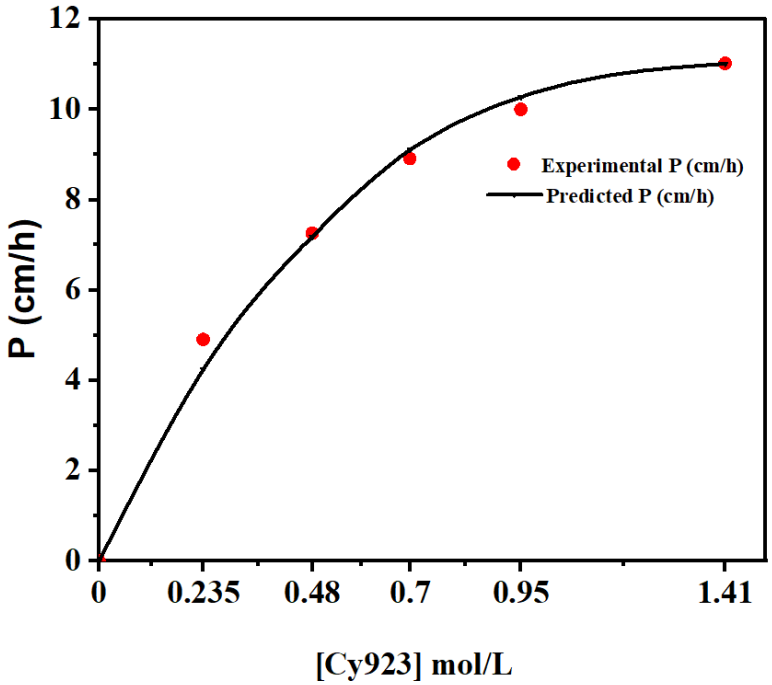


Figure 2 Permeability coefficient for different concentrations of Cy923.

3.3 Effect of water matrices

The transport of DCF with flat sheet SLM and 40 % Cy923 as an extractant was tested in real environmental matrices. Tap water and wastewater treatment plant effluent samples were spiked with 10 mg/L of diclofenac and the pH was adjusted to 5. The operational conditions employed were identical to the ones in section 3.1. The obtained results (shown in Figure 3) demonstrate a slight increase in the permeability coefficient with both tap water and real wastewater effluent samples. The substantial presence of diverse ions in the actual water matrices can effectively enhance the elimination of diclofenac from aqueous solutions. On the other hand, Güell et al (2010) tested the application of SLM system to remove arsenic acid from real water matrices, tap water, and river water. The results obtained indicated that the presence of various ions in the natural waters had no major differences in the values of permeability obtained [37]. The variance in permeability obtained in the current study can be explained by the increase of the undissociated form of diclofenac in the feed which promotes the extraction with Cy923. Subsequently, the effect of varying concentrations of NaCl on the transport of diclofenac was investigated. SLM experiments were carried out by introducing a range of NaCl concentrations into the feed (from 0.2 to 1 mol/L), with 0.94 mol/L Cy923 as the organic extractant. The feed solution was maintained at a pH of approximately 5, while the stripping phase was set at 10.

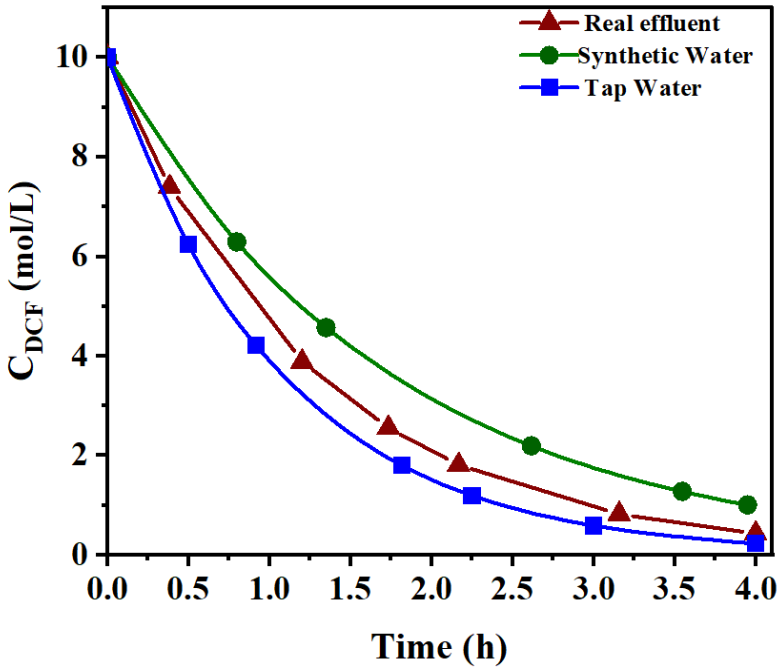


Figure 3 Concentration of DCF in different water matrices.

As shown in the outcome of Figure 3 the highest permeability coefficient was obtained with 0.1 M of NaCl in the feed. As a result, the ionic species within the feed solution can influence the efficiency of extraction. When considering the reactions of diclofenac and Cy923 in the aqueous phase, the equilibrium constant for the reaction can be expressed as follows:

$$k_{ex} = \frac{[\overline{Cy923 \cdot HA}]}{[HA]*[Cy923]} \quad \text{(Eq.7)}$$

In addition, in non-ideal systems, the equilibrium description is expressed by the thermodynamic chemical equilibrium equation. Thus, the thermodynamic dissociation constant, expressed in terms of activities a_i of species i, are as follows [38]:

$$Kc = \frac{a_{A^-} * a_{H^+}}{a_{HA}} = \frac{[A^-]*\gamma_{A^-}*[H^+]*\gamma_{H^+}}{[HA]*\gamma_{HA}} \quad \text{(Eq. 8)}$$

Taking into account the acidity constant of diclofenac in water:

$$Ka = \frac{[A^-]\cdot[H^+]}{[HA]} \quad \text{(Eq. 9)}$$

The equation relating the ionic strength (Eq.10) and the dissociation constant is obtained by combining (Eq 8) and (Eq 9):

$$Kc = Ka \cdot \gamma_{A^-} \cdot \gamma_{H^+} \quad \text{(Eq. 10)}$$

According to Davies equation, after the addition of ionic species, the ionic strength increases whereas the activity of species decreases [39]. Taking into account that Kc is a constant (Eq 10), the dissociation of diclofenac will increase to maintain a constant value. Hence, the concentration of undissociated diclofenac in the feed solution will be higher, thereby enhancing the extraction process with Cy923. As shown, the transport of DCF increased with the concentration of sodium chloride in the solution where the permeability with 40% (v/v) Cy923 was found to be 28 cm/h with 0.1 M of NaCl in the feed The results obtained are in accordance with the previous studies for the extraction of metals, phenols and batteries chemicals with Cy923 [40].

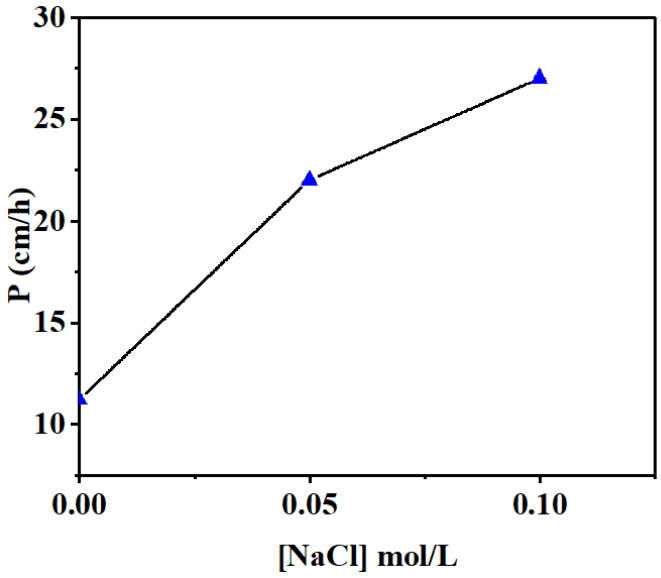


Figure 4. Effect of NaCl concentration on the permeability coefficient.

3.4 Hybrid system: SLM and Ozonation

Ozone is a powerful oxidant that potentially reacts with various organic compounds. It is a well-established technique for wastewater treatment, disinfection, odour, and colour removal [41].The decomposition reaction of ozone yields two molecules of hydroxyl radicals via a radical chain reaction:

$$3O_3 + HO^- + H^+ \rightarrow 2HO^{\cdot} + 4O_2$$

Diclofenac can be oxidized either through the direct reaction with ozone molecules or indirectly with hydroxyl radicals to produce by-products depending on the operational conditions adapted in the treatment process:

$$O_3 + DCF \rightarrow BP + O_2^{\cdot}$$

$$HO^{\cdot} + DCF \rightarrow BP + HO_2$$

While ozone has proven to be an effective and environmentally friendly method for water treatment, it is constrained by its limited mass transfer in water, often necessitating a substantial surface area for contact. This can result in high energy consumption and operational requirements [42, 43]. In fact, a recent review has highlighted the substantial cost of ozone, which can reach as high as $346 per day for a water treatment plant with a capacity of 0.38 hm^3/day [44].

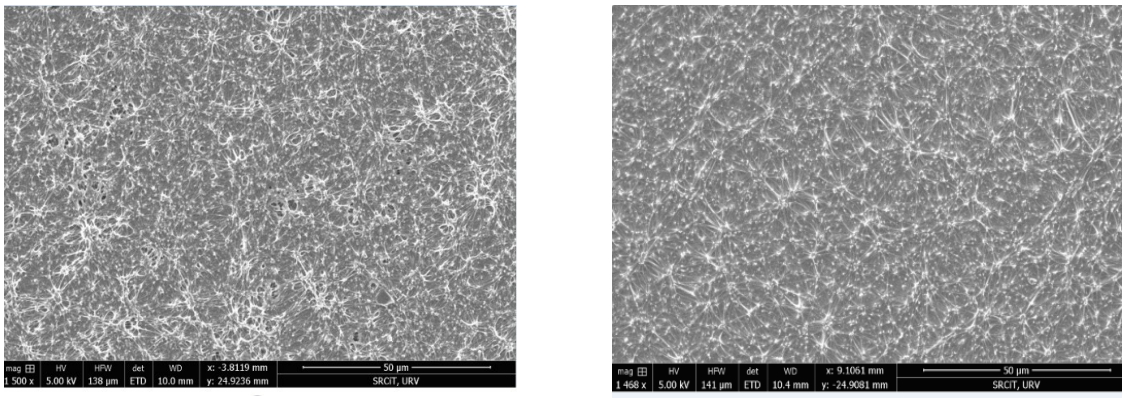
However, the integration of FSSLM prior to ozone treatment offers a promising solution. SLM enhances the preconcentration potential for compounds like diclofenac and increases the selectivity of oxidation towards this specific pharmaceutical, minimizing the need for extensive ozonation. This innovative approach not only improves the overall efficiency of the treatment process but also significantly reduces the consumption of ozone, making it a more cost-effective and sustainable solution for pharmaceutical pollutant removal in water treatment.

To address the challenges linked to ozonation techniques and improve the breakdown of diclofenac, a selective transport method using a liquid membrane as described in previous sections has been integrated as a prior step to the disinfection phase with ozone. The primary aim of this study is to extract the diclofenac that remains after conventional treatment and subject it to ozone treatment to encourage its breakdown and the mineralization of both the primary product and any by-products formed. The goal is to combine these two treatments in a mode to optimize membrane specifications and performance with minimal impact and alteration. Hence implementing ozone in separate cells.

Up to the present day, the most prevalent approach for employing ozonation in conjunction with polymeric membranes is as an alternative method for enhancing gas-liquid mass transfer [45]. These membranes serve as inert, permeable barriers between the liquid and gas phases. However, the scalability of ozone membrane contactors has often been hindered by the stability

of polymeric membranes when exposed to ozone molecules over extended periods. It's crucial to consider the potential for material alteration after prolonged exposure to ozone.

Direct contact of ozone with the PTFE polymeric membrane is discarded for several reasons but mainly to avoid any modification in the membrane specifications. In fact, the performance of both PVDF and PTFE polymeric support after exposure to ozone was investigated to treat dye wastewater [45]. The results obtained confirm that these membranes can enhance the dissolution of ozone in water however the alteration of their surfaces cannot be avoided [45, 46] In addition, the lifetime of polymeric membranes is estimated to be between one and five years with high exposure to ozone [44]. To confirm the statement with the published studies, the surface of PTFE membrane in direct contact with ozone after 6 hours, was examined and the scanning electron micrographs of its outer surface are shown in Figure. 5. As shown from the outer surface morphology, no significant modifications were noticed, thus the membrane exposed to ozone exhibits more stretched pores compared to the intact membrane. It is well known that the wider the pore diameter the more is probable for the organic extractant to leach out from the membrane.



(a) **(b)**

Figure 5.SEM images of PTFE membrane surface: **(a)** Ozone exposure; **(b)** Intact membrane

3.5 Transport of DCF in SLM at different Ozone concentrations

Experiments were conducted following the experimental setup illustrated in Figure. 1. In this setup, 10 mg/L of diclofenac was transported from the feed at pH=5, to the stripping phase with a pH=10 using 40% Cy923. The stripping phase was continuously recirculated into the ozone reactor, where three different initial gas flow rates were tested. The results shown in

Figure 6 illustrates the changes in diclofenac (DCF) concentration over time in both the feed and the stripping phase.

Ozone is decomposed to produce $OH^{\bullet}$ radical at basic conditions. The reaction of diclofenac with $OH^{\bullet}$ radical is very fast and therefore the diclofenac transported through the membrane was completely eliminated in less than 1 hour for all three different initial ozone concentrations**.** Concerning the feed phase, the transportation of DCF using this method appeared to be similar to the process without applying ozone, and the permeability coefficient was found to be 10.2 cm/h. According to research by Huber et al. (2005) achieving complete oxidation and degradation of DCF through ozone treatment requires a minimum molar ratio of ozone (O_3) to diclofenac of approximately 10:1 [45,47]. Therefore, it's crucial to ensure a sufficient supply of ozone to effectively remove pharmaceutical contaminants and their by-products from the solution.

To evaluate the effectiveness of this treatment, total organic carbon (TOC) levels were measured in both the feed phase and the stripping phase before and after the 4-hour experiment. Notably, the highest TOC removal rates were achieved when the initial ozone concentration was 45.3 g/Nm^3, with more than 83% TOC removal observed in the feed phase and 72% in the stripping phase. This indicates a substantial reduction in organic carbon content in the water.

Following these experiments, the oxidation with ozone, following a selective transport process involving 10 mg/L of DCF, led to a significant level of mineralization after three hours. However, it's important to note that the disappearance of the target pollutant alone does not necessarily indicate the success of a water treatment method. In many cases, the by-products generated during treatment can be even more harmful than the original pollutant. Therefore, the identification of by-products is conducted.

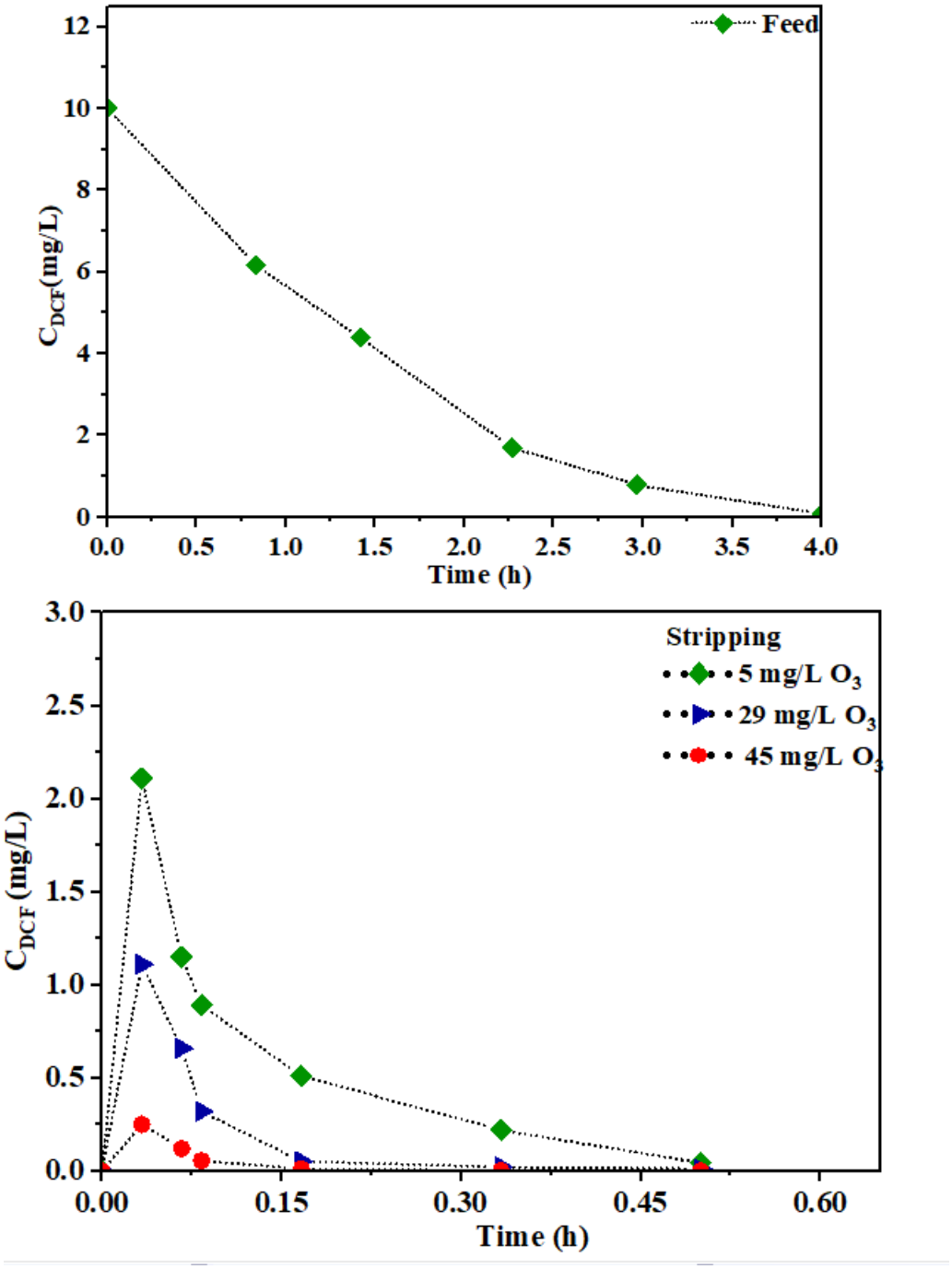


Figure 6. Concentration of Diclofenac in the feed and stripping cell in the hybrid system

3.6 By product Identification.

Complete removal of the Diclofenac transported through the membrane resulted in the identification of 9 by-products when applying ozone in a separate cell. High-resolution MS data for the identified by-products containing the measured and exact mass of the detected molecular ions are shown in Table 3.

Table 3. Identified by-products with LC-MS in positive and negative mode.

Compound	High-Resolution Ms data	Molecular Weight (g/mol)	Retention time (min)	Molecular Formula	Reference
	Exact measured Molecular ion $[M-H]^-$				
DCF	296.02	295.01	10.4	$C_{14}H_{12}NO_3Cl_2$	[47][48] [49]
D1	311.02	312.01	3.7	$C_{14}H_{12}NO_3Cl_2$	[47][48] [49]
D2	308.99	310.01.	2.94	$C_{14}H_{10}NO_3Cl_2$	[47][48] [49]
D3	327.01	328.13	1.46	$C_{14}H_{12}NO_4Cl_2$	[47][49]
D3a	327.01	328.13	1.74	$C_{14}H_{12}NO_4Cl_2$	[47][48] [49]
D5	284.99	286.01	3.0	$C_{12}H_{10}NO_3Cl_2$	[47][46]
D6	281.0	282.01	1.62	$C_{13}H_{10}NO_2Cl_2$	[47][48] [49]
D7	277.05	278.11	1.62	$C_{14}H_{10}NOCl_2$	[47][48] [49]
D8	296.99	298.01	3.05	$C_{13}H_{10}NO_3Cl_2$	[47][48] [49]
D9	258.97	259.99	1.39	$C_{10}H_8NO_3Cl_2$	[48] [49]

Ozonation of DCF in the stripping phase at basic conditions mainly involved hydroxylation reaction. The addition of hydroxyl groups in this case is indirectly via a hydroxyl radical produced from the reaction of ozone in an aqueous solution [46-48] The results obtained in Table 3 confirm the hydroxylation of DCF through the increase of one or more oxygen atoms with respect to DCF molecular. Although the reaction of the pharmaceutical with ozone molecules needs to be taken into consideration, including O_3-addition at different sites of two benzene rings and amino groups of diclofenac [44, 45] have been investigated. The evolution of by-products shifts during the reaction as some compounds decrease while new ones are formed. Initially, D1 (5 hydroxydiclofenac) was found in greatest abundance indicating that the DCF degradation is initiated by the hydroxylation of the phenylacetic ring. 5-hydroxydiclofenac was identified and analysed and the evolution of its concentration is shown in Figure 7.

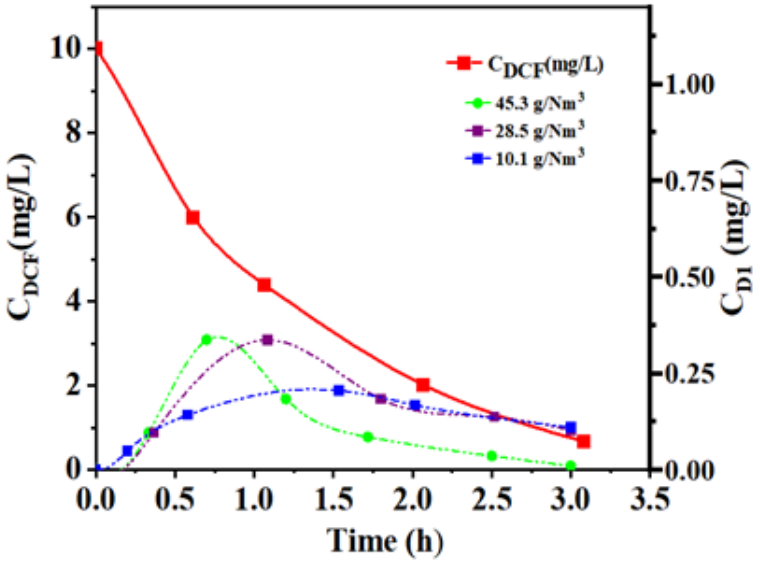


Figure 7 The evolution of DCF in the feed and D1 concentration in the stripping with time at different initial ozone gas concentrations.

The primary by-product of diclofenac was successfully identified and quantified. The highest concentration of this by-product, referred to as D1, was observed at high ozone concentrations reaching 0.35 mg/L with an initial DCF concentration of 10 mg/L. This trend aligns with previous findings reported by several studies that investigated the degradation of diclofenac under various ozone concentrations [43, 50]. It's worth noting that diclofenac's degradation with ozone can follow different pathways depending on the operational conditions.

D1 is a commonly detected and quantified by-product of diclofenac in such processes. Interestingly, after three hours, the concentration of D1 decreased significantly, reaching a minimum value when the solution was recirculated in the ozonation reactor. Moreover, the results of TOC after three hours of experimentation revealed a 72% decrease compared to its initial value (10 mg/L DCF). This outcome suggests a promising application of supported liquid membranes for selectively transporting and pre-concentrating streams containing emerging pharmaceutical contaminants. Subsequently, these contaminants can be effectively degraded with continuous exposure to ozone.However, it's crucial to highlight the importance of conducting toxicity assessments to measure the potential harm caused by these by-products. This information is vital for making informed recommendations regarding the safety and suitability of this treatment method in real-world applications, particularly with respect to environmental and human health.

4 Conclusion

The emerging of pharmaceutical contaminants and especially antibiotic residues in the environment is a crucial complex that requires more upgraded wastewater treatment technologies. Most conventional technologies are limited by their removal efficiencies, high operation costs, and increased energy consumption.

In this study, supported liquid membrane coupled with the oxidation method was evaluated as an alternative effective method for the removal of pharmaceutical diclofenac and its degradation products. The feasibility of the hybrid process was tested in a laboratory-scale flat sheet membrane in order to scale it up for a preconcentration and using the hollow fiber modules.

Diclofenac was transported through the liquid membrane with 0.94 mol/L equivalent to 40% (v/v) Cy923 at a transfer rate of 10.2 cm/h. and the equation to predict the permeability coefficients for DCF depending on the Cy923 concentration and the organic phase viscosity was calculated. Supported liquid membrane was tested with real water matrices and the removal of pharmaceutical contaminants was not influenced by the presence of counterions. Following that, ozone was applied to react with the extracted pharmaceutical to achieve a high degree of mineralization. The main contaminants were removed after three hours. The reaction of diclofenac with ozone generated 9 by-products and the formation of 5-hydroxydiclofenac was identified and quantified. The proposed approach leads to the additional removal of DCF and its intermediate compounds while preventing any contact of membrane materials with ozone molecules. Supported liquid membrane are simple and low-cost methods that can be successively integrated with well-established technologies like ozone for water treatment.

5 Acknowledgements

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6 References

[1] Agüera, A., Pérez Estrada, L. A., Ferrer, I., Thurman, E. M., Malato, S., Fernández-Alba, A. R. (2005). Application of time-of-flight mass spectrometry to the analysis of

phototransformation products of diclofenac in water under natural sunlight. Journal of Mass Spectrometry, 40(7), 908–915. https://doi.org/10.1002/jms.867

[2] Alessandretti, I., Rigueto, C. V., Nazari, M. T., Rosseto, M., & Dettmer, A. (2021). Removal of diclofenac from wastewater: A comprehensive review of detection, characteristics and tertiary treatment techniques. Journal of Environmental Chemical Engineering, 9(6), 106743. doi:10.1016/j.jece.2021.106743

[3] Rastogi, A., Tiwari, M. K., & Ghangrekar, M. M. (2021). A review on environmental occurrence, toxicity and microbial degradation of non-steroidal anti-inflammatory drugs (nsaids). Journal of Environmental Management, 300, 113694. doi:10.1016/j.jenvman.2021.113694

[4] Reygaert, W.C., (2018). An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiology, 4(3), 482–501. https://doi.org/10.3934/microbiol.2018.3.482

[5] Mussa, Z. H., Al-Qaim, F. F., Jawad, A. H., Scholz, M., & Yaseen, Z. M. (2022). A comprehensive review for removal of non-steroidal anti-inflammatory drugs attained from wastewater observations using carbon-based anodic oxidation process. Toxics, 10(10), 598. doi:10.3390/toxics10100598.

[6] Besha, A. T., Gebreyohannes, A. Y., Tufa, R. A., Bekele, D. N., Curcio, E., Giorno, L. (2017). Removal of emerging micropollutants by activated sludge process and membrane bioreactors and the effects of micropollutants on membrane fouling: A Review. Journal of Environmental Chemical Engineering, 5(3), 2395-2414. doi:10.1016/j.jece.2017.04.027

[7] Patel, M., Kumar, R., Kishor, K., Mlsna, T., Pittman, C. U., Mohan, D. (2019). Pharmaceuticals of emerging concern in aquatic systems: Chemistry, occurrence, effects, and removal methods. Chemical Reviews, 119(6), 3510-3673. doi:10.1021/acs.chemrev.8b00299.

[8] Miklos, D. B., Remy, C., Jekel, M., Linden, K. G., Drewes, J. E., Hübner, U. (2018). Evaluation of advanced oxidation processes for water and wastewater treatment – A critical review. Water Research, 139, 118-131. doi:10.1016/j.watres.2018.03.042.

[9] Landry, K. A., Sun, P., Huang, C.-H., Boyer, T. H. (2015). Ion-exchange selectivity of diclofenac, ibuprofen, ketoprofen, and naproxen in ureolyzed human urine. Water Research, 68, 510–521. https://doi.org/10.1016/j.watres.2014.09.056.

[10] Ansarimehr, M., Rahbar-Kelishami, A., Shayesteh, H. (2022). Diclofenac sodium solvent extraction based on two-phase flow patterns. Chemical Engineering & Technology, 46(2), 326–333. https://doi.org/10.1002/ceat.202100492

[11] Al-Hazmi, H. E., Mohammadi, A., Hejna, A., Majtacz, J., Esmaeili, A., Habibzadeh, S., Saeb, M. R., Badawi, M., Lima, E. C., Mąkinia, J. (2023). Wastewater reuse in agriculture: Prospects and challenges. *Environmental Research*, *236*, 116711. https://doi.org/10.1016/j.envres.2023.116711

[12] Obaideen, K., Shehata, N., Sayed, E. T., Abdelkareem, M. A., Mahmoud, M. S., Olabi, A. G. (2022). The role of wastewater treatment in Achieving Sustainable Development Goals (sdgs) and sustainability guideline. *Energy Nexus*, *7*, 100112. https://doi.org/10.1016/j.nexus.2022.100112

[13] Kostanyan, A. E., Voshkin, A. A., Belova, V. V., Zakhodyaeva, Y. A. (2023). Modelling and comparative analysis of different methods of liquid membrane separations. *Membranes*, *13*(6), 554. https://doi.org/10.3390/membranes13060554

[14] Malhotra, B. D., Ali, Md. A. (2018). Nanostructured biomaterials for in vivo biosensors. *Nanomaterials for Biosensors*, 183–219. https://doi.org/10.1016/b978-0-323-44923-6.00007-8

[15] Faramarzi, H., Arzani, M., Khosravanian, A., Mahdavi, H., Bakhtiari, O., Mohammadi, T. (2023). An overview of practical aspects of the design and application of

polymeric/ceramic supports in supported liquid membranes for gas separation. *Industrial & Engineering Chemistry Research*, *62*(32), 12443–12461. https://doi.org/10.1021/acs.iecr.3c00830

[16] San Roman, M. F., Bringas, E., Ibañez, R., Ortiz, I. (2010). Liquid Membrane Technology: Fundamentals and review of its applications. Journal of Chemical Technology & Biotechnology, 85(1), 2–10. https://doi.org/10.1002/jctb.2252

[17] Balasubramanian, A., Venkatesan, S. (2012). Removal of phenolic compounds from aqueous solutions by emulsion liquid membrane containing ionic liquid [bmim]+[pf6]− in tributyl phosphate. Desalination, 289, 27–34. https://doi.org/10.1016/j.desal.2011.12.027

[18] Santiago-Santiago, L. A., Reyes-Aguilera, J. A., Gonzalez, M. P., Cholico-Gonzalez, D., Avila-Rodríguez, M. (2012). Separation of Bi(III) and Sb(III) from Cu(II) HCl/H_2SO_4 mixed media by supported liquid membranes using Cyanex 921 as carrier. Industrial & Engineering Chemistry Research, 51(46), 15184–15192. https://doi.org/10.1021/ie301447x.

[19] Ganiyu, S. O., van Hullebusch, E. D., Cretin, M., Esposito, G., Oturan, M. A. (2015). Coupling of membrane filtration and advanced oxidation processes for removal of pharmaceutical residues: A critical review. Separation and Purification Technology, 156, 891–914. https://doi.org/10.1016/j.seppur.2015.09.059

[20] Qiu, Z., Sun, J., Han, D., Wei, F., Mei, Q., Wei, B. (2020). Ozonation of diclofenac in the aqueous solution: Mechanism, kinetics and ecotoxicity assessment. Environmental Research, 188, 109713. doi:10.1016/j.envres.2020.109713

[21] F.J. Beltrán, P. Pocostales, P. Alvarez, A. Oropesa, (2009). Diclofenac removal from water with ozone and activated carbon, J. Hazard. Mater. 163 768–776, https:// doi.org/10.1016/j.jhazmat.2008.07.033.

[22] Naddeo, V., Ricco, D., Scannapieco, D., Belgiorno, V. (2012). Degradation of antibiotics in wastewater during sonolysis, ozonation, and their simultaneous application: Operating conditions effects and processes evaluation. International Journal of Photoenergy, 2012, 1-7. doi:10.1155/2012/62427012

[23] Gao, G., Chu, W., Chen, Z., Shen, J. (2017). Catalytic ozonation of diclofenac with iron silicate-loaded pumice in aqueous solution. Water Supply, 17(5), 1458-1467. doi:10.2166/ws.2017.048

[24] Yaghmaeian, K., Yousefi, N., Bagheri, A., Mahvi, A. H., Nabizadeh, R., Dehghani, M. H., Akbari-adergani, B. (2022). Combination of advanced nano-fenton process and sonication for destruction of diclofenac and variables optimization using response surface method. Scientific Reports, 12(1). doi:10.1038/s41598-022-25349-1

[25] Othman, N. H., Alias, N. H., Fuzil, N. S., Marpani, F., Shahruddin, M. Z., Chew, C. M., Ismail, A. F. (2021). A review on the use of membrane technology systems in developing countries. Membranes, 12(1), 30. doi:10.3390/membranes12010030

[26] Kwarciak-Kozłowska, A. (2019). Removal of pharmaceuticals and personal care products by ozonation, advanced oxidation processes, and membrane separation. Pharmaceuticals and Personal Care Products: Waste Management and Treatment Technology, 151-171. doi:10.1016/b978-0-12-816189-0.00007-x

[27] Ganthavee, V., & Trzcinski, A. P. (2023). Removal of pharmaceutically active compounds from wastewater using adsorption coupled with electrochemical oxidation technology: A critical review. *Journal of Industrial and Engineering Chemistry*, *126*, 20–35. https://doi.org/10.1016/j.jiec.2023.06.003

[28] Real, F. J., Benitez, F. J., Acero, J. L., Roldan, G. (2012). Combined chemical oxidation and membrane filtration techniques applied to the removal of some selected pharmaceuticals from Water Systems. Journal of Environmental Science and Health,PartA,47(4),522–533.https://doi.org/10.1080/10934529.2012.650549

[29] Saquib, M., Vinckier, C., Van der Bruggen, B. (2010). The effect of UF on the efficiency of O3/H2O2 for the removal of organics from surface water. Desalination, 260(1–3), 39–42. https://doi.org/10.1016/j.desal.2010.05.003

[30] Abdelmelek, S. B., Greaves, J., Ishida, K. P., Cooper, W. J., Song, W. (2011). Removal of pharmaceutical and personal care products from reverse osmosis retentate using advanced oxidation processes. Environmental Science & Technology, 45(8), 3665–3671. https://doi.org/10.1021/es104287n

[31] Psaltou, S., Zouboulis, A. (2020). Catalytic ozonation and membrane contactors—a review concerning fouling occurrence and pollutant removal. Water, 12(11), 2964. doi:10.3390/w12112964

[32] Huang, F. Y., Arning, A. (2019). Performance comparison between polyvinylidene fluoride and polytetrafluoroethylene hollow fiber membranes for direct contact membrane distillation. Membranes, 9(4), 52. doi:10.3390/membranes9040052

[33] Peyrelasse, C., Jacob, M., Lallement, A. (2022). Multicriteria comparison of Ozonation, membrane filtration, and activated carbon for the treatment of recalcitrant organics in industrial effluent: A conceptual study. Environmental Processes, 9(1). doi:10.1007/s40710-022-00563-1.

[34] Farah, M., Giralt, J., Stüber, F., Font, J., Fabregat, A., Fortuny, A. (2022). Supported liquid membranes for the removal of pharmaceuticals from Aqueous Solutions. Journal of Water Process Engineering, 49, 103170. doi:10.1016/j.jwpe.2022.103170

[35] Pavón, S., Fortuny, A., Coll, M. T., Bertau, M., & Sastre, A. M. (2020). Permeability dependencies on the carrier concentration and membrane viscosity for Y(III) and Eu(III) transport by using liquid membranes. Separation and Purification Technology, 239, 116573 https://doi.org/10.1016/j.seppur.2020.116573

[36] Hiss, T.G. and Cussler, E.L. (1973), Diffusion in high viscosity liquids. AIChE J., 19: 698-703. https://doi.org/10.1002/aic.690190404

[37] Güell, R., Fontàs, C., Salvadó, V., Anticó, E. (2010). Modelling of liquid–liquid extraction and liquid membrane separation of arsenic species in environmental matrices. Separation and Purification Technology, 72(3), 319–325. https://doi.org/10.1016/j.seppur.2010.02.023

[38] Minami, K., & Kakiuchi, T. (2013). Determination of single-ion activity coefficients of hydrogen and bromide ions in aqueous hydrobromic acid solutions based on an ionic liquid salt bridge. Electrochimica Acta, 110, 822–828. https://doi.org/10.1016/j.electacta.2013.04.104

[39] Bird, R. B. (2002). Transport phenomena. Applied Mechanics Reviews, 55(1). https://doi.org/10.1115/1.1424298

[40] Dewulf, B., Batchu, N. K., Binnemans, K. (2020). Enhanced separation of neodymium and dysprosium by nonaqueous solvent extraction from a polyethylene glycol 200 phase using the neutral extractant Cyanex 923. ACS Sustainable Chemistry & Engineering, 8(51), 19032–19039. https://doi.org/10.1021/acssuschemeng.0c07207

[41] Mansas, C., Mendret, J., Brosillon, S., Ayral, A. (2020). Coupling catalytic ozonation and membrane separation: A Review. Separation and Purification Technology, 236, 116221. https://doi.org/10.1016/j.seppur.2019.116221

[42] Prada-Vásquez, M. A., Estrada-Flórez, S. E., Serna-Galvis, E. A., Torres-Palma, R. A. (2021). Developments in the intensification of photo-fenton and ozonation-based processes for the removal of contaminants of emerging concern in Ibero-american countries. Science of The Total Environment, 765, 142699. https://doi.org/10.1016/j.scitotenv.2020.142699

[43] Huber M, Göbel A, Joss A, Hermann N, Löffler D, Mcardell , C. (2005) Oxidation of Pharmaceuticals during ozonation of municipal wastewater effluents: a pilot study. Environ Sci Technol., 39: 4290-9. http://dx.doi.org/10.1021/es048396s

[44] Mundy, B., Kuhnel, B., Hunter, G., Jarnis, R., Funk, D., Walker, S., Burns, N., Drago, J., Nezgod, W., Huang, J., Rakness, K., Jasim, S., Joost, R., Kim, R., Muri, J., Nattress, J., Oneby, M., Sosebee, A., Thompson, C., Schulz, C. (2018). A review of ozone systems costs for municipal applications. report by the Municipal Committee – Ioa Pan American Group. Ozone: Science & Engineering, 40(4), 266–274. https://doi.org/10.1080/01919512.2018.1467187

[45] Bamperng, S., Suwannachart, T., Atchariyawut, S., Jiraratananon, R. (2010). Ozonation of dye wastewater by membrane contactor using PVDF and PTFE Membranes. Separation and Purification Technology, 72(2), 186–193. https://doi.org/10.1016/j.seppur.2010.02.006

[46] Santos, F. R., Borges, C. P., & Fonseca, F. V. (2015). Polymeric materials for membrane contactor devices applied to water treatment by ozonation. Materials Research, 18(5), 1015–1022. https://doi.org/10.1590/1516-1439.016715

[47] Coelho, A. D., Sans, C., Agüera, A., Gómez, M. J., Esplugas, S., Dezotti, M. (2009). Effects of ozone pre-treatment on diclofenac: Intermediates, biodegradability and toxicity assessment. Science of The Total Environment, 407(11), 3572–3578. https://doi.org/10.1016/j.scitotenv.2009.01.013

[48] Monteagudo, J. M., El-taliawy, H., Durán, A., Caro, G., Bester, K. (2018). Sono-activated persulfate oxidation of diclofenac: Degradation, kinetics, pathway and contribution of the different radicals involved. Journal of Hazardous Materials, 357, 457–465. https://doi.org/10.1016/j.jhazmat.2018.06.031

[49] Alharbi, S. K., Ansari, A. J., Nghiem, L. D., Price, W. E. (2022). New transformation products from ozonation and photolysis of diclofenac in the aqueous phase. Process Safety and Environmental Protection, 157, 106–114. https://doi.org/10.1016/j.psep.2021.10.050

[50] Kråkström, M., Saeid, S., Tolvanen, P., Kumar, N., Salmi, T., Kronberg, L., Eklund, P. (2021). Identification and quantification of transformation products formed during the ozonation of the non-steroidal anti-inflammatory pharmaceuticals ibuprofen and diclofenac. Ozone: Science & Engineering, 44(2), 157–171. https://doi.org/10.1080/01919512.2021.1898928

Chapter 5 Hollow Fiber Liquid Membrane: A Promising Approach for Elimination of Pharmaceutical Compounds from wastewater.

Abstract

Pharmaceutical compounds present in water pose significant challenges, particularly due to their low concentrations in water streams. Hollow fiber liquid membranes provide a flexible and easily manageable solution, enabling the concentration of specific contaminants. This concentration step significantly improves their effective removal from water systems.

The study focused on using hollow fiber liquid membrane technology to effectively remove diclofenac (DCF) and ibuprofen (IBU), two pharmaceutical compounds. A concentration of 40% Cyanex 923 (Cy923) dissolved in kerosene was selected as the preferred extractant due to its stability and quick extraction properties. The stability of the system was tested with a pseudo-emulsion, enabling repeated use of the system. Additionally, an analytical model was developed to calculate the membrane's permeability. In order to enhance the degradation and mineralization of the pharmaceutical compounds and their byproducts, ozonation was integrated with the hollow fiber liquid membrane system in a single system. Measurement of total organic carbon (TOC) revealed a significant reduction of 72% for diclofenac and 57% for ibuprofen with an initial ozone concentration of 10 mg/L and operating under the optimal conditions of hollow fiber liquid membrane.

Keywords: Liquid Membrane, Pharmaceutical Compounds, Ozonation; Neutral extractant ; Stability.

1 Introduction

Membrane-based separation techniques have gained significant attention over conventional methods like solvent extraction, precipitation, and ion exchange [1]. Particularly, liquid membrane (LM) processes are well known for their minimal extractant requirement, sustained operational effectiveness, and remarkable selectivity. Their concept involves the use of an organic extractant to selectively transport certain components or substances from one solution to another and the ability to combine extraction and stripping within a single unit. In this context, liquid membranes are widely employed in various applications, including extraction processes, chemical separations, and environmental remediation. They offer advantages such as high selectivity and efficiency, making them a valuable tool in industries ranging from pharmaceuticals to wastewater treatment. The composition of the liquid membrane can vary depending on the specific application and the substances being separated or transported [2] [3]. Supported liquid membranes (SLMs) consist of an organic solvent held within the pores of hydrophobic solid support. They are available in two configurations including flat sheets and hollow fiber. However, at a larger scale, the most common configuration adapted is the hollow fiber. Hollow fiber-supported liquid membranes (HFSLMs) are commonly studied for industrial application and implementation as they offer a large interfacial area per volume unit and easy regeneration of the degraded membranes [3]. HFSLM has been used in various applications to remove phenol, carboxylic acids, arsenic, and several metals. Also, they are adapted for analytical detection and environmental analysis. Patil el al. (2017) discussed the selective separation of different carboxylic acids such as acetic acid, phenylacetic acid, and formic acid from diluted streams with aliphatic amines using hollow fiber liquid membrane techniques [4]. In recent studies, the combination of HFSLM extraction and HPLC-UV analysis has showcased its capabilities in quantifying five bisphenols present in environmental water samples. This approach not only ensures precise quantification and reproducibility but also combines the extraction, clean-up, and enrichment processes into a single step [5]. They are also applied for extracting various drugs and pharmaceutical compounds from water for chromatographic analysis using green solvent [6].

However, it is essential to conduct a comprehensive study to enhance the performance of hollow fiber membranes when it comes to efficiently removing trace pharmaceutical concentrations from water. This is especially crucial for their potential large-scale applications in wastewater treatment and industrial water treatment [7, 8]. One of the key elements to consider is the stability of these membranes during the process which can limit their performance. The problem of instability associated with LM is caused by the loss of the organic

extractant out of the pores of the support due to different operational and physiochemical factors [9]. To overcome these issues in HFSLM, a pseudo-emulsion-based hollow fiber supported liquid membrane (PEHFSLM) has been developed to enhance stability and long-term performance. This technique combines the properties associated with emulsion liquid membrane by offering a greater surface area and maintaining continuous transfer of organic solution to the porous support. PEHFSLM is used over a wide range of organic extractants. To remove different contaminants from water [10]. Shirasangi et al. (2021) conducted a comparison between hollow fiber-supported liquid membrane (HFSLM) and pseudo-emulsion hollow fiber membrane strip dispersion (PEHFSD) for the separation of methylparaben from water. Their findings proved that PEHFSD exhibited better performance over extended periods of time [11]. In another study, the complete removal of propylparaben from water by PEHFSLM system was achieved using 1.4% w/v of Aliquat 336 [12]. Diclofenac (DCF) and ibuprofen (IBU) are two pharmaceuticals belonging to the non-steroidal anti-inflammatory group. They both contain a carboxylic group connected to the aromatic ring in their structure [13]. Although these pharmaceuticals are known to be completely metabolized, they can be administered in a gel leading to the possibility of the unmetabolized form being washed away. Within this frame, ibuprofen and diclofenac and their transformation products have been detected in various water bodies [14]. Ibuprofen, one of the most commonly used anti-inflammatories, shows adverse model organisms at low concentrations (250 ng/L) [15]. On the other hand, diclofenac has been included in the first watch list of the European Union for consecutive years, demonstrating its negative impact on the environment [15]. In the pharmaceutical industry, hollow fiber membranes are highly integrated for analytical measurements. The ability of HFSLM to pre-concentrate the stream and remove a variety of metals with low and less toxic solvents has been usually investigated, but few are applied to pharmaceutical contaminants [15]. Therefore, in this study, the feasibility of hollow fiber liquid membrane to remove diclofenac and ibuprofen with Cyanex 923 (Cy923) is investigated.

Regarding the improvement in performance, recent efforts to optimize HFSLM include incorporating strengthened carbon nanotubes (CNTs) into organic extractants [16]. Padabni et al. (2015) investigated molecular imprinted hollow fiber solid-phase as solid sorbents. In this case, the molecularly imprinted polymers (MIP) are prepared and coated on the surface of the hollow fiber for the extraction and determination of diclofenac. Introducing solid adsorbents has shown promising results in removing and pre-concentrating the targeted analytes [17]. Nonetheless, drawbacks associated with the use of these membranes should be considered, such as membrane fouling, high equipment cost, and low or moderate permeation fluxes. In

addition, most works reported on polymer inclusion membranes are mainly conducted with flat sheet modules [16].

The development of efficient technologies that combine removal yield, cost, practicality, environmental effect, and reliability are attractive subjects for researchers. However, existing technologies have distinct advantages and disadvantages. Therefore, the combination of two treatment methods offers the potential to achieve optimal pharmaceutical removal while mitigating individual drawbacks [18]. Several studies have proposed the integration of advanced membrane processes with well-established technologies.[19, 20]. For instance, nanofiltration is recently employed following reverse osmosis to mitigate the fouling effect and improve the pre-treatment procedure. [21, 22]. In another study, Baumgarten et al. (2007) compared the efficiency of combining MBR with each of powdered activated carbon (PAC), ozone, and membrane processes to remove different types of antibiotics from water effluent [18]. Also, Zhang et al. (2006) studied the removal of tetracycline with PAC and reverse osmosis systems to overcome the problem of fouling affecting these systems [23]. Numerous approaches have combined powdered activated carbon with traditional treatment methods, yet an additional step is required to activate or regenerate the selected adsorbent. One of the attractive subjects of research about water and wastewater treatment is the coupling membrane filtration and advanced oxidation processes (ozonation, H_2O_2, Fenton, photolysis) mainly to decrease fouling and enhance the degradation of generated concentrated pollutants [21, 22]. Lu et al. (2020) investigated the effect of pre-ozonation to sustain the flux in ceramic membranes for raw secondary effluent, they have found that pre-ozonation can extend the filtration cycle time by approximately 5 times for ceramic membranes [24]. Nonetheless, the application of ozonation as a pre-treatment stage can form oxidized foulants capable of blocking the pores of the membrane. In recent years, the application of ozonation has been a growing interest for wastewater treatment, especially to remove persistent pollutants and emerging contaminants such as synthetic dyes, carboxylic acids, phenolics, amoxicillin, and other pharmaceuticals [25, 26, 27]. Yet to date, achieving a complete mineralization on an industrial scale with ozone is challenging due to the high ozone dosages needed, its inability to effectively remove low concentrations, and the associated high costs [27]. For these reasons, the integration of ozonation with membrane processes emerges as a viable alternative to address these issues [28].

In fact, ozone can be joined with membrane processes in three ways as a pre-treatment step to primarily degrade contaminants. The second option is a post-treatment step to eliminate the non-rejected organic in the output of the membrane or in the highly concentrated stream of the

retentate. Finally, ozonation and membranes can be integrated with a single hybrid process where they are operated simultaneously as a batch or recirculation flow process. Coupling AOPs, such as ozonation, with membrane technologies offers a promising solution to address the challenges associated with energy demand and mass transfer [28]. The hybrid process not only improves the efficiency of the treatment but also provides flexibility in operation and scalability for various water treatment applications [28]. Recently, many studies have focused on using hollow fiber membrane contactors as an alternative option for bubble systems to diffuse ozone in water and increase its mass transfer [28, 29]. To this date, the ability to scale up ozone membrane contactors is rarely put into practice because of the potential instability of polymeric membranes when exposed to ozone molecules [30].

The main objective of this study is firstly to investigate the removal of diclofenac and ibuprofen in a hollow fiber liquid membrane. The focus was on developing a simplified and effective analytical model to calculate the permeability in these systems. Several experiments were conducted to increase the stability and improve the extraction efficiency. Furthermore, the integration of HFSLM and ozonation was explored to tackle the limitation associated with ozonation treatment and enhance the degradation and removal of pharmaceutical compounds.

2 Model Development

A simplified model to calculate the permeability in hollow fiber module is developed assuming pseudo-steady state and plug flow behaviour. The co-current flow was adopted in the hollow fiber setup to ensure a consistent pressure difference between the fibers' outer shell and inner lumen side. This arrangement ensures efficient separation or exchange processes to take place within the fibers. Additionally, it is assumed that the concentration of solute of interest (pharmaceutical compounds) in the stripping phase, which is the fluid flowing through the lumen, is negligible or close to zero.

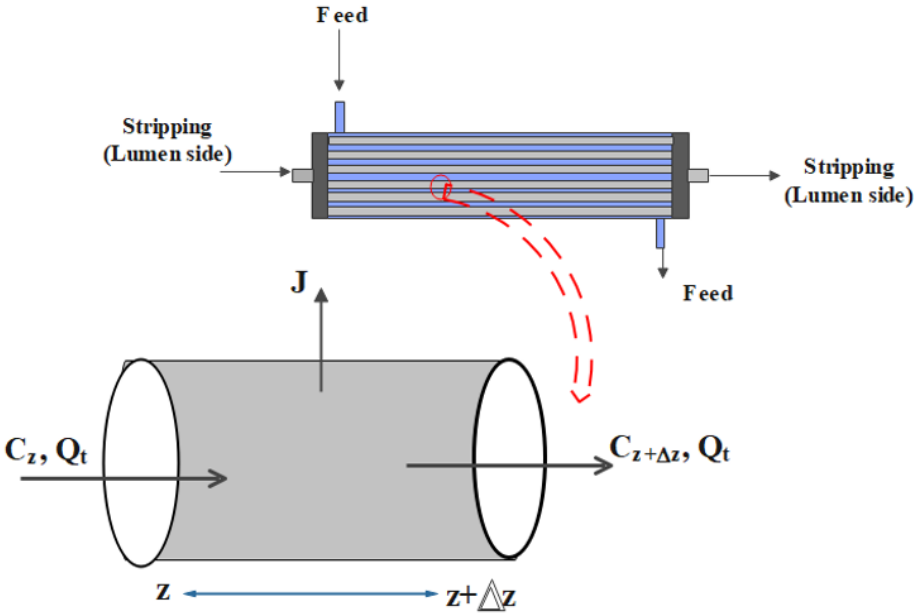

Figure 1 Mass balance of the cross-sectional area for a lumen side of the membrane.

Assuming, no accumulation in the membrane, the mass balance in the cross-section of one fiber is defined by Eq. (1):

$$\text{Input} = \text{Output}$$

$$q_f \cdot C_z - q_f \cdot C_{z+\Delta z} - J \cdot A_C = q_f \cdot C_Z - q_f \cdot C_{z+\Delta z} - J \cdot \pi \cdot d \cdot \Delta z \qquad \text{Eq. (1)}$$

Where q_f is the volumetric flow rate in the cross-sectional area (m^3/s), C_z and $C_{z+\Delta z}$ are the concentration of solute entering and exiting the fiber at in axial position z and z+Δz ,respectively (mol/L), *J* is the amount of the solute transferred by diffusion through the fiber wall(per time unit and area unit, equal to the overall mass transport flux, (mol/·m^2·s) and *d* is the fiber inner diameter (m).

Rearranging Eq. (1), the mass balance in the cross-sectional area of a fiber is shown in the following Eq. (2) :

$$-q_f \frac{dC}{dz} = J \cdot \pi \cdot d \qquad \text{Eq. (2)}$$

The permeability coefficient (P) is the speed with which pharmaceuticals are transported in the membrane. This parameter is related to the flux (J) by Eq.(3):

$$J = P \cdot C \qquad \text{Eq. (3)}$$

Where *P* is the permeability coefficient (m/s) and C is the concentration of the solute present in the feed at time t (mol/L).

The variation of concentration is calculated along the total fiber´s length as shown in Eq.(4), by applying the boundary conditions at z_0=0 and z=L, and combing (Eq.(2), and Eq, (3))

$$-q_f \cdot \ln\frac{C_{out}}{C_{in}} = P \cdot d \cdot \pi \cdot L \qquad \text{Eq. (4)}$$

Given L is the total length of the fiber (m).

Subsequently, the concentration exiting the membrane module is determined in Eq.(5) whereas the total flow rate and the total area are expressed by the following equation respectively:

$Q_f = q_f * N$; $A = d \cdot \pi \cdot L \cdot N$ (with N = number of fibers)

$$C_{m.out} = C_{m.in} \cdot e^{-\frac{P*A}{Q_f}} \qquad \text{Eq. (5)}$$

Given $C_{m.out}$ and $C_{m.in}$ are the concentration in the outlet and the inlet of the HFSLM, P the permeability coefficient (m/s), A total area (m^2), and Q_f is the total flow rate entering the membrane module.

Afterward, the pharmaceutical mass balance is established in the feed as described in Eq.(6)

$$\text{Input} - \text{Output} = \text{accumulation}$$

$$Q_f \cdot (C_{fin} - C_{fout}) = V\frac{dC}{dt} \qquad \text{Eq. (6}$$

With the V volume of the feed tank (m^3), C_{fin} and C_{fout} are the inlet and outlet concentrations of the feed tanks (mol/L).

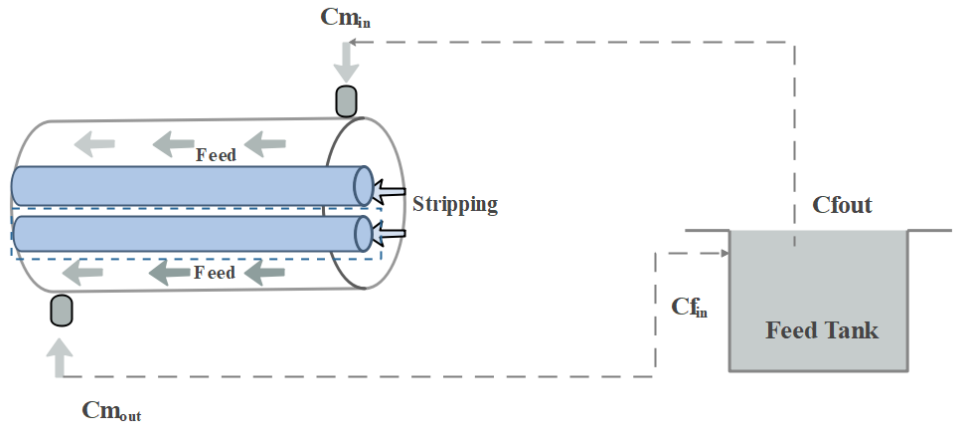

Figure 2. Mass balance in the feed tank of a HFSLM.

As seen in Figure 2, at specific time t,$C_{fout} = C_{mi}$ *and* $C_{fin} = C_{mout}$, consequently the variation of solute in the feed is obtained in Eq.(7) and the permeability coefficient in HFSLM is calculated :

$$ln\frac{C_f}{C_{0_f}} = -\frac{Q_f}{V} \cdot \left[1 - e^{-\frac{P \cdot A}{Q_f}}\right] \cdot t \qquad \text{Eq. (7)}$$

Where C_{0f} is the initial concentration of the solute in the feed phase.

3 Material and methods

3.1 Chemicals

All pharmaceuticals and their metabolites diclofenac (CAS No. 15307-79-2, 99%), ibuprofen (CAS No.15307-79-2, ≥98%), 4-Ethylbenzaldehyde (CAS No. 233633, ≥97.5%), 5-hydroxy diclofenac (CAS No.62248, ≥97%) were supplied by Sigma-Aldrich. Fresh test samples were prepared in adequate concentrations (1, 10, and 30 mg/L) in deionized water at ambient temperature (22 ± 2 °C). The selected concentrations were higher compared to the ones normally found in real water matrices to allow better monitoring and measurement of the removal efficiency with the available analytical techniques.

HPLC acetonitrile, reagent grade, NaOH, KI, and NaCl, were all obtained from Merck. Potassium indigo tri-sulfonate and potassium iodide were used for analysing residual ozone in the samples and were obtained from Sigma Aldrich. Cyanex 923 (91%) dissolved in kerosene at room temperature was purchased from Solvay and was selected as the organic extractant to remove ibuprofen and diclofenac [31].

3.2 Hollow fiber membrane transport

The experiments with HFSLM consisted of a hollow fiber module from Liqui-Cel^{TM} (G-502) and its characteristics are summarized in Table 1. Firstly, the liquid membrane phase was prepared by pumping 40 % (v/v) Cy923 dissolved in kerosene, through the lumen side of the module in recirculation mode for 10 min. The circulation of the organic extractant in the lumen side prior to any experimental runs ensures the proper soaking of membrane pores. Afterward, the module was washed with distilled water to remove any excess organic liquid. During the experimental runs, feed (shell side) and stripping (lumen side) streams flowed at 50 L/h in a co-current flow and a slightly positive pressure between the shell and the lumen side was maintained (P_f-P_s=0.3 bar) to prevent any Cy923 leakage to the shell side. The lab-scale plant worked with 9 L of the feed solution containing 10 mg/L of pharmaceutical contaminants and the stripping solution of 3 L consisted of distilled water at pH=11.

According to the literature, the concentration range of pharmaceutical residues in aquatic sources is between 0.12−1600 ng/L [28] but with the aim to test the feasibility of this method DCF and IBU concentrations were kept at (3.5−10 mg/L) and the pH at 5.5.

In an effort to increase the stability of liquid membranes, the organic extractant is mixed and dispersed in the stripping phase. The experimental setup is shown in Figure 3**.** Pseudo emulsion is highly adapted and strongly favoured when operating with hollow fiber membranes. Feed

phase (DCF, 9 L) in one stirred tank and, pseudo-emulsion phase (V_{org}/V_{aq}=1/38) was prepared in the other stirred tank. It involves the addition of a stripping phase (distilled water at pH=11.) with a requisite amount of extractant (preferably three 3times the volume of the membrane pores). The operation mode is similar to HFSLM where the feed and pseudo-emulsion phases were passed at the same flow rate of 47 L/h in the shell and lumen sides, respectively. The organic solution containing the extractant is immobilized in the pores of the hollow fibers due to its hydrophobic nature. The transmembrane pressure was kept at 0.3 bar. DCF molecules form a complex with Cy923 and diffuses through the membrane phase, followed by stripping within the internal phase of the pseudo-emulsion. Consequently, the stripping phase becomes enriched with DCF, achieving a threefold concentration.

At different time intervals, samples are taken from the feed and the stripping phase to measure the evolution of the concentration of pharmaceuticals. DCF from pseudo-emulsion was obtained by breaking and separating the organic and stripping solutions. The stripping phase will be abundant with DCF as it concentrates the pharmaceutical by 3 times.

3.3 Integration of HFSLM and ozonation in a single process

The ozone in the concentrated stream was generated from oxygen by the Anseros ozone generator (COM-AD-04) and introduced at the reactor's bottom through a porous diffuser. The initial concentration of ozone in feed gas was adjusted with a valve mounted on the reactor and the flow was kept constant at 25 NL/h. The solution was continuously mixed with a mechanical stirrer and the diffuser was kept in the middle of the reactor to ensure a uniform distribution of ozone bubbles in the stripping tank. The dissolved ozone was determined with indigo method. The excess gas and gas outflows are forced into an ozone destruction unit containing 2% (w/v) KI solution before releasing it into the atmosphere. During the ozonation experiment, the solution in the reactor is kept at a constant temperature. The solution pH is measured with a pH meter Crison GLP21. The stripping phase containing the pharmaceutical flows through the tubes of the membrane into the ozonation tank, where the dissolved ozone present in the bulk phase reacts with the pharmaceutical contaminants.

Samples were withdrawn from the feed and stripping cells at specific time intervals to evaluate the decay of concentration of the main compound and its by-products formed during the reaction. Total organic carbon (TOC) was measured using a Shimadzu TOC-L model analyzer at the beginning and end of the experiment. The experimental setup is shown in Figure 4.

3.4 Analytical measurement

The concentration of pharmaceutical compounds and their transformation product were analysed by high-performance liquid chromatography (HPLC, Agilent 1220 infinity series) with a diode array detector at 280 nm or 230 nm for diclofenac, and ibuprofen, respectively. The column used was Zorbax Eclipse Plus C18 (2.1x50mm) and the mobile phase consisted of a mixture of formic acid (25 mM) in water and Acetonitrile at 60:40 (v/v) with a flow rate of 0.2 mL/min and an injection volume of 50µL. The identification of by-products for IBU and DCF was accomplished with a combination of UHPLC Liquid Chromatograph and a Thermo Scientific™ Orbitrap IDXTribrid mass spectrometer equipped with an ESI interface. The column used was C18 column (4 x 25 mm) supplied by Agilent. Isocratic elution was conducted using a mixture of 25 mM formic acid (A) and acetonitrile (B) at a ratio of 60/40 (A/B), and the total runtime was 15 minutes. Mass spectrometry detection was performed using heated electrospray ionization settings in both negative and positive ionization modes.

Table 5 Details of Liquid gel liquid membrane G-502 from Liqui-Cel^{TM}*)*

Module diameter (cm)	7.7
Module length (cm)	27.7
Membrane Area (m^2)	1.4
Fibers OD/ID (µm)	300/200
Porosity (%)	40
Tortuosity	1.23
Membrane plotting material	Polypropylene /polyethylene
Hold-up volume shell side (cm^3)	400
Hold-up volume lumen side (cm^3)	150
Number of fibers	10000

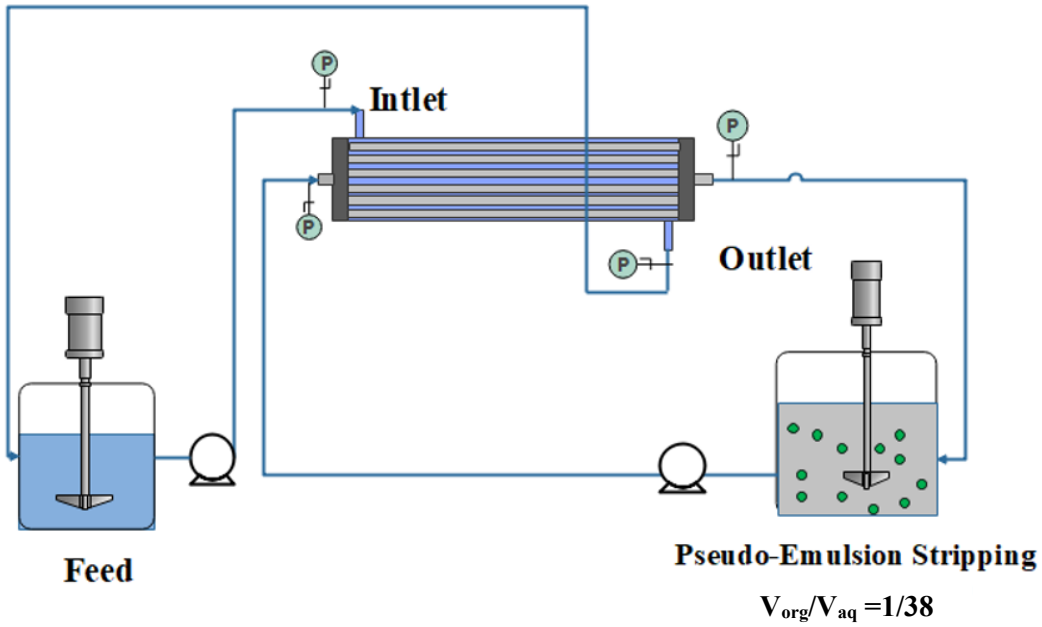

Figure 3. Experimental setup with pseudo-emulsion in the stripping phase

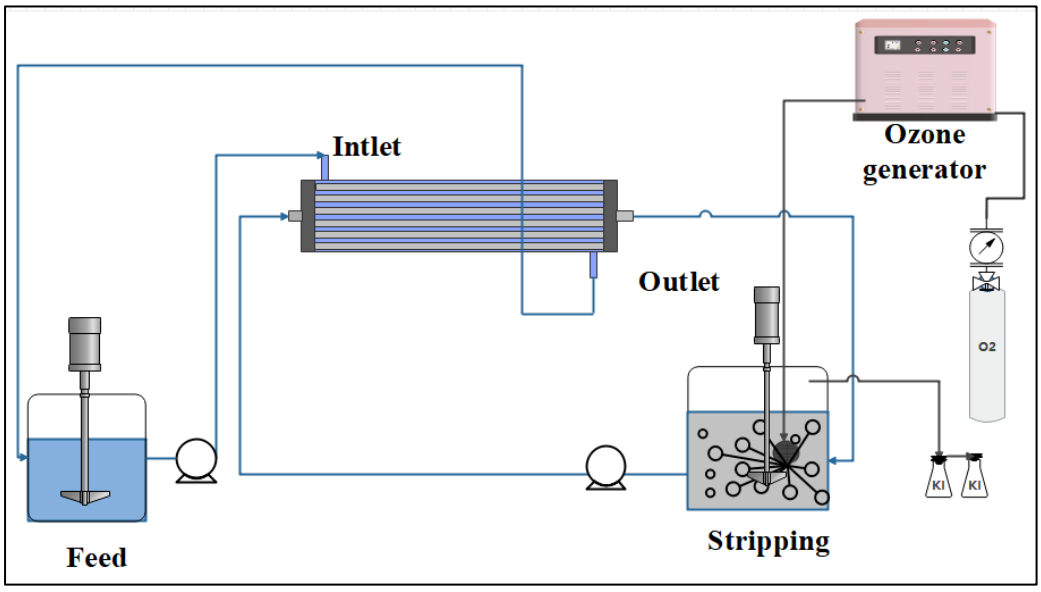

Figure 4. Experimental setup of HFSLM and ozonation

4 Results and Discussion

4.1 Removal of pharmaceuticals with HFSLM and PEHFLM

Hollow fiber supported liquid membrane (HFSLM) has been one of the most frequently used for extraction and preconcentration of several types of target analytes. Typical kinetic plots showing the removal of IBU and DCF from water are presented in **Figures 5.**

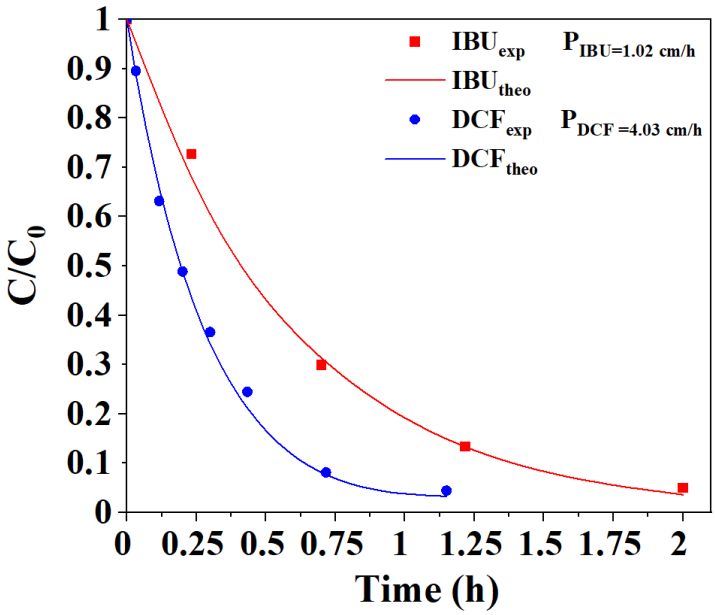

Figure 5. Pharmaceuticals concentration vs time in HFSLM. (Feed: C_0=10 mg/L, pH = 5.5; Q= 47 L/h; Organic extractant: 40% (v/v) Cy923/kerosene; Stripping phase: Q=47 L/h; pH=11).

The process is rather fast for DCF since more than 90% removal was transported in less than 1 hour and 89 % for IBU in two hours with 40% Cy923. The effectiveness of the selected organic solvent is assessed based on its ability to efficiently extract the desired solutes. It should also be compatible with the fiber, immiscible with the feed and the stripping phase, and have low volatility (high boiling point) to prevent losses [32]. Madikizela et.al. (2020) have reported the use of hydrophobic organic solvents such as 1-octanol for the enrichment of pharmaceuticals from the aqueous phase [33]. The optimal conditions to transport DCF and IBU were obtained previously with flat sheet module (FSSLM) and thereafter, selected to be applied in the following study to achieve the highest permeability coefficient for both compounds [31]. In flat sheet configuration, the permeability coefficient obtained with 40% (v/v) Cy923 was higher than the permeability coefficients obtained with HFSLM, measuring 11.2 cm/h and 7.2 cm/h for diclofenac and ibuprofen, respectively [31]. This can be attributed to different factors. Initially, the type of polymer and membrane specifications are diverse, and it is well understood that the membrane characteristics play a major role in the variation of the permeability coefficients of two different membranes. The permeability coefficient can be related using the diffusion coefficient, the extraction equilibrium constant (k_{ext}), the carrier concentration, the thickness (δ), and the tortuosity(τ), and the porosity (ε) given the following expression [34]:

$$P = D * K_{ext} * \frac{\varepsilon}{\tau * \delta} \qquad \text{Eq. (8)}$$

Similar observations were presented when the permeability coefficient for rare earths was calculated in both flat sheet and hollow fiber-supported liquid membranes [31]. In addition, the effect of Cy923 concentrations ranging from 0.33 to 0.99 mol/L (equivalent to 10-60 % v/v) was studied in HFSLM to remove DCF from water. The results obtained in Figure 6 show a nonlinear increase in the permeability coefficient with extractant concentration. The highest permeability was obtained at 40 % Cy923 in kerosene. Using a higher concentration of the organic extractant did not lead to increased permeability, thus confirming that 40% Cy923 is sufficient. Similar findings have been observed in various studies examining the relationship between organic extractant concentration and permeability [34] [35]. These studies indicate that beyond a certain concentration of organic extractant, the permeability does not improve. This occurs because of the increase of the viscosity in the membrane pores.

It can be deduced that the transport of the pharmaceutical was governed by the diffusivity effect and by the viscosity [35].

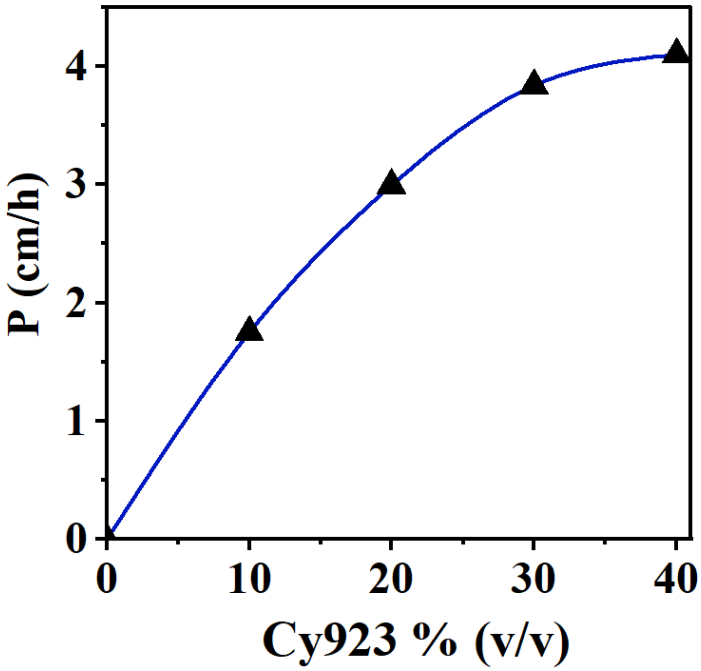

Figure 6. Effect of Cy923 concentration on the permeability in HFSLM (Feed: C_0 =10 mg/L, pH = 5.5 , Q=47 L/h ;. Stripping phase: Q= 47 L/h; pH = 11).

4.2 **Stability study**

To test the efficiency of HFSLM, several experiments were conducted with diclofenac (10 mg/L), by replacing the feed and the stripping tanks by fresh solutions. Diclofenac was selected for the multiple runs as more than 95 % of pharmaceuticals were transported in less than 1 hour. The results of successive runs are shown in Figures 7 and 8. The permeability reaches its

minimum value of 0.7 cm/h after five runs. It was also observed a significant shift in removal efficiency after the third run which corresponds to an experimental duration of 3 hours. One potential interpretation of results obtained is that when the trans-membrane pressure surpasses the capillary pressure, the organic extractant within the fiber's pores may be displaced, resulting in membrane failure [36]. The instability of SLM is the main key that hinders their industrial application. The major reason for a supported liquid membrane to become unstable is the loss the organic carrier from the pores of the support. This can be caused by several factors such like the pressure difference over the membrane wetting of support pores, and blockage of the pores [36, 37]. Several researchers have investigated different methods to increase the stability of SLM, unfortunately, most of these techniques are only applicable to flat sheet membranes which are easily manipulated. To overcome the issue of stability and ensure continuous operations, HFSLM systems are usually upgraded to pseudo-emulsion hollow fiber supported liquid membranes (PEHFSLM). Their main objective is to reduce and limit any possible displacement of organic extractant out of the porous membrane. It is one of the best alternatives that can increase the stability, save time required for cleaning, and improve the performance of the system [36, 37].

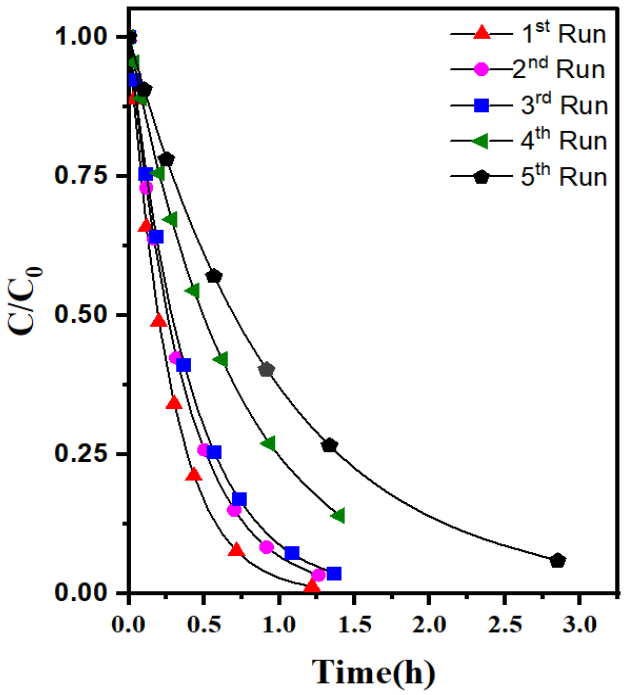

Figure 7. Concentration change of DCF for successive runs.(Feed: $C_{0=}$10mg/L; pH = 5.5; Q=47 L/h. Organic extractant: 40% (v/v) Cy923/kerosene. Stripping phase: Q= 47 L/h; pH = 11).

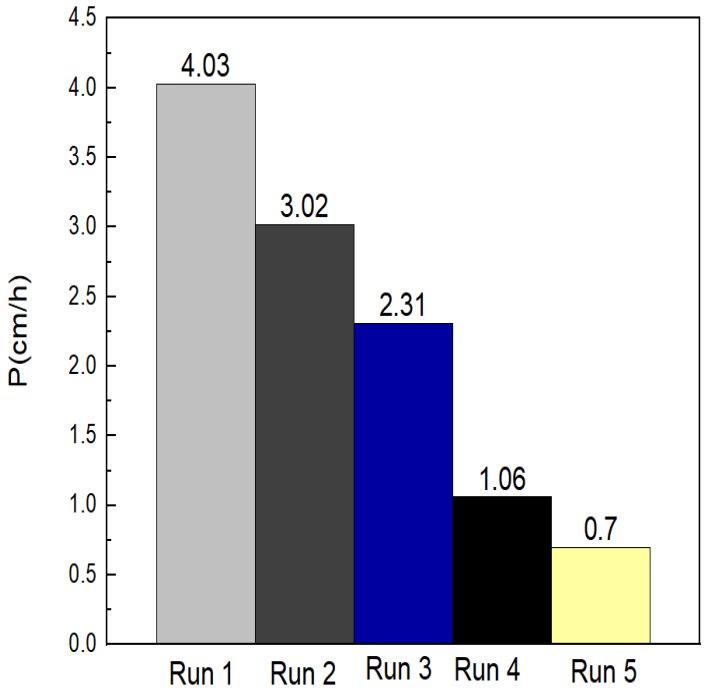

Figure 8. Permeability obtained for each consecutive run with HFSLM.

4.3 **Pseudo-emulsion Hollow fiber**

In the subsequent study, the stripping phase was mixed with 80 mL of Cy923/kerosene. The amount is added accounting the volume of the membrane to ensure that the pores are completely filled with the organic extractant. The evolution of DCF concentration in the feed and stripping phase for PEHFSLM and HFSLM are presented in Figure 9. The regeneration of the liquid membrane layer can automatically and continuously replace the loss of organic extractant to counter the liquid membrane instability and prevent its degradation [35]. An efficient approach based on the strip dispersion method was introduced and reported by several studies [10, 11, 38]. Mixing the organic extractant can tackle the instability of the liquid membrane and improve the recovery efficiency of target analytes [35, 38]. SLM strip dispersion system was able to improve the yield of cephalexin removal from 32% to 42% with hollow fiber membrane using Aliquat 336 as the organic extractant [39].

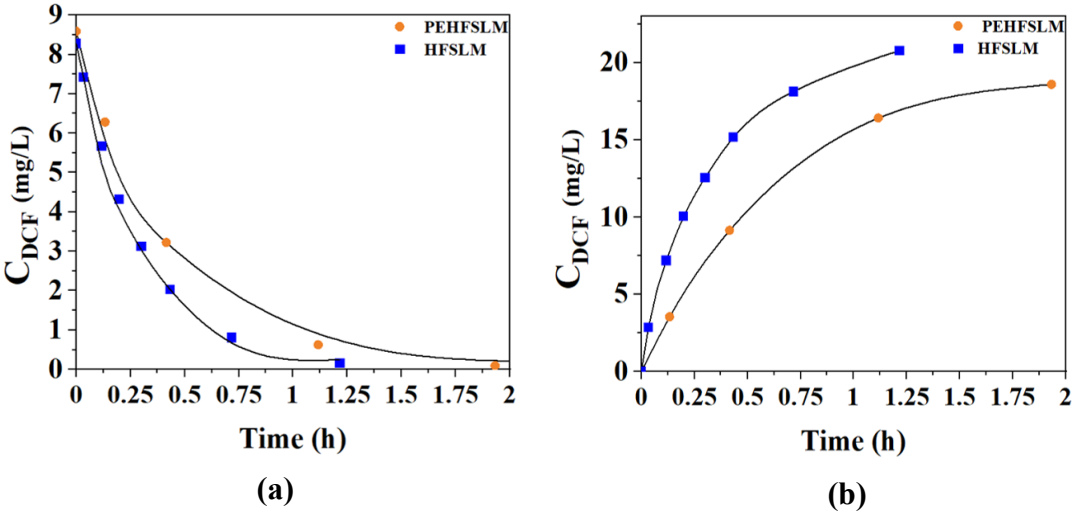

Figure 9 Comparison between HFSLM and PEHFSLM in (a) Feed phase: $C_{0=}$10mg/L, pH = 5.5, V= 9 L,Q=47 L/h. Organic extractant: 40% (v/v) Cy923/kerosene and (b) stripping phase: V=3 L ; Q= 47 L/h; pH = 11).

As shown in the Figure 8a and 8b the initial transport rate with PEHFSLM is lower compared to the hollow fiber. The permeability obtained for DCF (10 mg/L) with 40% Cy923 was 2.04 cm/h. Diclofenac at a concentration of 10 mg/L was successfully extracted within a two-hour period with pseudo emulsion, and the diclofenac was concentrated in the stripping phase. After the two-hour extraction period, the highest concentration recuperated were 21 mg/L for HFSLM and 19.5 mg/L for PEHFSLM.

Nonetheless, after 6 consecutive runs, the transport rate was maintained and the permeability coefficient obtained was between 2.04-2.11 cm/h.

The overall mass transfer for the diffusion process in hollow fiber membrane depends on three mass transfer resistances [40]: the aqueous boundary layer formed on the internal side of the fiber, the diffusion of the DCF-carrier complex across the liquid membrane, and the aqueous boundary layer formed on the external side of the fiber [39,40]. Several operational parameters can affect the performance of pseudo emulsions such as the size of droplets size and their distribution. This decrease of the overall permeability is due to a lower interfacial coefficients for the internal and external aqueous boundary layers. Similar observations were reported with when comparing peudo-emulsion hollow fiber strip dispersion and aqueous stripping phase to remove diclofenac with Di-2-ethylhexyl phosphoric acid. Although the stability was maintained, the permeability was lower [41]. Moreover, when it comes to recycling battery waste, the use of Cy923 in the emulsion phase during the stripping process shows a comparable pattern of initial transport rate reduction. [34].

4.4 Recyclability of pseudo-emulsion phase

In the aim to make the process more economical, the regeneration of stripping phase was investigated. The recycling operations were carried out with optimum conditions. The recyclability of the pseudo-emulsion stripping phase was examined by contacting the fresh feed (1 mg/L DCF, 9 L) with the same stripping solution for three consecutive runs. (3 L). DCF extraction from the feed are shown in Figure 9. During the 3rd run, DCF removal decreased by ~79% when the fresh feed was contacted with the pseudo-emulsion phase compared to the removal efficiency obtained from 1st run. Extraction efficiency decreased due to a decrease in the concentration gradient of DCF molecules. Kohli et al. (2019) conducted a study on the recyclability of the pseudo emulsion phase to remove endocrine-disrupting compounds from water. The findings revealed that the removal efficiency decreased to 43% after the third run within a total time of 120 minutes [42]. Hence, several factors could contribute to this observation. One possibility is that the stripping phase becomes saturated and reaches its maximum capacity to extract further substances. Another factor could be the alteration of the solvent composition due to its solubility in the aqueous phase.

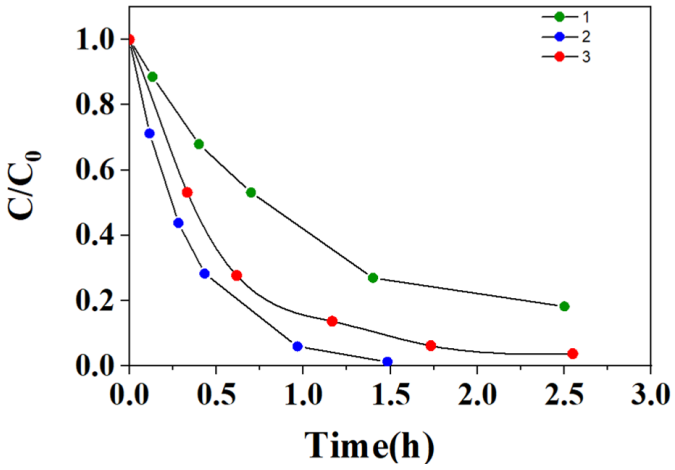

Figure 10 Recyclability of pseudo-emulsion phase.(Feed Phase: C_0=1 mg/L,V= 9 L, Q=47 L/h, pH=5.5 ; Organic extractant: 40% (v/v) Cy923/kerosene ; Stripping phase : V=3 L, Q=47L/h, pH=11, Vorg/Vaq=1/38).

4.5 Ozonation and generation of by products

Ozone was introduced in the stripping phase (pH = 11 and V = 2 L) therefore the indirect reaction of ozone is favoured through generation of hydroxyl radicals [43]. A preliminary series of experiments was done to select the initial ozone concentration, the inlet ozone concentration was set at 10 mg/L and the gas flowrate at 25 NL/h. A pharmaceutical containing feed solution with initial concentration of 10 mg/L was extracted from the shell side into the lumen side of the membrane. The concentrated stream was subsequently exposed to ozone to eliminate diclofenac and ibuprofen respectively. The reaction of diclofenac with $OH^{\bullet}$ radical is very fast; therefore, the diclofenac transported through the membrane was completely eliminated after 10 minutes. On the other hand, the conversion of ibuprofen was at a lower rate since the concentration of ibuprofen transported from the feed was still detected after ozonation. The degradation of pharmaceuticals with ozone was previously studied and diclofenac is proven to be highly reactive with ozone [25, 43].

The reaction of ozone with diclofenac and ibuprofen can result in the formation of intermediates and by-products which further undergo transformation or mineralization. The expected attack site after identifying the by-products by LC-MS for each of diclofenac and ibuprofen are shown in Figure 11, Tables 2 and 3.

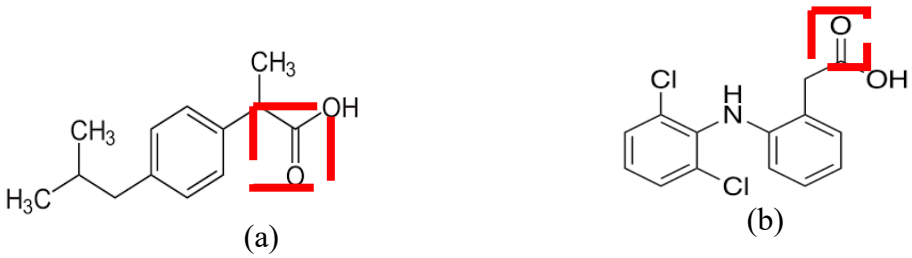

Figure 11. Expected attack site of pharmaceuticals toward molecular ozone.

Table 2. Mass spectrometry-Liquid chromatography (MS-LC) data for diclofenac oxidation products.

	High Resolution Ms data	Retention time (min)	Molecular Formula	Reference
Compound	$[M-H]^-$			
DCF	295.02	10.4	$C_{14}H_{11}NO_2Cl_2$	This study
BP1	310.02	3.7	$C_{14}H_{12}NO_3Cl_2$	[44][45] [46]
BP2	308.99	2.94	$C_{14}H_{10}NO_3Cl_2$	[45][46]
BP3	326.01	1.46	$C_{14}H_{12}NO_4Cl_2$	[44] [45]
BP4	326.01	1.74	$C_{14}H_{12}NO_4Cl_2$	[44][45] [46]
BP5	284.01	3.0	$C_{12}H_{10}NO_3Cl_2$	[45] [46]
BP6	279.91	1.62	$C_{13}H_{10}NO_2Cl_2$	[44]
BP7	277.05	1.62	$C_{14}H_{10}NOCl_2$	[45] [46]
BP8	296.95	3.05	$C_{13}H_{10}NO_3Cl_2$	[45] [46]
BP9	258.95	1.39	$C_{10}H_8NO_3Cl_2$	[44][46]

Table 3. Mass spectrometry-Liquid chromatography (MS-LC) data for ibuprofen oxidation products.

	High Resolution Ms data	Retention time (min)	Molecular Formula	Reference
Compound	$[M-H]^-$			
IBU	205	13.2	$C_{13}H_{18}O_2$	This study
BP1	221.12	4.65	$C_{13}H_{17}O_3$	[47] [48]
BP2	177.13	3.05	$C_{12}H_{17}O$	[47] [48]
BP3	133.07	3.5	C_9H_9O	[47] [48]

The degradation of DCF through ozonation is quite fast as evidenced by the absence of detectable traces of the pharmaceutical in the stripping phase at the end of the experiment. The

reaction of ozone with diclofenac involves the hydroxylation reaction. This reaction leads to the incorporation of one or more oxygen atoms into the diclofenac molecule, indicating the formation of hydroxylated byproducts [45, 46]. 5-Hydroxydiclofenac (BP1) is a significant hydroxylated compound formed during the degradation of diclofenac. This by-product is generated when a hydroxyl group (-OH) is added to the diclofenac molecule through a hydroxylation reaction In the case of ibuprofen degradation, multiple reactions contribute to its breakdown, including hydroxylation, decarboxylation, and demethylation [48]. The hydroxylation reaction results in the addition of a hydroxyl group (OH) or an oxo group to the ibuprofen molecule. LC/MS analysis of the degradation products revealed the presence of prominent by-products, notably 4-ethyl benzaldehyde (BP3) and 2-[4-(1-hydroxy-2-methylpropyl) phenyl] propionic acid (BP1).

4.6 Degradation of by-products in the stripping phase

The effect of ozone on DCF and IBU and their transformation products was investigated individually. The concentration changes of both transformation products were monitored, and the results are presented in Figure 12 and 13. The by-products shift during the reaction as some compounds decrease while new ones are formed. Initially, BP1 (5 hydroxydiclofenac) was found in the greatest abundance indicating that the DCF degradation is initiated by the hydroxylation of the phenylacetic ring. After three hours of continuous ozonation in the stripping side, the concentration of BP1 reached a minimum level and the parent compound was removed completely. Regarding ibuprofen (Figure 12), the rate of degradation when exposed to ozone at pH 11 is comparatively slower than that of DCF. Even after continuous ozonation for 4 hours, a minimal amount of the transported ibuprofen can still be detected in the stripping phase (0.3 mg/L). In addition, the reaction rate of the detected by-product when exposed to ozone was initially slow which is in accordance with Huang et al. (2015) in which they studied the process of ozone disinfection of ibuprofen.[49].

Assessing the mineralization efficiency of pollutants such as ibuprofen (IBU) and diclofenac (DCF) is of paramount importance for environmental considerations. The highest TOC removal efficiency measured at the end of reaction time was 72 % for DCF while for IBU the TOC decreased by 57% after 5 hours. Ozone can initiate oxidation reactions that break down organic compounds into simpler inorganic forms through a process called mineralization [50]. It is important to note that the mineralization process involves the complete decomposition of organic molecules, typically through the successive oxidation of their chemical bonds which

requires sufficient exposure time and ozone concentration. The specific conditions necessary for complete mineralization can vary depending on factors such as ozone concentration, temperature, pH, and the presence of other chemical species. Environmental factors and wastewater characteristics play a significant role in determining the extent of mineralization [51, 52]. In another study by Hama et al. (2017), TOC removal efficiency peaked during the degradation of DCF using a photocatalytic ozonation process [53]. Additionally, Olak et al. (2021) demonstrated the effectiveness of ozonation for the degradation of ibuprofen and its derivatives with an initial ozone concentration of 11.38 mg/L, they achieved a removal of 91.52% and 98.43% for IBU and its metabolite OHIBF, respectively, and a corresponding 44% removal of TOC [54]. Another study compared the mineralization percentage of IBU using ozone alone and catalytic ozone, reporting a 55% TOC removal efficiency at an initial concentration of 10 mg/L with solely ozone. [55]. Removal efficiency and mineralization rate can be further enhanced by combining ozonation with different catalytic reactions to promote the elimination of persistent pharmaceutical contaminants.

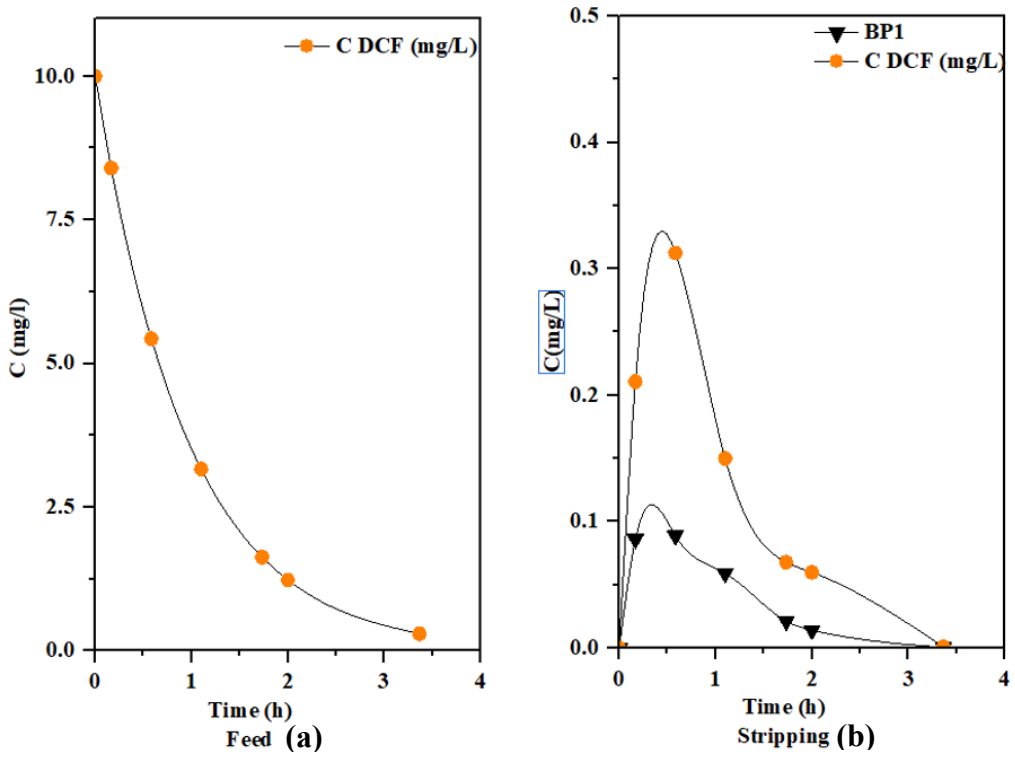

Figure 12. Concentration of DCF and by-product BP1 in (a) Feed: C_0=10mg/L, V= 9 L, Q=47 L/h, pH=5.5; Organic extractant: 40% (v/v) Cy923/kerosene (b). Stripping phase: V=2 L; pH=11; Q= 47 L/h; Inlet ozone concentration 10.2 mg O_3/L.

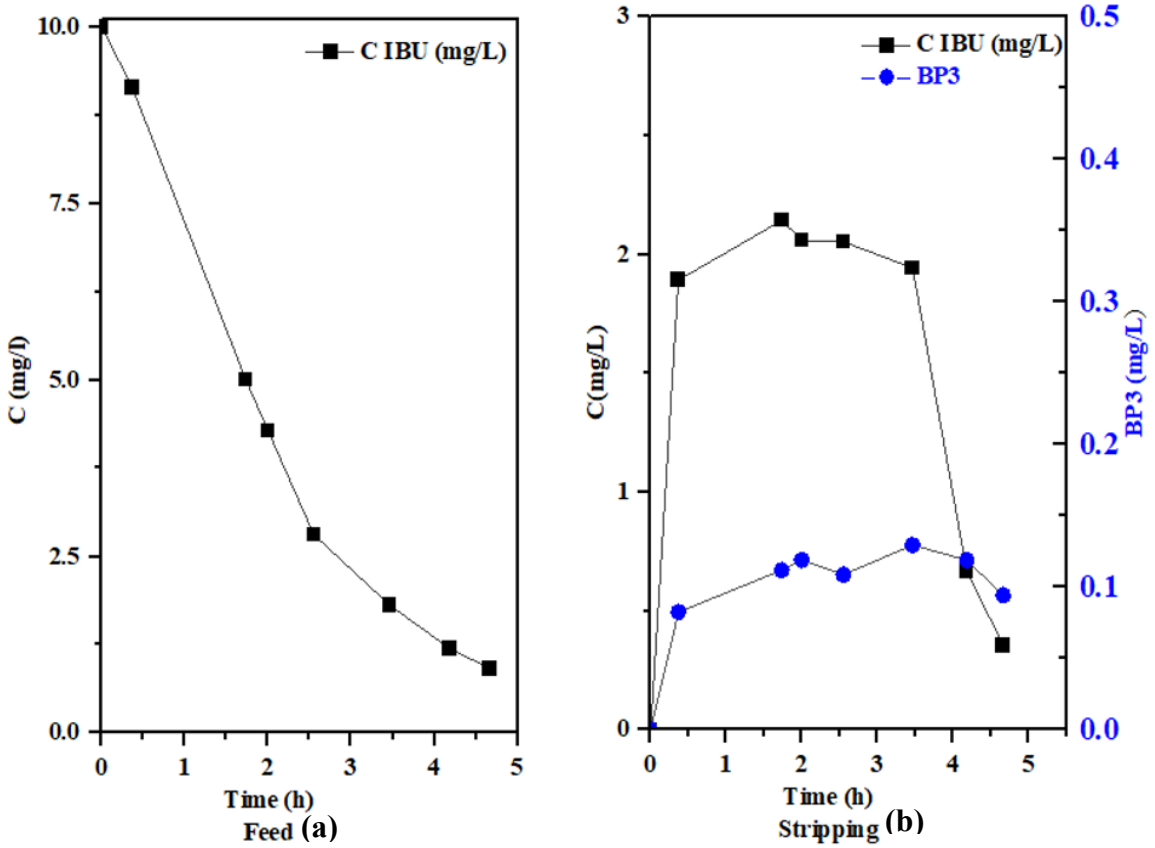

Figure 13. Concentration of IBU and by-product BP3 in (a) Feed: C_0=10mg/L, V= 9 L, Q=47 L/h, pH=5.5; Organic extractant: 40% (v/v) Cy923/kerosene (b).Stripping phase: V=2 L; pH=11; Q= 47 L/h; Inlet ozone concentration 10.2 mg O_3/L.

5 Conclusions

The application of a hollow fiber liquid membrane, containing 40% Cy923, has demonstrated high efficiency in extracting diclofenac and ibuprofen from aqueous solutions. The system's stability has been significantly improved through the incorporation of a pseudo emulsion, enhancing its longevity and extraction efficiency. Moreover, the solvent used in the process can be recycled indefinitely unless it degrades or its solubility increases. It is recommended to introduce fresh solutions of organic extractant after the second run. The integration of the hollow fiber membrane system with ozonation in a single step has led to a significant reduction in the concentration of diclofenac and ibuprofen, along with their abundant by-products 5-hydroxydiclofenac and 4-ethybenzaldehyde, enabling the degradation of the extracted pharmaceutical compounds and other organic pollutants in the system. The results show that high mineralization of 72% was achieved for diclofenac and around 52% for ibuprofen at the end of experiment time, thus improving overall water quality. Despite the generation of ozone-by-products, this approach, which includes hollow fiber liquid membrane extraction, improved

pseudo-emulsion stability, and ozonation, provides a promising solution for detecting and selectively treating pharmaceutical contaminants found at low concentrations.

6 Acknowledgements

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7 References

[1] Talukder, M. E., Alam, F., Mishu, M. M., Pervez, M. N., Song, H., Russo, F., Galiano, F., Stylios, G. K., Figoli, A., Naddeo, V. (2022). Sustainable Membrane Technologies for by-product separation of non-pharmaceutical common compounds. Water, 14(24), 4072. https://doi.org/10.3390/w14244072

[2] Olasupo, A., Suah, F. B. (2022). Trends in hollow fibre liquid phase microextraction for the preconcentration of pharmaceutically active compounds in aqueous solution: A case for polymer inclusion membrane. Journal of Hazardous Materials, 431, 128573. https://doi.org/10.1016/j.jhazmat.2022.128573

[3] Harun, M. H., Ahmad, A. L. (2022). Sustainable and effective contaminants transport beyond stability barrier of supported liquid membrane: How crucial and vital is the green membrane system. Journal of Water Process Engineering, 49, 103172. https://doi.org/10.1016/j.jwpe.2022.103172

[4] Patil, N. D., Sharma, A. D., Patwardhan, A. W. (2017). Carboxylic acid separation using hollow fiber liquid membrane Indian Chemical Engineer, 57(3–4), 300–321. https://doi.org/10.1080/00194506.2015.1036815

[5] Dong, L.-J., Tan, Z.-Q., Chen, M., & Liu, J.-F. (2015). Hollow fiber supported liquid membrane coupled with high-performance liquid chromatography for highly sensitive determination of bisphenols in environmental water samples. Analytical Methods, 7(4), 1380–1386. https://doi.org/10.1039/c4ay02635g

[6] Chen, L., Wu, Y., Dong, H., Meng, M., Li, C., Yan, Y., Chen, J. (2018). An overview on membrane strategies for rare earths extraction and separation. Separation and Purification Technology, 197, 70–85. https://doi.org/10.1016/j.seppur.2017.12.053

[7] Suren, S., Ampronpong, W., Pancharoen, U., Maneeintr, K. (2021). The elimination of trace arsenic via hollow fiber supported liquid membrane: Experiment and Mathematical Model. https://doi.org/10.21203/rs.3.rs-134534/v1

[8] Asadi, M., Dadfarnia, S., Haji Shabani, A. M., Abbasi, B. (2016). Hollow fiber liquid phase microextraction method combined with high-performance liquid chromatography for simultaneous separation and determination of ultra-trace amounts of naproxen and Nabumetone in cow milk, water, and biological samples. Food Analytical Methods, 9(10), 2762–2772. https://doi.org/10.1007/s12161-016-0449-y

[9] Yuliusman, S., Nurqomariah, A., Fajaryanto, R. (2019). Extraction of Co and ni metals using emulsion liquid membrane and liquid-liquid extraction with Cyanex 272 as extractant. AIP Conference Proceedings. https://doi.org/10.1063/1.5095049

[10] Kumar A., Roy, S., Sonawane, J , Alguacil, F., Sastre, A. (2008). Strip dispersion technique: Application for strategic and precious metal separation and treatment of wastewater streams. (2008). Handbook of Membrane Separations, 1077–1090. https://doi.org/10.1201/9781420009484-47

[11] Shirasangi, R., Kohli, H. P., Gupta, S., Chakraborty, M. (2021). Separation of methylparaben from aqueous source stream by pseudo-emulsion hollow fiber membrane strip dispersion technique: Optimization of process parameters using grey-taguchi method. Chemical Engineering and Processing - Process Intensification, 161, 108302. https://doi.org/10.1016/j.cep.2021.108302

[12] Parihar, B. P., Chakraborty, M., Gupta, S. (2017). Application of pseudo-emulsion hollow fiber strip dispersion system for the removal of Propylparaben from the Aqueous Solutions. Desalination And Water Treatment, 73, 301–307. https://doi.org/10.5004/dwt.2017.0729

[13] Kråkström, M., Saeid, S., Tolvanen, P., Kumar, N., Salmi, T., Kronberg, L., Eklund, P. (2021). Identification and quantification of transformation products formed during the ozonation of the non-steroidal anti-inflammatory pharmaceuticals ibuprofen and diclofenac. Ozone: Science & Engineering, 44(2), 157–171. https://doi.org/10.1080/01919512.2021.1898928

[14] Parolini, M., Binelli, A., Provini, A. (2011). Chronic effects induced by ibuprofen on the freshwater bivalve Dreissena polymorpha. Ecotoxicology and Environmental Safety, 74(6), 1586–1594. https://doi.org/10.1016/j.ecoenv.2011.04.025

[15] Simon, E., Duffek, A., Stahl, C., Frey, M., Scheurer, M., Tuerk, J., Gehrmann, L., Könemann, S., Swart, K., Behnisch, P., Olbrich, D., Brion, F., Aït-Aïssa, S., Pasanen-Kase, R., Werner, I., Vermeirssen, E. L. M. (2022). Biological effect and Chemical Monitoring of watch list substances in European Surface Waters: Steroidal estrogens and diclofenac – effect-based methods for monitoring frameworks. Environment International, 159, 107033. https://doi.org/10.1016/j.envint.2021.107033

[16] Song, X.-Y., Shi, Y.-P., Chen, J. (2012). A novel extraction technique based on carbon nanotubes reinforced hollow fiber solid/liquid microextraction for the measurement of Piroxicam and diclofenac combined with high performance liquid chromatography. Talanta, 100, 153–161. https://doi.org/10.1016/j.talanta.2012.08.042

[17] Pebdani, A. A., Shabani, A. M., Dadfarnia, S., Khodadoust, S. (2015). Solid phase microextraction of diclofenac using molecularly imprinted polymer sorbent in hollow fiber combined with fiber optic-linear array spectrophotometry. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 147, 26–30. https://doi.org/10.1016/j.saa.2015.03.057

[18] Baumgarten, S., Schröder, H. Fr., Charwath, C., Lange, M., Beier, S., Pinnekamp, J. (2007). Evaluation of Advanced Treatment Technologies for the elimination of pharmaceutical compounds. Water Science and Technology, 56(5), 1–8. https://doi.org/10.2166/wst.2007.550

[19] Borghi, A. A., Palma, M. S. (2014). Tetracycline: Production, waste treatment and environmental impact assessment. Brazilian Journal of Pharmaceutical Sciences, 50(1), 25–40. https://doi.org/10.1590/s1984-82502011000100003

[20] Dolar, D., Košutić, K. (2013). Removal of pharmaceuticals by Ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO). Analysis, Removal, Effects and Risk of Pharmaceuticals in the Water Cycle - Occurrence and Transformation in the Environment, 319–344. https://doi.org/10.1016/b978-0-444-62657-8.00010-0

[21] Hou, J., Chen, Z., Gao, J., Xie, Y., Li, L., Qin, S., Wang, Q., Mao, D., Luo, Y. (2019). Simultaneous removal of antibiotics and antibiotic resistance genes from pharmaceutical wastewater using the combinations of up-flow anaerobic sludge bed, anoxic-oxic tank, and Advanced Oxidation Technologies. Water Research, 159, 511–520. https://doi.org/10.1016/j.watres.2019.05.034

[22] Nasrollahi, N., Vatanpour, V., Khataee, A. (2022). Removal of antibiotics from wastewaters by membrane technology: Limitations, successes, and future improvements. Science of The Total Environment, 838, 156010. https://doi.org/10.1016/j.scitotenv.2022.156010

[23] Zhang, J., Giorno, L., Drioli, E. (2006). Study of a hybrid process combining pacs and membrane operations for antibiotic wastewater treatment. Desalination, 194(1–3), 101–107. https://doi.org/10.1016/j.desal.2005.11.004

[24] Lu, Z.-Y., Ma, Y.-L., Zhang, J.-T., Fan, N.-S., Huang, B.-C., Jin, R.-C. (2020). A critical review of antibiotic removal strategies: Performance and Mechanisms. Journal of Water Process Engineering, 38, 101681. https://doi.org/10.1016/j.jwpe.2020.101681

[25] Rekhate, C. V., Srivastava, J. K. (2020). Recent advances in ozone-based advanced oxidation processes for treatment of wastewater- A Review. *Chemical Engineering Journal Advances*, *3*, 100031. https://doi.org/10.1016/j.ceja.2020.100031

[26] Paucar, N. E., Kim, I., Tanaka, H., Sato, C. (2018). Ozone treatment process for the removal of pharmaceuticals and personal care products in wastewater. *Ozone: Science & Engineering*, *41*(1), 3–16. https://doi.org/10.1080/01919512.2018.1482456

[27] Lim, S., Shi, J. L., von Gunten, U., McCurry, D. L. (2022). Ozonation of organic compounds in water and wastewater: A critical review. *Water Research*, *213*, 118053. https://doi.org/10.1016/j.watres.2022.118053

[28] Loganathan, P., Vigneswaran, S., Kandasamy, J., Cuprys, A. K., Maletskyi, Z., & Ratnaweera, H. (2023). Treatment trends and combined methods in removing pharmaceuticals and personal care products from wastewater—a review. *Membranes*, *13*(2), 158. https://doi.org/10.3390/membranes13020158

[29] Schmitt, A., Mendret, J., Roustan, M., Brosillon, S. (2020). Ozonation using Hollow Fiber Contactor Technology and its perspectives for micropollutants removal in water: A Review. Science of the Total Environment, 729, 138664. https://doi.org/10.1016/j.scitotenv.2020.138664

[30] Zhang, T., Lv, K., Lu, Q., Wang, L., Liu, X. (2021). Removal of antibiotic-resistant genes during drinking water treatment: A Review. Journal of Environmental Sciences, 104, 415–429. https://doi.org/10.1016/j.jes.2020.12.023

[31] Farah, M., Giralt, J., Stüber, F., Font, J., Fabregat, A., Fortuny, A. (2022). Supported liquid membranes for the removal of pharmaceuticals from aqueous solutions. Journal of Water Process Engineering, 49, 103170. doi:10.1016/j.jwpe.2022.103170

[32] Almeida, H. F., Marrucho, I. M., Freire, M. G. (2017). Removal of nonsteroidal anti-inflammatory drugs from aqueous environments with reusable Ionic-liquid-based systems. ACS Sustainable Chemistry & Engineering, 5(3), 2428–2436. https://doi.org/10.1021/acssuschemeng.6b02771

[33] Madikizela, L. M., Pakade, V. E., Ncube, S., Tutu, H., Chimuka, L. (2020). Application of hollow fibre-liquid phase microextraction technique for isolation and pre-concentration of pharmaceuticals in water. *Membranes*, *10*(11), 311. https://doi.org/10.3390/membranes10110311

[34] Pavón, S., Fortuny, A., Coll, M. T., Bertau, M., Sastre, A. M. (2020). Permeability dependencies on the carrier concentration and membrane viscosity for y(iii) and eu(iii) transport by using liquid membranes. Separation and Purification Technology, 239, 116573. https://doi.org/10.1016/j.seppur.2020.116573

[35] Alguacil, F. J., Robla, J. I. (2023). Transport of chromium(VI) across a supported liquid membrane containing Cyanex 921 or Cyanex 923 dissolved in Solvesso 100 as carrier phase: Estimation of diffusional parameters. Membranes, 13(2), 177. https://doi.org/10.3390/membranes13020177.

[36] Zeng, L., Liu, Q., Luo, L., Liu, L., Tang, K. (2019). Enhancement mechanism of an improved liquid membrane using selective permeation retardant for heavy metal ions separation. Chemical Engineering Science, 201, 1–14. https://doi.org/10.1016/j.ces.2019.02.017

[37] Zeh, M., Wickramanayake, S., Hopkinson, D. (2016). Failure mechanisms of hollow fiber supported ionic liquid membranes. Membranes, 6(2), 21. https://doi.org/10.3390/membranes6020021

[38] Obotey Ezugbe, E., Rathilal, S. (2020). Membrane Technologies in wastewater treatment: A Review. Membranes, 10(5), 89.

[39] Hao, Z., Wang, Z., Zhang, W., Winston Ho, W. S. (2014). Supported liquid membranes with organic dispersion for recovery of cephalexin. Journal of Membrane Science, 468, 90–97. https://doi.org/10.1016/j.memsci.2014.05.052

[40] Pantoleontos, G., Anagnostara, I. M., Syrigou, M., Konstandopoulos, A. G. (2022). Solutions of the mass continuity equation in hollow fibers for fully developed flow with some notes on the Lévêque Correlation. Carbon Capture Science & Technology, 2, 100027. https://doi.org/10.1016/j.ccst.2021.100027

[41] Kohli, H. P., Gupta, S., Chakraborty, M. (2019). Separation of diclofenac using pseudo-emulsion hollow fiber membrane: Optimization by box-behnken response surface design. Journal of Water Process Engineering, 32, 100880. https://doi.org/10.1016/j.jwpe.2019.100880

[42] Kohli, H. P., Gupta, S., Chakraborty, M. (2020). Characterization and stability study of pseudo-emulsion hollow fiber membrane: Separation of Ethylparaben. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 587, 124308. https://doi.org/10.1016/j.colsurfa.2019.124308

[43] Zoumpouli, G. A., Siqueira Souza, F., Petrie, B., Féris, L. A., Kasprzyk-Hordern, B., Wenk, J. (2020). Simultaneous ozonation of 90 organic micropollutants including illicit drugs and their metabolites in different water matrices. Environmental Science: Water Research & Technology, 6(9), 2465–2478. https://doi.org/10.1039/d0ew00260g

[44] Coelho, A. D., Sans, C., Agüera, A., Gómez, M. J., Espulgas, S., Dezotti, M. (2009). Effects of ozone pre-treatment on diclofenac: Intermediates, biodegradability and toxicity assessment. Science of the Total Environment, 407(11), 3572–3578. https://doi.org/10.1016/j.scitotenv.2009.01.013

[45] Monteagudo, J. M., El-taliawy, H., Durán, A., Caro, G., Bester, K. (2018). Sono-activated persulfate oxidation of diclofenac: Degradation, kinetics, pathway and contribution of the different radicals involved. Journal of Hazardous Materials, 357, 457–465. https://doi.org/10.1016/j.jhazmat.2018.06.031

[46] Alharbi, S. K., Ansari, A. J., Nghiem, L. D., Price, W. E. (2022). New transformation products from ozonation and photolysis of diclofenac in the aqueous phase. Process Safety and Environmental Protection, 157, 106–114. https://doi.org/10.1016/j.psep.2021.10.050

[47] Caviglioli, G. P., Valeria, P. Brunella, B. Gaetano, B. Gaetano, B. Gaetano, B. Gaetano.(2002). “Identification of Degradation Products of Ibuprofen Arising from Oxidative and Thermal Treatments.” Journal of Pharmaceutical and Biomedical Analysis 30:499–509. doi: 10.1016/s0731-7085(02)00400-4.

[48] Da Silva, J. C. C., Teodoro, J. A. R., Afonso, J. J. C., Aquino, S. F., Augusti, R. (2014). ”Photolysis and photocatalysis of ibu-profen in aqueous medium: characterization of by-products via liquid chromatography coupled to high-resolution mass spectrometry and assessment of their toxicities against Artemia Salina.” Journal of mass spectrometry, 49:145-153. doi: 10.1002/jms.3320.

[49] Huang, H., Liu, G. (2015). Ozone-oxidation products of ibuprofen and toxicity analysis in simulated drinking water. Journal of Drug Metabolism & Toxicology, 6(3). https://doi.org/10.4172/2157-7609.1000181

[50] He, Y., Wang, L., Chen, Z., Shen, B., Wei, J., Zeng, P., Wen, X. (2021). Catalytic ozonation for metoprolol and Ibuprofen Removal Over Different mno2 nanocrystals: Efficiency, transformation and mechanism. Science of The Total Environment, 785, 147328. https://doi.org/10.1016/j.scitotenv.2021.147328.

[51] Bourgin, M., Beck, B., Boehler, M., Borowska, E., Fleiner, J., Salhi, E., Teichler, R., von Gunten, U., Siegrist, H., McArdell, C. S. (2018). Evaluation of a full-scale wastewater treatment plant upgraded with ozonation and biological post-treatments: Abatement of micropollutants, formation of transformation products and oxidation by-products. Water Research, 129, 486–498. https://doi.org/10.1016/j.watres.2017.10.036

[52] Thobejane, M. P., van Blerk, N., & Welz, P. J. (2023). Influence of seasonality, wastewater treatment plant process, geographical location and environmental parameters on bacterial community selection in activated sludge wastewater treatment plants treating municipal sewage in South Africa. *Environmental Research*, *222*, 115394. https://doi.org/10.1016/j.envres.2023.115394

[53] Hama Aziz, K. H., H. Miessner, S. Mueller, D. Kalass, D. Moeller, I. Khorshid, M. A.. (2017). "Degradation of Pharmaceutical Diclofenac and Ibuprofen in Aqueous Solution, a Direct Comparison of Ozonation, Photocatalysis, Ozone: Science & Engineering and Non-Thermal Plasma." Chemical Engineering Journal 313: 1033–41. doi: 10.1016/j.cej.2016.10.137

[54] Olak-Kucharczyk, M., Foszpańczyk, M., Żyłła, R., Ledakowicz, S. (2022). Photodegradation and ozonation of ibuprofen derivatives in the water environment: Kinetics approach and assessment of mineralization and biodegradability. Chemosphere, 291, 132742. https://doi.org/10.1016/j.chemosphere.2021.132742

[55] Wang, W., Chen, Z., Shen, J., Yan, P., Wang, B., Yuan, L., Kang, J., Zhao, S., Liu, Y. (2023). Continuous flow experimental study on ozonation of ibuprofen catalyzed by silicate-based microfiltration membrane. Water, 15(12), 2184. https://doi.org/10.3390/w15122184

Chapter 6 Application of Ionic Liquid Aliquat 336 Liquid Membrane for Efficient Penicillin Removal: Mathematical Modelling and Optimization

Abstract

Penicillin-G (Pen-G), a pharmaceutical compound was removed from aqueous media by means of quaternary ammonium salt (Aliquat 336) in both flat sheet (FS) and hollow fiber (HF) supported liquid membrane (SLM). This study calculates the extraction constant of pen-G with Aliquat 336 (K_{ext}=1.62) after a series of liquid-liquid extraction. Furthermore, a mathematical model was developed to simulate the mass transfer of Pen-G and chloride ions in both systems The mass transfer coefficients for the aqueous feed (K_{aq}) and the organic membrane phase (K_{org}) were optimized using Matlab (2021b). The model showed good agreement with the experimental data, The results reveal that the transport process is mostly controlled by the diffusion or the viscosity of the organic membrane depending on the carrier concentration This study provides valuable insights into the transport mechanism of penicillin-G and highlights the potential of supported liquid membrane systems for efficiently removing pharmaceutical compounds from aqueous media.

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1. Introduction

Nowadays, a wide range of unregulated chemicals of natural origin or synthetic production are being detected in different water bodies. Even though their environmental concentration is low, these compounds are being widely studied due to their potential health effects, pervasive nature, and difficult degradation through conventional techniques [1,2]. The production and consumption of pharmaceuticals have experienced a notable surge in recent decades. Consequently, these compounds are frequently discharged and detected in water streams and wastewater [2]. Pharmaceuticals are vital for human well-being, serving as remedies for various illnesses and infections. They are classified into different groups or classes based on their chemical structures, mechanisms, and mode of action. [3,4]. Penicillin-G (Pen-G) is a common antibiotic frequently consumed due to its broad spectrum of activity and excellent distribution in the human body [3]. However, the occurrence of penicillin G in water sources can have serious environmental impacts and potential risks to human health [3,4]. In fact, the occurrence of antibiotics in nature and water streams even at low concentrations can contribute to the development of antibiotic resistance. [3]. According to Du et al (2011), approximately 90% of residual antibiotics are released via feces and urine and they can eventually reach the sewage and water systems [5]. In addition, Kumar et al. (2005) have discussed the potential ground and surface water contamination by antibiotics through leaching processes and their introduction via agricultural runoff [6]. As an example, the human body absorbs only about 15% to 30% of Pen-G and the remaining is excreted without undergoing metabolism [7]. Several studies have reported the detection of penicillin in water bodies at a relatively low concentration of 0.93 μg/L due to its bioaccumulation. Hence, to preserve the well-being and ecological balance of aquatic systems, safeguard the quality of drinking water sources, and minimize potential human health hazards, it is essential to ensure the appropriate removal of antibiotics like penicillin G [8]. Several techniques have been studied to remove penicillin -G from different water matrices. Advanced oxidation processes (AOPs) such as ozone or hydrogen peroxide with ultraviolet (UV) irradiation or with persulfate are investigated for penicillin removal [9, 10, 11, and 12]. Zhang et al (2020) proved that 95 % of penicillin was removed through catalytic ozonation using natural zeolite in less than 15 minutes [9]. Moreover, Norzaee et al. (2017) examined the feasibility of UV-activated persulfate as an alternative to hydroxyl radicals to degrade Pen-G from water [11]. Their research revealed that ($SO_4^{\cdot}$) effectively eliminated the antibiotic, achieving over 95% removal within 90 minutes.

However, the implementation of AOPs is still constrained and associated with high operating costs, energy requirements, and generation of by-products [12]. Recently, Correa et al. (2020) suggested that the synergistic effects between oxidation processes should be investigated on a pilot scale to analyse the formation of by-products as well [13]. Among the various methods for Pen-G removal, adsorption has emerged as one of the most established techniques. It is widely recognized for its efficiency and simple operation. The removal of Pen-G has been explored using a variety of adsorbents, including commercial activated carbon (AC) [14], catalytic-induced AC [15], powdered AC [14], and chestnut shells [16]. Certain adsorbents require prior activation treatments, such as chemical or thermal activation, to enhance their surface areas and these treatments require critical temperature and pH conditions, which can add cost and complexity to the process. For instance, Ania et al. (2010) highlighted the necessity of prior acid and base activation for activated carbon to effectively remove penicillin from water [17]. Furthermore, to this date, most adsorption studies remain limited to batch experiments, and the potential regeneration of the adsorbent requires further exploration. Among different conventional and advanced processes to remove Pen-G from water, membrane processes are gaining more attention [18]. The application of pressure-driven membranes such as membrane filtration, reverse osmosis, and nanofiltration methods are being developed to remove different types of antibiotics [18]. The main principle of membranes is based on size exclusion or molecular sieving to prevent the passage of larger molecules, including pharmaceutical compounds. Additionally, the antibiotic's physicochemical properties (particle size, pKa, etc.), membrane properties (nature of the material, pore size, etc.), and characteristics of the medium (pH, ionic strength, etc.) play a major role in the performance and rejection rate [18, 19]. Though membrane processes are not as popular as adsorption for PEN-G, nanofiltration is the most studied membrane process due to its high efficiency.[18,19]. High promising results were obtained with nanofiltration for the removal of different antibiotics from real effluent of wastewater [20]. On the other hand, a combination of ultrafiltration and electrolysis yielded a maximum of 42 % of penicillin removal [21]. The major drawback associated with the membrane process is the fouling mechanism that can affect the performance and increase operating costs due to maintenance, cleaning agents, and equipment shutdown [19]. On another hand, solvent extraction has been employed as well to recover and extract Pen-G from water, and fermentation broth. It is a highly developed method for penicillin G recovery, yet it requires a high quantity of solvent to achieve promising results. Rescheke et al (1984) showed that potential loss of penicillin G results with n-butyl acetate

solvent extraction due to the instability of the antibiotic at low pH [22]. To tackle the limitations associated with solvent extraction and pressure-driven membranes, liquid membranes emerge as the best alternative option. [23]. By definition, liquid membranes (LM) selectively separate and concentrate specific compounds from mixtures by combining extraction and stripping into a single integrated unit [23,24]. The membrane is a liquid organic extractant that can successfully transport the desired solute. In previous studies, the extraction of Pen-G was investigated with different types of Lm such as bulk liquid membrane (BLM) [25], emulsion liquid membrane (ELM) [26], and supported liquid membrane (SLM) (flat sheet and hollow fiber) [27] using anionic liquid (Aliquat 336) or neutral extractant (TBP). Aliquat 336 is an ionic liquid, which means it consists of large organic cations and small inorganic anions. This unique structure contributes to its excellent solvation properties and high extraction efficiency for polar compounds like penicillin [27,28,29]. In comparison with the different listed types, SLM is particularly studied, for a wide range of applications, including pharmaceuticals [24]. The most common configurations are flat sheet (FSSLM) and hollow fiber (HFSLM) yet despite their simplicity, they are still prone to the instability of organic extractants [24]. For scale-up purposes, the studies are directed toward hollow fiber liquid membranes due to their resistance to stability issues [24]. The distinctive geometry of hollow fibers, characterized by a high packing density and a high volume-to-area ratio, enables them to withstand significant pressure, ensuring greater stability in various applications [28]. Notably, previous investigations of Penicillin-G (Pen-G) removal in hollow fiber supported liquid membranes (HFSLM) using Aliquat 336, yet the primary focus was on process design, with limited attention given to understanding the underlying mechanism and conducting comprehensive mass transfer studies [29].

To the best of our knowledge, no work has been reported addressing the extraction equilibrium, mass transfer analysis of penicillin-G and Aliquat 336, along with the comparison between the performance of a flat sheet liquid membrane (FLSLM) and hollow fiber membrane (HFSLM). The main objective is to gain a deeper understanding of the mechanism and enhance the practical application of liquid membrane technology in industrial settings for the removal of penicillin G from water. In the following study, the removal of Pen-G from water was investigated with both FSLM and HFSLM using ionic liquid extractant (Aliquat 336) and KCl as stripping agent. Firstly, Liquid-liquid extraction (L-L) was conducted to determine the equilibrium constant and the optimum operational parameters including extractant concentration, pH of the feed, and stripping agent concentration. Finally, mathematical models

were developed for both configuration modules. These models serve as valuable toolsets to predict the performance of these systems. They offer a valuable toolset to better understand and optimize operations and address any troubleshooting prior to any applications.

2. Materials

Penicillin G sodium salt (CAS 13752, 96%) was obtained from Sigma Aldrich. Quaternary ammonium salt (Aliquat 336) (CAS 63393, 90.9%), provided by Alfa Aesar was selected as the organic extractant. Kerosene (CAS 8008-20, ≥99%) was used as the diluent, and Decanol (CAS 112-30, ≥99.9 %) as a phase modifier were purchased from sigma Aldrich. All remaining reagents, including potassium chloride (KCl), acetonitrile, sodium hydroxide (NaOH), and hydrogen chloride (HCl) were analytical grade and obtained from Sigma-Aldrich. The feed was prepared by dissolving a specified concentration of the antibiotic in distilled (pH =6.0) and stored at a low temperature (2 ^{o}C) until use. The organic extractant solution was prepared by dissolving a specific concentration of Aliqaut 336 in 10 %(v/v) decanol /kerosene. The stripping solution used was an aqueous solution of 0.5 mol/L of KCl in distilled water.

In FSSLM, The polymeric solid support used is Millipore polytetrafluoroethylene (PTFE) Supplied by Merk and the membrane specifications are listed in Table 1. Hollow fiber membrane module (G-502 from Liqui-Cel^{TM}) was selected, and its specifications are summarized in Table 2.

Table 1. Specifications of PTFE support (Fluoropore^{TM} FHLP04700).

Parameters	Value
Material	PTFE
Diameter (mm)	47
Pore diameter (µm)	0.45
Porosity (%)	85
Effective area (cm^2)	11.4
Thickness (µm)	150
Tortuosity	2.5

Table 2. Hollow fibre membrane module (G-502 from Liqui-Cel^{TM}).

Parameters	Value
Membrane/plotting material	Polypropylene /polyethylene
Module diameter (cm)	7.7
Module length (cm)	27.7
Membrane Area (m^2)	1.4
OD/ID (µm)	300/200
Porosity (%)	40
tortuosity	2.7
Hold-up volume shell side (cm^3)	400
Hold-up volume lumen side (cm^3)	150
Number of fibers	10000

3. Methods

3.1. Liquid-liquid extraction (L-L)

To determine operational parameters and asses the extraction of Pen-G with Aliquat 336, L-L experiments were conducted initially. A volume of 10 mL aqueous phase containing 30 mg/L of Pen-G was added to 4 mL Aliquat 336 with concentration ranging from, (0-10) %v/dissolved in 10 % (v/v) in decanol/kerosene.

The mixture was stirred at 140 rpm for 20 minutes at room temperature. This time was determined to be sufficient to reach equilibrium. Afterward, the phases were allowed to settle, and separate. Samples were taken from the aqueous phase and the concentration of antibiotics was measured by HPLC. To determine the concentration of Pen-G in the loaded organic phase, a mass balance calculation was performed by comparing the antibiotic quantity before and after extraction. The accuracy of the mass balance was further confirmed by measuring the concentration of Pen-G in the stripped aqueous phase. In order to determine the conditions in the stripping phase, L-L experiments were performed by adding different concentrations of KCL (0-0.5M) to the solution and measuring the concentration of Pen-G after phase separation. The concentration of penicillin in the aqueous phase was determined by Agilent 2200 HPLC with a Hypersil ODS C18-5M (4 x 250mm) column and a UV detector at 230nm. The mobile phase consisted of 0.02 mol/L KH_2PO_4 and methanol in a volume ratio of 38:62. The flow rate

of the mobile phase was 1.0 mL/min. All pH-value changes in both aqueous solutions were measured by a Crison pHmeter GLP21. The viscosity of various concentrations of Aliquat 3386 was measured with a ThermoHake viscometer at 25 ºC.

3.2. **FSSLM Experiment**

In the flat sheet, a polymeric, hydrophobic, and porous material is used as a support for the organic extractant. The impregnated support is placed between the feed and stripping solutions to separate the two phases. The experimental setup followed the methodology described by Farah et al. [30]. The feed constituted 220 mL of adequate Pen-G concentration dissolved in water at pH 6 and the stripping cell contained 0.1 M of KCl. The PTFE polymeric support was immersed in a 5 mL solution of the organic extractant, (a specific concentration of Aliquat 336 diluted in a 10% mixture of decanol and kerosene). After soaking for several minutes, the support was positioned between the two cells. Following this, the stripping and feed phases were introduced respectively. Both phases were mechanically stirred at 1000 rpm and maintained at room temperature (20 ± 2 °C). The pH was continuously measured in both cells and samples were periodically collected to measure the concentration of Pen-G as described in section 3.1.

3.3. **Hollow fiber transport**

The experiments with hollow fiber supported liquid membrane (HFSLM) were conducted with G-502 module with different volumes in the feed (8L) and the stripping tanks (2 L) in order to pre-concentrate the streams.

Firstly, a desired concentration of the organic extractant, Aliquat 336 in 10% (v/v) decanol/kerosene was circulated through the lumen side (inside the tubes). Afterward, the membrane was washed with distilled water to remove any extra organic from the tubes. The feed with a concentration of Pen-G at pH 6 was circulated in the shell side while the stripping containing 0.1 mol/L of KCL was passed in the lumen side. The two phases flowed concurrently at a rate of 50 L/h, with a slightly positive pressure maintained to prevent any leakage of organic extractant from the pores. The hydrophobic nature of the membrane material helped to immobilize the organic extractant in the pores. Pen-G diffused from the shell side through the membrane phase to the lumen side. Samples were taken from the feed and stripping phases at different time intervals to evaluate the evolution of Pen-G concentration. All

experiments were conducted in duplicates only since the reproducibility of the data was always within ±5% error.

In addition, this study explored the impact of Aliquat 336 concentration, and the various concentrations of organic extractants and their corresponding viscosities are detailed in Table 3. When employing a hollow fiber module, it becomes necessary to completely remove the organic extractant within the pores when transitioning between different concentrations of Aliquat 336. For this reason, the transmembrane pressure was changed to -1 bar to force the organic extractant to cross the fiber pores to the feed phase. The membrane is refilled with a new concentration by obtaining three times the volume of the pores in the feed. All experiments were conducted in duplicates only since the reproducibility of the data was always within ±5% error.

Table 3 Different concentrations of Aliquat 336 in decanol/kerosene used in experimental studies.

Aliquat 336 (mol/L)	**Viscosity (mPa·s) at 25 ºC**
0	2.36
0.0179	2.53
0.089	3.25
0.125	3.84
0.179	4.68

4. Development of the model

4.1. Liquid-Liquid Extraction

Penicillin G (Pen-G) is a weak acid (pK_a = 2.75) that contain carboxylic and amide functional groups within its molecular structure. It can be found in aqueous solutions either in neutral form (HP) or its anionic form (P^-). Pen-G behaviour depends on the pH of the solution and the dissociation equilibrium can be expressed as:

$$HP \leftrightharpoons H^+ + P^-$$

In the following study, the pH was kept at 6 (pH>pKa) thus the dominant form in the solution is the anionic species (P^-). In this case, the ionic liquid, Aliquat 336 $[R_4N\ Cl^-]_{org}$ forms a complex with targeted compounds, P-, in the feed phase, to obtain $[R_4\ N^+ \cdot P^-]$. These complexes are more soluble in the membrane and are successively transported to the stripping phase by countertransport mechanism. The facilitated transport by countertransport is ensured by the

presence of charged molecules in the stripping phase (Cl^-) that release (P^-) from the membrane by ion exchanges [29,31]. Initially, the concentration of dominant species can be calculated from (Eq.1) according to the dissociation constant and initial pH of the solution:

$$C_f = C_0 \cdot \frac{10^{-pK_a}}{10^{-pH} + 10^{-pK_a}} \quad \text{Eq. (1)}$$

With C_f, the concentration of the anionic species (P^-), and $C_{0,}$ the initial concentration (Pen-G) present in the feed.

As mentioned previously, the reactive extraction of the anions (P^-) with Aliquat 336 $(R_4N^+Cl^-)_{org}$ is based simultaneously on the transport and the counter transport of two different anions to maintain the solution electro neutrality [31]. The reaction occurring between the feed and the organic extractant at the feed-membrane interface is given by:

$$R_4N^+Cl^-_{(org)} + P^-_{(aq)} \leftrightharpoons R_4N^+ \cdot P^-_{(org)} + Cl^-_{(aq)}$$

The main purpose of L-L experiments is to determine the extraction constant (K_{ext}) of Pen-G and Aliquat 336 at equilibrium. It is a fundamental parameter for liquid membrane transport that measures the affinity of the solute to the organic extractant. K_{ext} is defined as the ratio of the concentration of the solute in the extracting phase to its concentration in the feed at equilibrium [24,31]. Based on the extraction reaction of Pen-G with Aliquat 336, K_{ext} can be expressed as the following:

$$K_{ext} = \frac{[R_4N^+ \cdot P^-] \cdot [Cl^-]}{[P^-] * [R_4N^+ \cdot Cl^-]}$$

Knowing that the concentration of Pen-G in the aqueous solution is given by Eq.(1), K_{ext} is calculated using Eq.(2)

$$Kext = \frac{C_{mfi} \cdot [Cl^-]}{C_0 \cdot 10^{-pK_a}/(10^{-pH} + 10^{-pK_a}) \cdot C_{org}} \quad \text{Eq. (2)}$$

With C_{mfi}, the concentration of the complex formed in the organic membrane; $[Cl^-]$, the concentration of the stripping agent and C_{org}, the concentration of Aliquat 336.

4.2. Transport in FSSLM

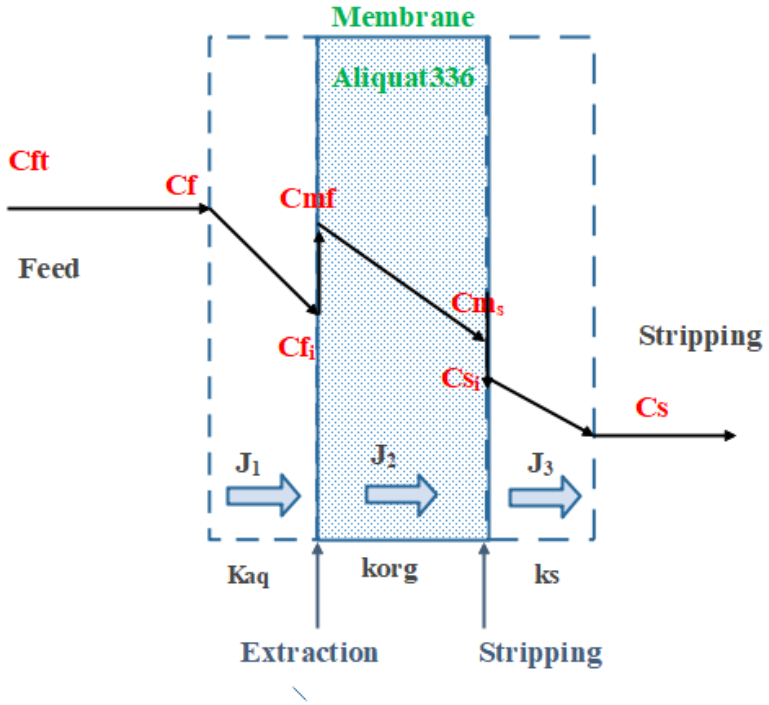

Figure 1. Concentration profile for the transport in liquid membrane considering the three different resistances (diffusion on feed and stripping sides and through the membrane).

The transport of Pen-G through supported liquid membrane (SLM) is facilitated by a coupled carrier, following a cotransport mechanism. Specific assumptions are adapted for understanding and modeling the diffusion of this pharmaceutical in these membrane systems:

- Steady-state conditions are applied in the interfaces and the membrane; hence all fluxes are equal.
- The diffusion process is controlled by 1st Fick´s law of diffusion.
- Instantaneous extraction and stripping reactions at the interfaces.
- The concentration of anionic species (P^-) in stripping phase is maintained near to zero (C_{ms} = 0) since the concentration of chloride present is much greater than the pharmaceutical transported.

4.2.1. Overall Mass transport flux

The transport through the membrane involves three types of resistance: (1) diffusion resistance on the feed aqueous boundary layer, (2) diffusion through the liquid membrane, and (3) diffusion resistance on the stripping side [24,31,32]. The overall concentration profile is depicted in Figure 1. Yet assuming an instantaneous stripping reaction, the diffusion through

the feed phase and the membrane are considered the main contributors to the overall mass transfer flux (J).

The flux in the feed liquid film and the membrane are expressed in the following equations Eq. (3) and (4), respectively.

$$J_1 = K_{aq} \cdot (C_f - C_{fi}) \quad \text{Eq. (3)}$$

$$J_2 = K_{org} \cdot (C_{mf} - C_{ms}) \quad \text{, with } C_{ms} = 0 \quad \text{Eq. (4)}$$

Given J_1, flux through the aqueous feed diffusional film ($mol \cdot cm^{-2} \cdot s^{-1}$); J_2, flux through the liquid membrane diffusional film, ($mol \cdot cm^{-2} \cdot s^{-1}$); K_{aq} and K_{org} are respectively the mass transfer coefficients in the aqueous feed and organic membrane, ($cm \cdot s^{-1}$); C_f , Pen-G concentration in the bulk feed solution; C_{fi}, Pen-G concentration at the feed-membrane interface, and C_{mf}, Pen-G concentration in the feed/membrane interface.

In steady-state conditions, the flux remains constant, this means that $J=J_1=J_2$,

Additionally, at different concentrations of organic extractant, the mass transfer in the membrane is dependent on the viscosity (μ) as shown in Eq. (5)

$$K_{org} = K' \cdot \mu^{-\alpha} \quad \text{Eq. (5)}$$

Where α is a coefficient with a value of 0.5 for high viscous liquid [33], μ, the viscosity (mPa·s) and K′, proportionality constant $(mPa \cdot s)^{1/2} \cdot cm/s$)

Subsequently, the correlation between the different Aliquat 336 concentrations of and their relative viscosities was established and presented in Eq. (6)

$$\mu = 28.733 \cdot C_{org}^2 + 7.895 \cdot C_{org} + 2.365 \quad \text{Eq. (6)}$$

Finally, the flux as shown in Eq.(7) in the membrane is obtained by combing the three equations Eq.(4),(5), and (6).

$$J_2 = K' \cdot \left(28.733 \cdot C_{org}^2 + 7.895 \cdot Corg + 2.365\right)^{-0.5} \cdot C_{mf}\right) \quad \text{Eq. (7)}$$

4.2.2. **Solute Mass Balance**

The mass balance in the feed tank is given by:

Input + Generation – Output + Consumption = Accumulation

In the case of FSSLM, the feed and stripping cells are treated as perfectly mixed reactors. This implies that there are no changes in solute concentration in either the radial or axial directions or mass transfer or chemical reactions are taking place within the system. As a result, the mass balance in the feed is simplified and expressed in Eq. (8)

Accumulation = - Output

$$V \cdot \frac{dC}{dt} = -J \cdot A \qquad \text{Eq. (8)}$$

Where J, the molar flux J ($mol \cdot cm^{-2}\ s^{-1}$), A, area of the membrane (cm^2), V, the volume of the feed (cm^3), dC/dt , the rate change of the total concentration of Pen-G in the feed.

4.3. Transport in HFSLM

The overall mass transfer coefficients in hollow fiber modules can be either determined experimentally or by using theoretical correlations. The mass transfer coefficients in hollow fiber modules depend on the flow conditions in the shell and lumen side (tube). Various correlations expressing these dependencies are available in the literature [34, 35].

The simplified plug-flow modelling approach is adapted considering solely the axial variation of the solute concentration (Pen-G) and with negligible radial variation.

The model considers the solute concentration changes in the circulating fluids within the membrane module and the feed tank.

4.3.1. Mass balance in the membrane

The primary difference between flat sheet and hollow fiber membranes lies in the concentration change that occurs not only over time but also along the length of the membrane.

The boundary conditions are established as follow:

At initial time t_0, $C_{fout}=C_0$ and $C_{Cl^-}=0$

With C_f and C_0 are Pen-G concentrations in the feed at time t and t_0 respectively.

The feed and the stripping solution flow through the module in a concurrent flow, they enter the membrane at a position at z = 0 and exit at a position z= L, the boundary conditions are as follows:

for z= 0 $Cm_{in} = C_f$, and z=L $Cm_{out}=Cf_{in}$;

Cm_{out} and Cm_{in} are Pen-G concentrations in the inlet and outlet of the membrane and Cf_{in} and C_f are Pen-G concentrations entering and exiting the tank, respectively.

In HFSLM, the residence time of the feed tank is significantly longer than the residence time of the fluids passing through the module, therefore the mass balance in the membrane under pseudo steady state condition is obtained in Eq.(9).

$$J = \frac{Q}{A}\,(Cm_{in} - Cm_{out}) \qquad \text{Eq. (9)}$$

Where Q, is the volumetric flow rate ($cm^3 \cdot s^{-1}$) ; A, is the total area of the membrane (cm^2);

J, is the amount of Pen-G transferred by diffusion to the aqueous feed phase per unit time and unit area and equal to the overall mass transport flux ($mol \cdot cm^{-2} \cdot s^{-1}$), and Cm_{in} and Cm_{out} are the concentrations of Pen-G entering and exiting the module, respectively.

4.3.2. Mass balance in the feed tank

The general mass balance of Pen-G under non-steady-state conditions in the feed is simplified and expressed as shown in Eq. (10):

Input – Output = Accumulation

$$V_f \cdot \frac{dC_f}{dt} = Q_f \cdot (C_{f_{in}} - C_f) \qquad \text{Eq. (10)}$$

Given V_f , the volume in the feed tank (cm^3); Q_f, , volumetric flow rate ($cm^3 \cdot s^{-1}$) and C_{fin},, C_f are the concentrations in and out of the feed tank and are equivalent to the concentrations exiting and entering the membrane module, respectively.

5. Results

5.1. Liquid –Liquid extraction (L-L) and K_{ext} determination

Understanding and controlling the equilibrium constant is essential in optimizing liquid membrane processes for various separation and purification applications.

The feasibility of Aliquat 336 for extracting Pen-G from aqueous solutions was investigated in a series of L-L experiments. The primary objective of these L-L experiments was to establish the extraction constant (K_{ext}) which would subsequently be used in the mathematical modelling for both FSSLM and HFSLM.

This study examined the impact of various parameters on the extraction efficiency, including the initial pH, concentration of the organic extractant, and stripping agent. The specifics of the experimental conditions are presented in Table 4. All experiments were carried out with a constant initial concentration of Pen-G dissolved in water (C_0=30 mg/L). This concentration, although relatively higher than the one typically found in water matrices, was chosen to ensure the precise detection of concentration variations and to minimize potential analytical errors.

Table 4. Range of individual parameters selected for L-L extraction (C_0=30 mg/L, T=25±°C).

C_{org} (mol/L)	Cl^- (mol/L)	pH
0.0179	0.05	2
0.053	0.1	5

0.089	0.35	8
0.179	0.51	11

The impact of the organic extractant, ranging from 0.0179 to 0.199 mol/L was studied at constant Pen-G and KCl concentrations of 30 mg/L and 0.1 mol/L, respectively. The results presented in Figure 2 show that the extraction of Pen-G increased with increasing Aliquat 336 concentration in decanol/kerosene. An extraction of 98% of Pen-G was obtained with 0.179 mol/L of Aliquat 336. Similar trends were obtained when varying the concentration of different ionic liquids to separate Cd(II) and Cu(II) and to extract boron [35]. A high concentration of organic extractant enhances the formation of the following complex [$R_4\ N^+ \cdot P^-$] (Aliquat336-Pen-G) and therefore the extraction of penicillin-G from aqueous solution. Moreover, the stoichiometric coefficient for the extraction reaction involving Pen-G and Aliquat 336 was calculated. In addition, the correlation between the logarithm of the distribution coefficient (log(D)) and the logarithm of the Aliquat 336 concentration, as shown in Figure 3, indicates the participation of one mole of Aliquat 336 in the process. Similar conclusions have been reached by other researchers, that one mole of the antibiotic extracted by one mole of Aliquat 336 [28, 36]. These findings provide further evidence for the extraction mechanism and the stoichiometry of the complex formed during the extraction process. Hence, the extraction reaction can be represented by:

$$R_4N^+Cl^-_{(org)} + P^-{}_{(aq)} \leftrightharpoons R_4N^+P^-{}_{(org)} + Cl^-{}_{(aq)}$$

The extraction process can also be influenced by the pH of the solution. Therefore, the effect of pH was also determined at an initial Pen G concentration of 30 mg/L and a constant Aliquat 336 concentration of 0.179 mol/L. Different samples were prepared from pH 2 to 11 either by adding a few drops of HCl or NaOH. The results obtained in Figure 4, prove that the extraction of Pen-G is pH dependent. The extraction efficiency increases with pH to reach a maximum value at pH between 5- 6. Pen-G is essentially a weak monocarboxylic acid with pk_a of 2.75, when the pH is lower than the pKa, the anionic species (P-) dominate in the solution facilitating its interaction with Aliquat 336. However, a further increase in the pH can result in a significant reduction in extraction efficiency as shown in Figure 3. This decrease can be explained by the possible hydrolysis of nucleophilic β-lactam ring within the structure of penicillin G [36].

To determine the optimal conditions for the stripping phase in SLM experiments, the influence of chloride concentration in the extraction process was examined, varying from 0 to 0.5 mol/L,

All other parameters remained constant, including a Pen-G concentration of 30 mg/L, a pH of 6, and an Aliquat 336 concentration of 0.179 mol/L. As shown in Figure 5, the extraction efficiency decreased with increasing of chloride ion (Cl^-) reaching a minimum value of 0.5 M. As previously explained, the transport mechanism with Aliquat 336 requires the sequential reaction with a charged stripping agent (Cl^-) to break the complex formed in the membrane and release the pharmaceutical in the stripping tank. Potassium chloride (KCl) was chosen as the stripping agent, whereas various studies have explored different stripping agents such as K_2CO_3 and NaCl [37, 38]. Bi et al. (2009) achieved a substantial extraction of Pen-G with ionic liquid and NaCl in the stripping phase [38].

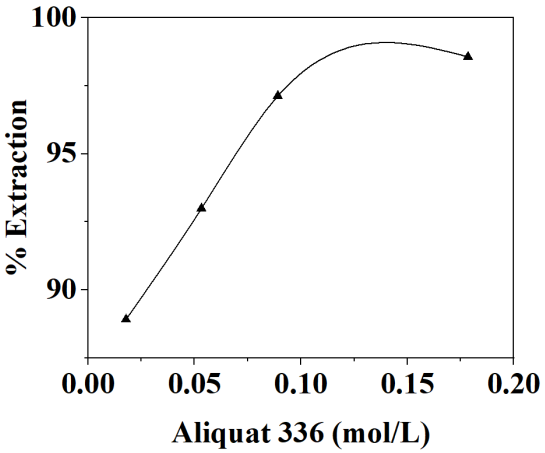

Figure 2 Influence of Aliquat 336 concentration on Pen-G extraction

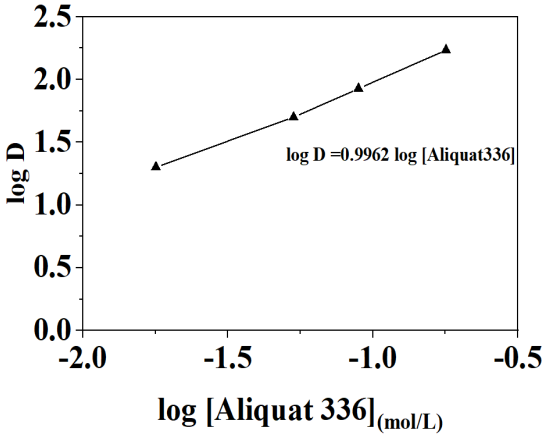

Figure 3 Log D vs. log [Aliquat336] to show 1:1 reaction mechanism.

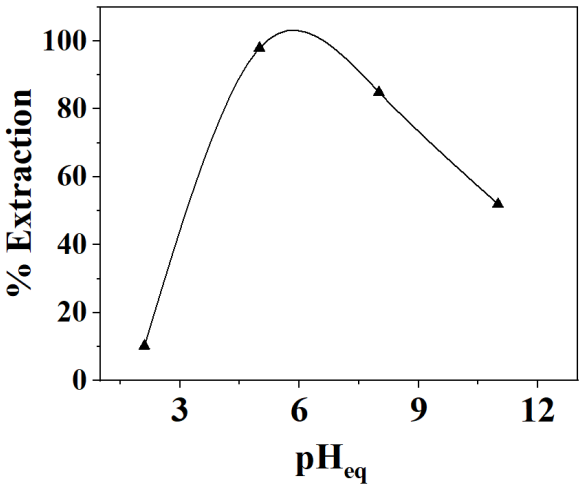

Figure 4. Influence of pH_{eq} on Pen-G extraction.

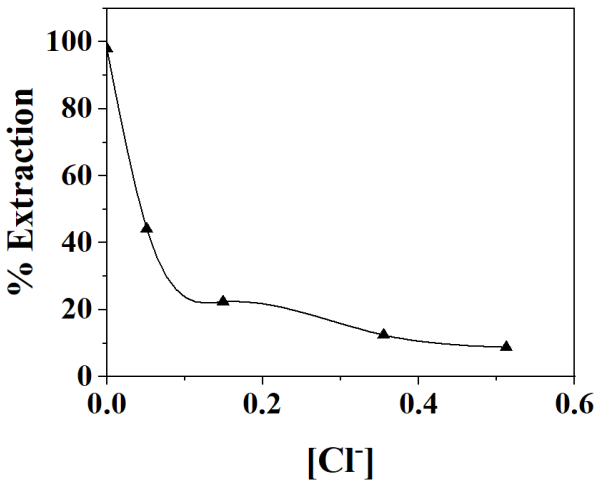

Figure 5. Influence of KCl concentration on Pen-G extraction.

To date, no prior research has reported the extraction constant (Kext) for Pen-G) extraction using Aliquat 336. Consequently, Kext =1.62 was consistently obtained at various L-L experimental conditions. However, it was not possible to compare this result with existing data. This constant value was subsequently applied in the modelling of FSSLM and HFM.

5.2. **Model development**

5.2.1. FSSLM

Preliminary experiments in flat sheet membranes aim to provide a better understanding of the system before transitioning to more advanced membrane configurations. In the previous section 4.1, a model describing the transport mechanism of Pen-G and chloride ions (Cl^-) was derived based on diffusional parameters using the 1st Fick's law and the flux equation. The diffusion process is governed by the resistance in the feed phase boundary layer and the liquid membrane phase. Therefore, the mass transfer coefficients K_{aq} and K_{org} were determined and optimized by solving various differential equations using Matlab (R2021b). The experimental data was introduced at the start of the program as four matrices. The experiments conducted in FSSLM are summarized in the following Table 5 and the full description of the model is shown in Figure 6.

Table 5 Conducted experiments with FSSLM.

n_{exp}	C_{org} (% v/v)	C_{org} (mol/L)	Viscosity (mPa·s)	C_0 (mg/L)	$[Cl^-]$ (mol/L)
1	1	0.0179	2.526	30	0.1
2	5	0.089	3.258	30	0.1
3	7	0.125	3.845	30	0.1
4	10	0.179	4.68	30	0.1

- Each experiment is repeated in duplicate.

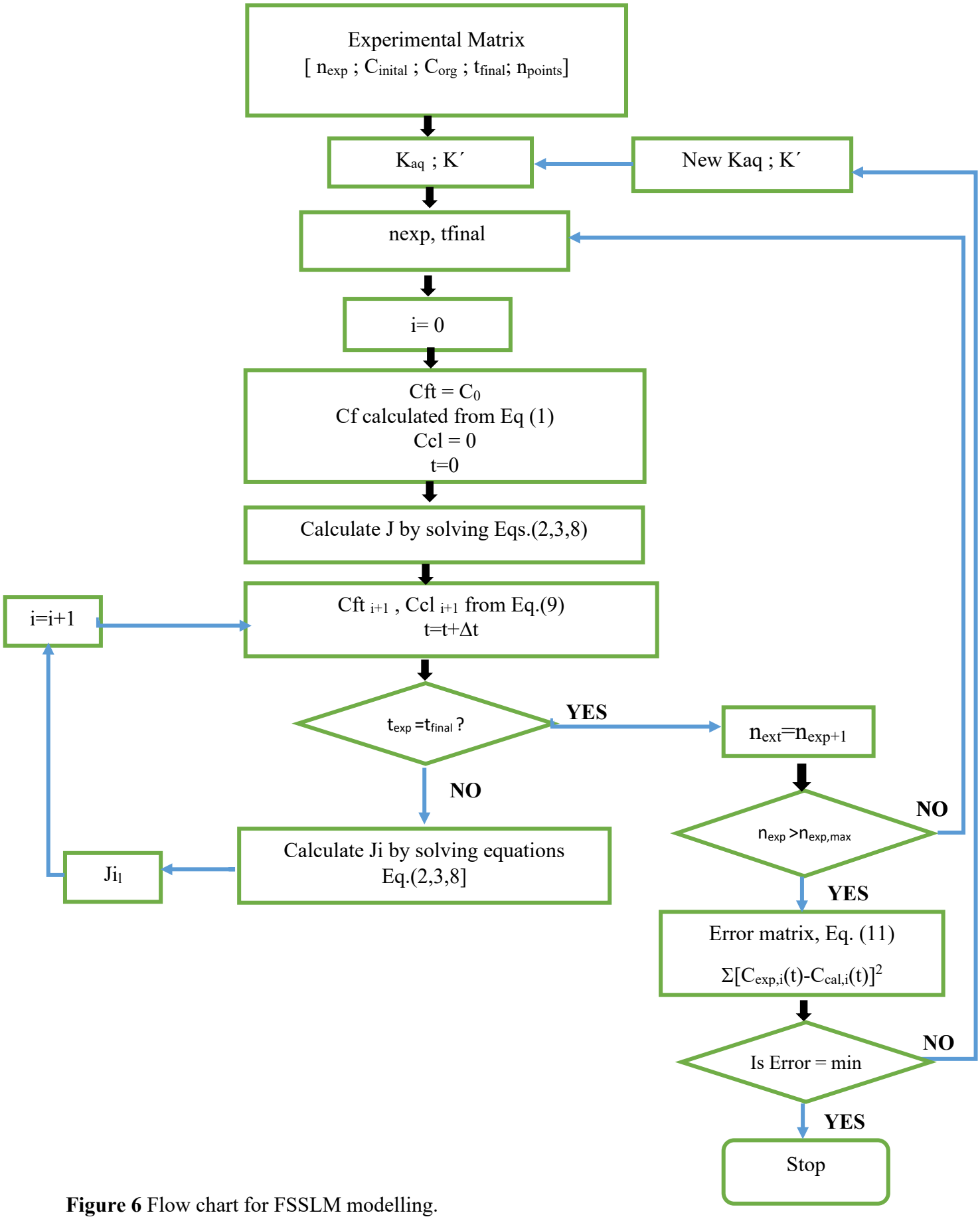

Figure 6 Flow chart for FSSLM modelling.

Firstly, initial values of K_{aq} and K_{org} were provided, and the calculations were performed within an inner loop for each experimental condition (i) at various time points (t). The *fsolve* function was employed to solve the series of nonlinear equations as described in section 4.2.1 and to calculate the mass transport flux (J). This latter function is linked to an external minimization function, *fmincon*, an optimization function that helps find the minimum or maximum of a given objective function E(x) presented in Eq. (11), subject to constraints. It determines the error between the calculated (Cf_{calc}) and experimental (Cf_{exp}) of the pharmaceutical in the feed. If the error of the objective function is reduced to a minimum, the calculation process concludes; otherwise, it proceeds by proposing new values for K' and K_{aq}. This iterative process is repeated until the error is minimized. In this manner, the program systematically seeks the transport coefficients, adjusting them until the simulated data aligns with the experimental results, thereby achieving the lowest value of the objective function.

$$\mathrm{Error(i)} = \sum_{i=1}^{N} (Cf_{exp,i} - Cf_{calc,i})^2 \qquad \text{Eq.(11)}$$

The mass transport coefficient in the aqueous and the membrane phases in FSSLM system are presented in Table 6.

Table 6 Optimization parameters values.

K_{aq} x10^{-2} (cm/s)	K´x10^{-4} ($\sqrt{mPa \cdot s} \cdot$ cm/s)
0.48	0.12

5.2.2. HFSLM

For industrial purposes and high extraction and separation results, hollow fiber configurations are more adapted as they provide more accurate assessment of the effectiveness and the performance of liquid membranes. A series of experiments were conducted with Pen-G and Aliquat 336 (Table 7) in order to calculate and optimize the mass transfer coefficient of these systems.

The developed mathematical model for the HFSLM is based on mass balances for the species Pen-G and chloride (Cl^-) involved in the extraction and stripping respectively. A full description of the model is presented in Figure7.

Table 7 Experimental conditions for HFSLM

n_{exp}	C_{org} (% v/v)	C_{org} (mol/L)	Viscosity (mPa·s)	C_0 (mg/L)	Cl^- (mol/L)
1	10	0.179	4.68	10	0.1
2	10	0.179	4.68	10	0.5
3	1	0.0179	2.52	10	0.1
4	5	0.089	3.25	10	0.1
5	7	0.125	3.845	10	0.1
6	10	0.179	4.68	10	0.1

*Each experiment is conducted in duplicate

Compared to flat sheet membranes, the variation of Pen-G concentrations in HFSLM are influenced by mass balances in both the feed and the membrane module, whereas in FSSLM, it relies solely on mass transfer within the feed. The change in concentration is influenced by factors such as the axial position within the membrane module and the time-dependent alterations in the feed and stripping tanks.

The mass transfer coefficients in the aqueous feed (K_{aq}) and the proportionality constant (K′) were determined using Matlab (2021b). Firstly, the boundary conditions are set as described in the previous section (4.3.2) and initial values were given to each of K_{aq} and K′.

The inner loop is initiated for a specific condition (i) at various experimental times (t) in the membrane module. The concentrations of both species in the axial position were calculated by dividing the membrane into subdivisions (n steps). Each subdivision was considered as a flat

sheet membrane, and the mass balance for Pen-G and Cl^- is established to determine the flux (J) and the concentration exiting at each subdivision. At the final subdivision ($n_{step} = n_{stepfinal}$), the mass balance was defined in the feed tank, and the concentration of both species exiting the feed phase was calculated. Ultimately, The optimization function ¨*fmincon*¨ was introduced to minimize the error of the objective function E(x) as described previously in Eq.(11) by adjusting the values of K´ and K_{aq}. This process is repeated until the lowest objective function and the calculated concentration matches the experimental results.

The model enables the calculation of K_{aq} and K´, as presented in Table 8 in HFSLM

Table 8. Optimized parameters for HFSLM

$K_{aq} \cdot 10^{-2}$ (cm/s)	$K' \cdot 10^{-8}$ ($\sqrt{mPa \cdot s}$ ·cm/s)
3.39	0.32

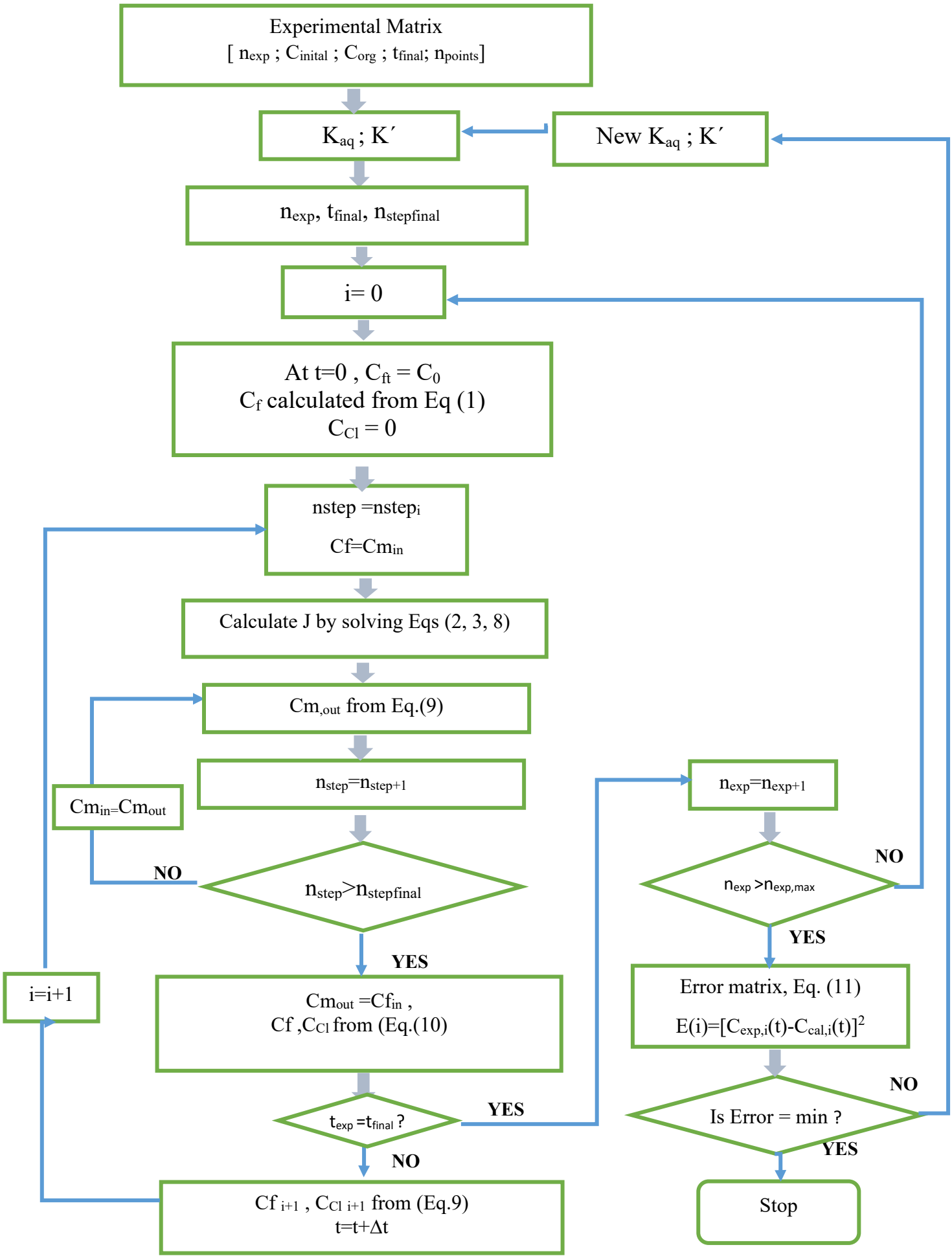
Experimental Matrix
[nexp ; Cinital ; Corg ; tfinal; npoints]
Kaq ; K´
New Kaq ; K´
nexp, tfinal, nstepfinal
i= 0
At t=0 , Cft = C0
Cf calculated from Eq (1)
CCl = 0
nstep =nstepi
Cf=Cmin
Calculate J by solving Eqs (2, 3, 8)
Cm,out from Eq.(9)
nstep=nstep+1
Cmin=Cmout
NO
nstep>nstepfinal
YES
i=i+1
Cmout =Cfin ,
Cf ,CCl from (Eq.(10)
texp =tfinal ?
YES
NO
Cf i+1 , CCl i+1 from (Eq.9)
t=t+Δt
nexp=nexp+1
NO
nexp >nexp,max
YES
Error matrix, Eq. (11)
E(i)=[Cexp,i(t)-Ccal,i(t)]2
NO
Is Error = min ?
YES
Stop

Figure 7. Model development Flow chart for HFM modelling.

5.3. Mass transfer studies

5.3.1. FSSLM

Based on the optimized value of K´ obtained by the model, the mass transport coefficient in the organic membrane (K_{org}) is calculated as describe by Eq. (5) at different carrier concentrations.

Additionally, the diffusion coefficient in the membrane (D_m) can be determined using the following Eq. (12) [34]:

$$K_{org} = D_m \cdot \frac{\varepsilon}{\delta \cdot \tau} \quad \text{Eq. (12)}$$

With ε, δ, and τ representing the porosity, membrane thickness, and tortuosity as specified in Table 1.

The individual mass transfer in the organic membrane at different concentrations (K_{org}) and the diffusion coefficients are calculated and presented in Table 9.

Table 9. Organic mass transfer (K_{org}) and diffusion coefficient (D_m) at different Aliquat 336 concentrations in FSSLM

C_{org} %(v/v)	$\mu^{-0.5}$ ($\sqrt{mPa \cdot s}$)	$K_{org} \cdot 10^{-2}$ (cm /s)	$D_m \cdot 10^{-7}$ (cm^2/s)
1	0.629	2.71	1.98
5	0.554	2.31	1.75
7	0.509	2.19	1.61
10	0.462	1.98	1.46

The results obtained in Table 7 reveal that the mass transfer coefficient in the membrane (K_{org}) is notably lower when compared to the mass transport coefficient across the feed phase boundary layer (Kaq $=0.48 \cdot 10^{-2}$cm/s), indicating a higher level of resistance within the membrane. These findings confirm that the diffusion of Pen-G in FSSLM with Aliquat 336 is predominantly influenced by resistance in the membrane, consistent with the outcomes of several prior studies that employed numerical, theoretical, and mathematical methods [40, 41]. Conversely, higher concentrations of organic extractant lead to increased viscosity, which inversely affects the diffusion coefficient according to Eq. (12). This rise in viscosity hinders

the diffusion of the complex formed within the membrane phase. Additionally, the mass transfer coefficient in the aqueous feed is determined and is found to be greater than what is typically observed in flat sheet membranes. However, it is noteworthy that many studies employing Aliquat 336 do not calculate or consider aqueous mass transfer. For instance, a study by Castillo et al. (2002) evaluated the diffusion coefficient in the organic membrane (D_m) for Chromium(VI) in PVDF membrane using 0.2 mol/L of Aliquat 336, they obtained D_{rn} equal to 2.44 10^{-7} cm²/s [42]. The developed mathematical model provides a means to calculate the mass transfer coefficients of Pen-G in the flat sheet supported liquid membrane with Aliquat 336 and aids in optimizing the transport process, thereby enhancing the removal efficiency of pharmaceutical extraction from aqueous solutions.

5.3.2. HFSLM

Similiar to FSSLM process, the individual mass transfer coefficient in the organic hollow fiber membrane (K_{org}) is calculated for different Aliquat 336 concentrations by considering the viscosity factor as expressed in Eq. (5).

In HFSLM, the diffusion in the membrane (D_m) is expressed in Eq. (13) [43]:

$$K_{org} = \frac{\varepsilon \cdot D_m}{\tau^2 \cdot r_i \cdot \ln(r_o/r_i)} \quad \text{(Eq.16)}$$

Where r_i and r_o are the inner and outer radius of the membrane, respectively (cm), and τ, tortuosity and ε the porosity as specified in Table 2

The specific K_{org} at different concentrations of Aliquat 336 (C_{org}) and its relative diffusion coefficient are presented in Table 10.

Table 10. Organic mass transfer and diffusion coefficient in HFSLM.

C_{org} % (v/v)	$\mu^{-0.5}$ ($\sqrt{mPa \cdot s}$)	k_{org} 10^{-7} (cm/s)	D_m 10^{-9} (cm^2/s)
0.0179	0.629	0.201	5.07
0.089	0.554	0.178	4.47
0.125	0.509	0.163	4.11
0.179	0.462	0.147	3.73

In the exact context of flat sheet membranes, the membrane mass transport coefficient is directly linked to the diffusion coefficient (D_m) of the organic complexes present in the membrane. The diffusion coefficient, in turn, is inversely proportional to the viscosity of the organic extractant. As Aliquat 336 concentration increases, the viscosity also increases, leading

to a decrease in diffusion and subsequently a low mass transport in the membrane coefficient [44, 45]. The values obtained were in the range of 10^{-8} cm/s which is lower than the typical range obtained by previous studies [46, 47]. However, it's essential to grasp the various factors impacting the mass transfer rate within the membrane. These factors encompass membrane specifications (including material type, porosity, and thickness), the physico-chemical properties of the system, and the characteristics of the organic extractant employed [48].

The selected ionic liquid, Aliquat 336, is known for its high viscosity, which can increase the resistance in the membrane. For instance, Ortiz et al. (2001) achieved a K_{org} value of $9.44 \cdot 10^{-7}$ cm/s when extracting cadmium with a high concentration of 30% Aliquat 336 [49]. Whereas, in a study by Buachan et al. (2009), they utilized empirical equations to calculate K_{org} and D_m, obtaining values of around $1.39 \cdot 10^{-7}$ cm/s and $2.19 \cdot 10^{-9}$ cm^2/s, respectively, while using a lower concentration of Aliquat 336 solution (4%). [50].

As for the mass transfer in the aqueous feed, few studies calculated K_{aq} based on empirical calculations and assumptions, and the value of K_{aq} was generally found around 10^{-3} cm/s [45-47].The problem arises when attempting to determine the mass transfer coefficient in the shell side of a hollow fiber module due to the complex geometry of the system, variations in fiber spacing and diameters, and the potential for flow irregularities among fiber [43, 45]. In this current study, K_{aq} was calculated and optimized by the proposed mathematical model. The value of K_{aq} ($3.39 \cdot 10^{-2}$) is higher compared to the one presented in the literature and calculated with empirical equations. Buanchan et al. (2009) estimated the aqueous mass transfer in the tube side, assuming laminar flow, and obtained a value of $1.19 \cdot 10^{-5}$ cm/s [50]. Furthermore, a notable advantage of HFSLM over FSSLM can be observed when comparing the mass transfer in the aqueous feed phase. In FSSLM, K_{aq} is equal to $0.48 \cdot 10^{-2}$ cm/s, while in HFSLM, it significantly increases to $3.36 \cdot 10^{-2}$ cm/s. This substantial improvement in the aqueous mass transfer in HFSLM can be attributed to its larger volume-to-surface area ratio, indicating more efficient and faster transport of the pharmaceutical.

5.4. Effect of Carrier concentration

The effect of organic extractant concentration on Pen-G transport in FSSLM and HFSLM was investigated at different Aliquat 336 (0.0179-0.179 mol/L). The results displayed in Figures 8 and 9. confirm the model's accuracy between calculated and experimental concentrations.

Pen-G is transported more rapidly from the feed to the stripping phase at a highest Aliquat 336 concentration (0.179 mol/l in decanol/kerosene). In fact, at increasing concentrations of Aliquat

336 in the membrane phase, a higher complex is formed at the feed-membrane interface and eventually leads to a greater flux through the membrane. Harun et al. (2023) studied the performance of ionic liquid in supported liquid membranes to remove ibuprofen at different organic concentrations [51]. It has been observed that increasing the concentration to 0.7 mol/L of Aliquat 336 significantly increased the transport of the species by 90% from the feed phase. Similar results were obtained when working with the same organic extractant to transport salicylic acid in FSSLM. Kuki et al. (2017) showed that the extraction percentage slightly increases from 73.2% to 75.9% when the Aliquat 336 concentration goes from 1% to 10%. However, as the concentration is further raised from 13% to 100%, the recovery efficiency decreases significantly, reaching 20.6% [52]. Several factors, including viscosity and membrane specifications, significantly influence the transport mechanism in SLM system. The diluent serves as an inactive organic solvent that does not participate in the extraction of Pen-G. It essentially acts as a solvent for organic extractant (Aliquat 336) and is used to lower the viscosity in the membrane phase. The decrease in extraction percentage beyond an optimal Aliquat 336 concentration for both systems is likely due to increased viscosity in the organic solution. As depicted in Table 7, the higher the viscosity, the lower the diffusion coefficient in the membrane phase. These findings are aligned with several researchers using the same carrier. [52,53]. As anticipated, the removal of Pen-G was significantly faster when using HFSLM. In just two hours, more than 80% of Pen-G was eliminated from the feed. Hollow fiber modules have a notable advantage over flat sheet modules, primarily because they provide a superior volume-to-area ratio and can efficiently process larger volumes. This means they can handle a substantial amount of the substance being treated relative to their surface area, making them highly effective for certain applications. Prior studies have typically explored the impact of one factor at a time to optimize operational parameters for hollow fiber liquid membrane systems. However, it is crucial to investigate the interactions between various parameters and variables to comprehensively assess the system's performance in removing different types of contaminants. In the current study, a concentration of 0.179 mol/L Aliquat 336 has been chosen for the removal of Pen-G antibiotic with the SLM process.

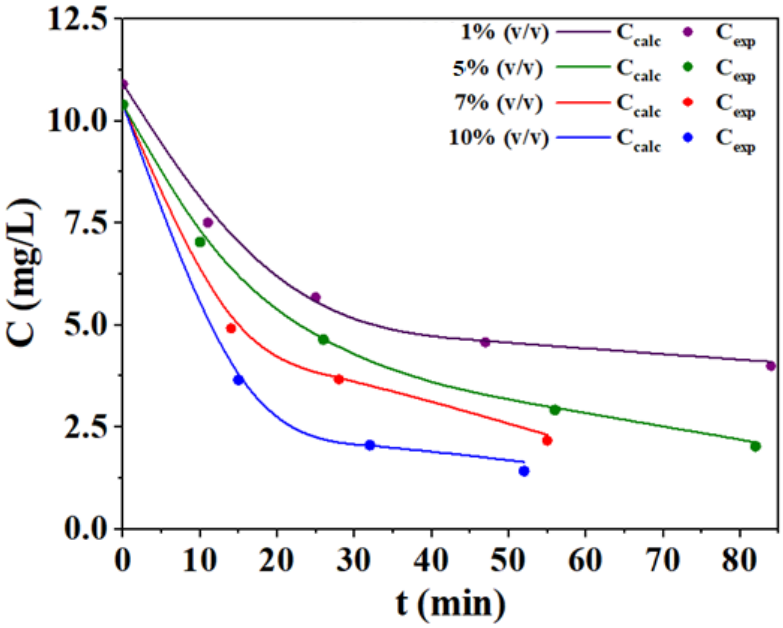

Figure 8 The evolution of Pen-G (mg/L) at different concentrations of Aliquat 336. (Feed: C0=30 mg/L, pH=6.01, 1000 rpm. Stripping: KCl=0.1 mol/L, pH = 7.75, 1000 rpm).

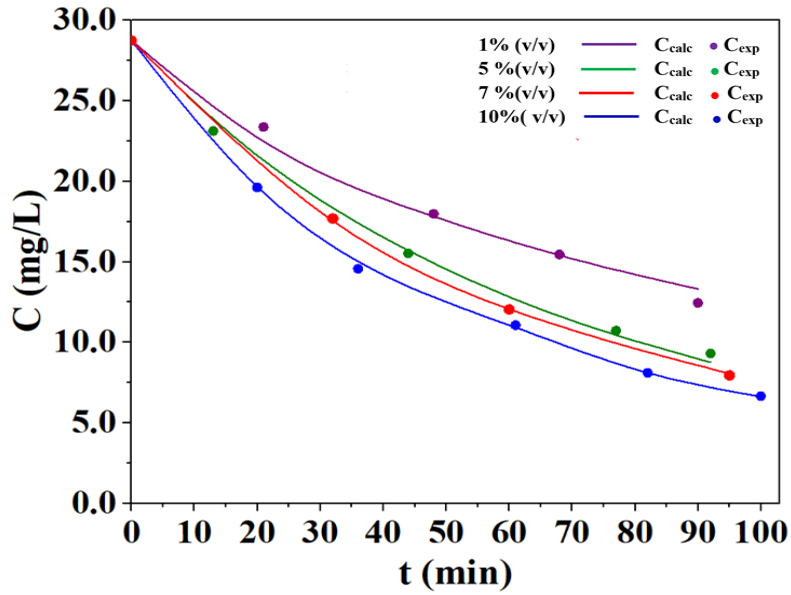

Figure 9 The evolution of pen-G (mg/L) at different concentration of Aliquat 336. (Feed: C_0=13 mg/L, pH=6.01, Q=47 L/h. Stripping: KCl=0.1 mol/L, pH = 7.75, Q=47 L/h).

5.5. Effect of KCl concentration in the stripping phase

The simultaneous separation and concentration of Pen-G from dilute aqueous solutions in HFSLM using 0.179 mol/L of Aliquat 336 dissolved in decanol/kerosene was investigated with 0.1 and 0.5 mol/L of KCl in the stripping phase. The results depicted in Figure 10 show that a higher concentration of potassium chloride leads to a faster recovery and concentration of pharmaceuticals without any delay in diffusion. However, the increase in concentration of the stripping agent did not significantly enhance the transport from the feed interface to the membrane bulk phase. The presence of KCl increases the ionic strength of the stripping phase, which intensifies the competition between chloride ions (Cl^-) and (P^-) with the extractant molecules. As a result, more Pen-G molecules are released into the stripping phase, facilitating faster recovery. In a study conducted by He et al. (2016), a higher concentration of K_2CO_3 concentration in the stripping phase was important to recover penicillin G and to maintain the pH in the stripping tank [43]. When working with ionic liquids, it is advisable to use an appropriate concentration of the stripping agent to maximize the selectivity for penicillin G and minimize the co-extraction of unwanted compounds. This ensures a more efficient and effective separation process. Although to avoid any additional cost, the concentration of stripping agent was kept at 0.1 mol/L .

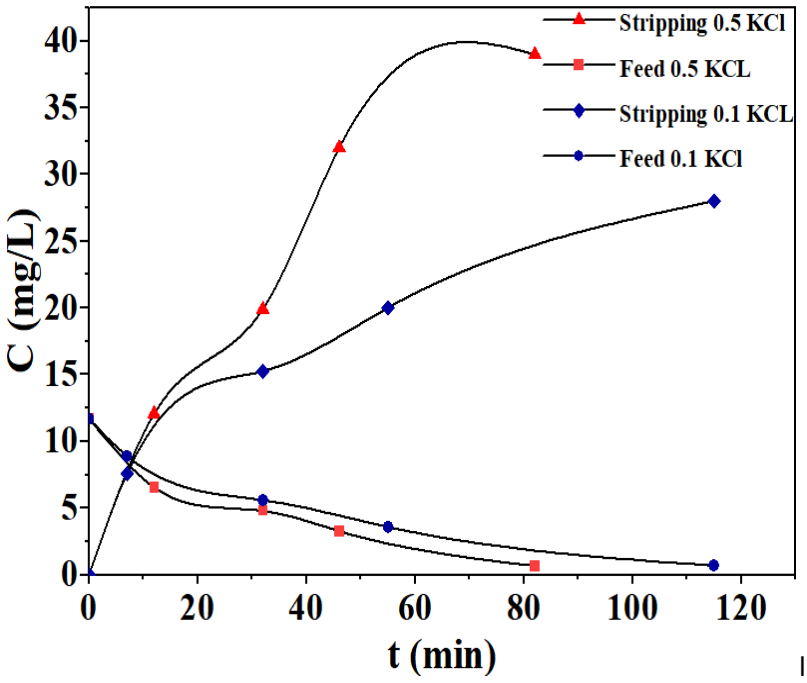

Figure 10 Effect of concentration of KCl on extraction and stripping of Pen-G. (Feed: C_0=13 mg/L pH=6.01 Q=47 L/h. Stripping pH=7.45, Q=47 L/h).

6. Conclusion

Nowadays it more than necessary to safeguard water quality and promote a sustainable approach to water management. This study highlights various findings to mitigate penicillin G contamination and provide efficient treatment strategies with liquid membrane.

Penicillin G was successfully extracted from water with flat sheet and hollow fiber supported liquid membrane, using the quaternary amine salt Aliquat 336. The best conditions for extraction and stripping were achieved with 0.179 mol/L Aliquat 336 and 0.1 M KCl stripping solution. A mathematical model was developed to calculate and optimize the mass transfer coefficients in the aqueous feed phase and organic membrane (K_{aq} and K_{org}) for both modules. The mass transfer in the membrane was found to be lower, indicating that the diffusion of the complex (Penicillin-Aliquat 336) in the membrane is the limiting step in this process. In essence, mathematical modelling in liquid membranes provides a systematic approach to understanding mass transfer, predicting their value, and optimizing the processes. Moreover, it serves as a bridge between laboratory experimentation and large-scale industrial applications, ensuring a unified transition. This modelling approach helps researchers to compare and contrast various liquid membrane configurations and formulations to ultimately select the most suitable options for specific purposes. Finally, hollow fiber liquid membrane demonstrated higher mass transfer rates due to the large surface area, enabling more efficient extraction and separation of the target compounds from the feed solution (Kaq, HFSLM: 7.76·10-2 cm/s > Kaq, FSSLM: 0.36×10-2 cm/s).

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8. References

[1] De Ilurdoz, M. S., Sadhwani, J. J., Reboso, J. V. (2022). Antibiotic removal processes from water & wastewater for the protection of the aquatic environment - A Review. Journal of Water Process Engineering, 45, 102474. https://doi.org/10.1016/j.jwpe.2021.102474

[2] Kümmerer, K. (2001). Drugs in the environment: Emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources – A Review. Chemosphere, 45(6–7), 957–969. https://doi.org/10.1016/s0045-6535(01)00144-8

[3] Baralla, E., Demontis, M. P., Dessì, F., Varoni, M. V. (2021). An overview of antibiotics as emerging contaminants: Occurrence in bivalves as biomonitoring organisms. Animals, 11(11), 3239. https://doi.org/10.3390/ani11113239.

[4] Samal, K., Mahapatra, S., Hibzur Ali, M. (2022). Pharmaceutical wastewater as emerging contaminants (EC): Treatment technologies, impact on environment and human health. Energy Nexus, 6, 100076. https://doi.org/10.1016/j.nexus.2022.100076

[5] Du, L., Liu, W. (2011). Occurrence, fate, and ecotoxicity of antibiotics in agro-ecosystems. A Review. Agronomy for Sustainable Development, 32(2), 309–327. https://doi.org/10.1007/s13593-011-0062-9

[6] Kumar, K., C. Gupta, S., Chander, Y., Singh, A. K. (2005). Antibiotic use in agriculture and its impact on the terrestrial environment. Advances in Agronomy, 1–54. https://doi.org/10.1016/s0065-2113(05)87001-4

[7] Mejía-López, A. C., Ramírez-García, J. J., Solache-Ríos, M. (2022). Removal of penicillin from wastewater: A short review. Desalination And Water Treatment, 272, 144–155. https://doi.org/10.5004/dwt.2022.28815

[8] Yang, Q., Gao, Y., Ke, J., Show, P. L., Ge, Y., Liu, Y., Guo, R., Chen, J. (2021). Antibiotics: An overview on the environmental occurrence, toxicity, degradation, and removal methods. Bioengineered, 12(1), 7376–7416. https://doi.org/10.1080/21655979.2021.1974657

[9] Zhang, J., Xiong, Z., Wei, J., Song, Y., Ren, Y., Xu, D., Lai, B. (2020). Catalytic ozonation of penicillin G using cerium-loaded natural zeolite (cz): Efficacy, mechanisms, pathways and toxicity assessment. Chemical Engineering Journal, 383, 123144. https://doi.org/10.1016/j.cej.2019.123144

[10] Zangeneh, H., Zinatizadeh, A. A. L., Feizy, M. (2014). A comparative study on the performance of different advanced oxidation processes (UV/O3/H2O2) treating linear alkyl benzene (lab) production plant's wastewater. Journal of Industrial and Engineering Chemistry, 20(4), 1453–1461. https://doi.org/10.1016/j.jiec.2013.07.031

[11] Norzaee, S., Bazrafshan, E., Djahed, B., Kord Mostafapour, F., Khaksefidi, R. (2017). UV activation of persulfate for removal of penicillin G antibiotics in aqueous solution. The Scientific World Journal, 2017, 1–6. https://doi.org/10.1155/2017/3519487

[12] Caglayan, I. A., Ozonation, A. E. (2005). Ozonation of procaine penicillin g formulation effluent part I: process optimization and kinetics. Chemosphere, 59(1), 31–39. https://doi.org/10.1016/j.chemosphere.2004.10.014

[13] Cuerda-Correa, E. M., Alexandre-Franco, M. F., Fernández-González, C. (2019). Advanced oxidation processes for the removal of antibiotics from water. an overview. Water, 12(1), 102. https://doi.org/10.3390/w12010102 .

[14] Aksu, Z., & Tunç, Ö. (2005). Application of biosorption for penicillin G removal: Comparison with activated carbon. Process Biochemistry, 40(2), 831–847. https://doi.org/10.1016/j.procbio.2004.02.014

[15] Hekmatshoar, R., Khoramnejadian, S., Allahabadi, A., Saghi, M. H. (2020). Synthesis and characterization of an NH4CL-induced ESKANBIL activated carbon (EAC) for the removal of penicillin G from contaminated water. Journal of Environmental Health Science and Engineering, 18(2), 483–493. https://doi.org/10.1007/s40201-020-00476-

[16] Mohammadi, A. S., Sardar, M., Almasian, M. (2016). Equilibrum and kinetic studies on the adsorption of penicillin G by Chestnut Shell. Environmental Engineering and Management Journal, 15(1), 167–173. https://doi.org/10.30638/eemj.2016.018

[17] Ania, C. O., Pelayo, J. G., Bandosz, T. J. (2010). Reactive adsorption of penicillin on activated carbons. Adsorption, 17(3), 421–429. https://doi.org/10.1007/s10450-010-9271-

[18] Ighalo, J. O., Igwegbe, C. A., Aniagor, C. O., & Oba, S. N. (2021). A review of methods for the removal of penicillins from water. Journal of Water Process Engineering, 39, 101886. https://doi.org/10.1016/j.jwpe.2020.101886

[19] Nasrollahi, N., Vatanpour, V., Khataee, A. (2022). Removal of antibiotics from wastewaters by membrane technology: Limitations, successes, and future improvements. Science of The Total Environment, 838, 156010.https://doi.org/10.1016/j.scitotenv.2022.156010

[20] Zazouli, M., Ulbricht, M., Naseri, S., Susanto, H. (2010). Effect of hydrophilic and hydrophobic organic matter on amoxicillin and cephalexin residuals rejection from water by nanofiltration. Iranian Journal of Environmental Health Science & Engineering, 7(1), 15–24.

[21] Lu, H., Zou, W., Chai, P., Wang, J., & Bazinet, L. (2016). Feasibility of antibiotic and sulfate ions separation from wastewater using electrodialysis with ultrafiltration membrane. Journal of Cleaner Production, 112, 3097–3105. https://doi.org/10.1016/j.jclepro.2015.09.091

[22] Reschke, M., & Schügerl, K. (1984). Reactive extraction of penicillin II: Distribution coefficients and degrees of extraction. The Chemical Engineering Journal, 28(1). https://doi.org/10.1016/0300-9467(84)85016-9

[23] Sastre, A., Kumar, A., Shukla, J., Singh, R. (1998). Improved techniques in liquid membrane separations: An overview. Separation and Purification Methods, 27(2), 213–298. https://doi.org/10.1080/03602549809351641

[24] Kocherginsky, N. M., Yang, Q., Seelam, L. (2007). Recent advances in supported liquid membrane technology. Separation and Purification Technology, 53(2), 171–177. https://doi.org/10.1016/j.seppur.2006.06.022

[25] Lee, C.-J., Yeh, H.-J., Yang, W.-Y., Kan, C.-R. (1994). Separation of penicillin G from phenylacetic acid in a supported liquid membrane system. Biotechnology and Bioengineering, 43(4), 309–313. https://doi.org/10.1002/bit.260430407.

[26] Ren, Z., Lv, Y., & Zhang, W. (2008). Facilitated transport of penicillin G by bulk liquid membrane with TBP as carrier. Applied Biochemistry and Biotechnology, 152(2), 286–294. https://doi.org/10.1007/s12010-008-8242-z

[27] Lee, S. C., Chang, J. H., Ahn, B. S., Lee, W. K. (1998). Mathematical modeling of penicillin G extraction in an emulsion liquid membrane system containing only a surfactant in the membrane phase. Journal of Membrane Science, 149(1), 39–49. https://doi.org/10.1016/s0376-7388(98)00178-1

[28] Cao, Y., Khan, A., Sarkar, S., Albadarin, A. B. (2021). Extraction of penicillin G from aqueous solution using a membrane contactor: Numerical investigation. Arabian Journal of Chemistry, 14(7), 103230. https://doi.org/10.1016/j.arabjc.2021.103230

[29] He, L., Li, L., Sun, W., Zhang, W., Zhou, Z., Ren, Z. (2016). Extraction and recovery of penicillin G from solution by cascade process of hollow fiber renewal liquid membrane. Biochemical Engineering Journal, 110, 8–16. https://doi.org/10.1016/j.bej.2016.02.002

[30] Farah, M., Giralt, J., Stüber, F., Font, J., Fabregat, A., Fortuny, A. (2022). Supported liquid membranes for the removal of pharmaceuticals from Aqueous Solutions. Journal of Water Process Engineering, 49, 103170. doi:10.1016/j.jwpe.2022.103170

[31] Bringas, E., San Román, M., Irabien, J., Ortiz, I. (2009). An overview of the mathematical modelling of liquid membrane separation processes in hollow fibre contactors. Journal of Chemical Technology & Biotechnology, 84(11), 1583–1614. https://doi.org/10.1002/jctb.2231

[32] Alguacil, F. J., Alcaraz, L., Rodríguez Largo, O., & López, F. A. (2020). Transport of Au(Iii) from Hcl Medium across a Liquid Membrane Using r3NH+Cl-/Toluene Immobilized on a Microporous Hydrophobic Support: Optimization and Modelling. https://doi.org/10.20944/preprints202011.0371.v1

[33] Hiss, T. G., Cussler, E. L. (1973). Diffusion in high viscosity liquids. AIChE Journal, 19, 698–703.

[34] Drioli, E., Criscuoli, A, Curcio, E. (2006). Membrane contactors: fundamentals, application and potentialities. Elsevier, https://doi.org/10.1016/s0927-5193(05)80002-6

[35] Fischer, L., Falta, T., Koellensperger, G., Stojanovic, A., Kogelnig, D., Galanski, M. S., Krachler, R., Keppler, B. K., Hann, S. (2011). Ionic liquids for extraction of metals and metal containing compounds from communal and industrial waste water. Water Research, 45(15), 4601–4614. https://doi.org/10.1016/j.watres.2011.06.011

[36] Mora-Ochomogo, M., Lohans, C. T. (2021). B-lactam antibiotic targets and resistance mechanisms: From covalent inhibitors to substrates. RSC Medicinal Chemistry, 12(10), 1623–1639. https://doi.org/10.1039/d1md00200g

[37] Javanbakht, M., Pishro, K. A., Nasab, A. H., Akbari-adergani, B. (2012a). Extraction and purification of penicillin g from fermentation broth by water-compatible molecularly imprinted polymers. Materials Science and Engineering: C, 32(8), 2367–2373. https://doi.org/10.1016/j.msec.2012.07.009

[38] Liu, Q., Li, Y., Li, W., Liang, X., Zhang, C., Liu, H. (2015a). Efficient recovery of penicillin G by a hydrophobic Ionic liquid. ACS Sustainable Chemistry & Engineering, 4(2), 609–615. https://doi.org/10.1021/acssuschemeng.5b00975

[39] Bi, P. Y., Dong, H. R., Guo, Q. Z. (2009a). Separation and purification of penicillin G from fermentation broth by solvent sublation. Separation and Purification Technology, 65(2), 228–231. https://doi.org/10.1016/j.seppur.2008.10.028

[40] Kandwal, P., Dixit, S., Mukhopadhyay, S., Mohapatra, P. K., Manchanda, V. K. (2011). Mathematical modeling of Cs(I) transport through flat sheet supported liquid membrane using calix-[4]-bis(2,3-naptho)-18-crown-6 as the Mobile Carrier. Desalination, 278(1–3), 405–411. https://doi.org/10.1016/j.desal.2011.05.062

[41] Marchese, J., Valenzuela, F., Basualto, C., Acosta, A. (2004). Transport of molybdenum with Alamine 336 using supported liquid membrane. Hydrometallurgy, 72(3–4), 309–317. https://doi.org/10.1016/j.hydromet.2003.07.003

[42] Castillo, E., Granados, M., & Cortina, J. L. (2002). Liquid-supported membranes in chromium (VI) optical sensing: transport modelling. Analytica Chimica Acta, 464(2), 197–208. https://doi.org/10.1016/S0003-2670(02)00473-7

[43] He, L., Li, L., Sun, W., Zhang, W., Zhou, Z., & Ren, Z. (2016). Extraction and recovery of penicillin G by a cascade process of hollow fiber renewal liquid membrane. Biochemical Engineering Journal, 110, 8–16. https://doi.org/10.1016/j.bej.2016.02.002.

[44] Ventura, S. P., e Silva, F. A., Quental, M. V., Mondal, D., Freire, M. G., & Coutinho, J. A. (2017). Ionic-liquid-mediated extraction and separation processes for bioactive compounds: Past, present, and future trends. Chemical Reviews, 117(10), 6984–7052. https://doi.org/10.1021/acs.chemrev.6b00550.

[45] Dehaan, A. B., Bartels, P. V., & Degraauw, J. (1993). Extraction of metal-ions from waste-water-modeling of the mass-transfer in a supported-liquid membrane process. Journal of Membrane Science, 80(1–3), 1–11. https://doi.org/10.1016/s0376-7388(00)80520-7.

[46] Costello, M. J., Fane, A. G., Hogan, P. A., Schofield, R. W. (1993). The effect of shell side hydrodynamics on the performance of Axial Flow Hollow Fibre Modules. Journal of Membrane Science, 80(1), 1–11. https://doi.org/10.1016/0376-7388(93)85127-i

[47] Zheng, J.-M., Xu, Y.-Y., Xu, Z.-K. (2003). Shell side mass transfer characteristics in a parallel flow hollow fiber membrane module. Separation Science and Technology, 38(6), 1247–1267. https://doi.org/10.1081/ss-120018808

[48] Kamran Haghighi, H., Irannajad, M., Fortuny, A., Sastre, A. M. (2018a). Mathematical modeling on non-dispersive extraction of germanium from aqueous solutions using aliquat 336. Water Science and Technology, 78(12), 2489–2499. https://doi.org/10.2166/wst.2019.002 .

[49] Ortiz, I., Alonso, A. I., Urtiaga, A. M., Demircioglu, M., Kocacik, N., Kabay, N. (1999). An Integrated Process for the Removal of Cd and U from Wet Phosphoric Acid. Industrial & Engineering Chemistry Research, 38, 2450–2459. https://doi.org/10.1021/ie980686s

[50] Buachuang, D., Ramakul, P., Leepipatpiboon, N., Pancharoen, U. (2011). Mass transfer modeling on the separation of tantalum and niobium from dilute hydrofluoric media through a hollow fiber supported liquid membrane. Journal of Alloys and Compounds, 509(39), 9549–9557. https://doi.org/10.1016/j.jallcom.2011.07.078

[51] Harun, M. H., & Ahmad, A. L. (2023). Removal of low concentration ibuprofen using green diluent and novel formulated supported Ionic Liquid Membrane. Journal of Environmental Chemical Engineering, 11(3), 109972https://doi.org/10.1016/j.jece.2023.109972.

[52] Kouki, N., Tayeb, R., & Dhahbi, M. (2013). A flat-sheet supported liquid membrane based on aliquat®336 as carrier for the removal of salicylic acid from aqueous solution. Desalination and Water Treatment, 52(25–27), 4745–4754. https://doi.org/10.1080/19443994.2013.814325.

[53] Yamini, Y., Reimann, C. T., Vatanara, A., & Jo¨nsson, J. A. (2006). Extraction and preconcentration of salbutamol and terbutaline from aqueous samples using hollow fiber supported liquid membrane containing anionic carrier. Journal of Chromatography A, 1124, 57–67. https://doi.org/10.1016/j.chroma.2006.05.001.

Chapter 8 Conclusion and Recommendations

1. Conclusions

The increasing consumption of pharmaceuticals and their frequent detection in the aqueous system to provide more effective and industrial sustainable processes and potential management solutions. For this purpose, liquid membrane processes have been developed to separate these contaminants present at low. The main key elements obtained by different chapters are obtained:

- Flat sheet Supported Liquid Membranes (FSSLMs) was evaluated for pharmaceutical removal in wastewater treatment, despite limitations in current technologies due to low efficiency, high costs, and energy consumption. Various pharmaceuticals like Diclofenac, Ibuprofen, and Carbamazepine were tested with a membrane comprising Cy923, TOA, TBP, Aliquat 336, Versatic acid 10, diluted in kerosene. Different drugs exhibited varying optimal conditions, requiring specific pH levels and distinct extractants for effective removal. The permeability coefficient served as a crucial unit of measurement to assess the performance of the liquid membrane (LM). Increasing Cy923 concentration to 40% improved transfer efficiency without membrane accumulation for diclofenac and ibuprofen. Stability testing favored PVDF polymer support over consecutive runs. In addition, Techniques like ultrasound assistance and prolonged membrane soaking in organic solvent enhanced efficiency and stability, promising prolonged application. SLM integration removed 98% of pharmaceuticals with minimal extractants, indicating potential for efficient wastewater treatment. The study advocates further research to integrate SLMs with existing methods for enhanced efficiency, cost reduction, and lower energy consumption in wastewater treatment processes.
- Furthermore, to addresses the challenge with elimination of pharmaceutical contamination at low concentration, supported liquid membrane combined with oxidation was investigated for diclofenac removal, and its by-products' using laboratory-scale flat sheet membranes. Conventional methods often fall short due to limited effectiveness, high operational expenses, and increased energy usage. The hybrid process demonstrated promise for selective transport and oxidation of diclofenac. Additionally, transporting diclofenac through the membrane with 40% Cy923 yielded promising in different water matrices unaffected by counterions. Ozone treatment successfully removed major contaminants and identified by-products like 5-hydroxydiclofenac. This approach efficiently removed diclofenac and its intermediates while safeguarding membrane materials from ozone contact.

- Subsequently, the application of a hollow fiber liquid membrane, containing 40% Cy923, has demonstrated high efficiency in extracting diclofenac and ibuprofen from aqueous solutions. The system's stability has been significantly improved through the incorporation of a pseudo emulsion, enhancing its longevity and extraction efficiency. Moreover, it has been found that the solvent used in the process can be recycled indefinitely unless it degrades, or its solubility increases. It is recommended to introduce fresh solutions of organic extractant after the second run. The integration of the hollow fiber membrane system with ozonation in a single step has led to a significant reduction in the concentration of diclofenac and ibuprofen, along with their abundant by-products 5-hydroxydiclofenac and 4-ethybenzaldehyde, enabling the degradation of the extracted pharmaceutical compounds and other organic pollutants in the system. Despite the generation of ozone- by-products, this approach, which includes hollow fiber liquid membrane extraction, improved pseudo-emulsion stability, and ozonation, provides a promising solution for detecting and selectively treating pharmaceutical contaminants found at low concentrations.
- Ionic liquid Aliquat 336 extracted Penicillin G from water using flat sheet and hollow fiber supported liquid membranes. The mechanism of transport was based on cotransport of charged ions. The Mechanistic model based on the mass transfer of species was obtained by a mathematical model. The results obtained revealed lower mass transfer in the membrane, identifying complex diffusion as the limiting step. This modelling approach aids in understanding mass transfer, predicting values, and optimizing liquid membrane processes, facilitating a seamless transition from laboratory experiments to industrial scales. Notably, the hollow fiber liquid membrane exhibited higher mass transfer rates due to its larger surface area, enabling more efficient extraction and separation of target compounds from the feed solution. It allows for comparison of different membrane configurations, aiding researchers in selecting the most suitable options.
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2. Future Recommendations

Based on the primary discoveries and conclusions from this study, several suggestions are outlined below for potential advancements in this field.

- Further research into stabilizing liquid membranes, especially in industrial-scale applications, could explore advanced additives or modifications to enhance durability against various environmental factors. Hollow fiber membrane needs to be structurally

modified to maintain a high stability of organic extractant and prevent its dispersion while taking into account the performance of the membrane.

- Researching cost-effective and sustainable materials for liquid membranes that maintain high efficiency while being economically viable for widespread implementation in liquid membrane.
- Integration with Advanced Treatments: Exploring the integration of liquid membranes with advanced treatment techniques, such as hybrid systems involving oxidation processes or photocatalysis, to enhance contaminant removal efficiency.
- Application in Emerging Contaminants: Expanding research to include emerging contaminants beyond pharmaceuticals, such as microplastics or personal care products, to address evolving environmental challenges.
- Modelling and Simulation: Utilizing advanced modelling and simulation techniques to predict and optimize liquid membrane performance under various conditions, aiding in design and implementation.

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