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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 unregulated 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 extractant, 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 pharmaceutical 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.

UNIVERSITAT ROVIRA I VIRGILI
ENHANCED PHARMACEUTICAL ELIMINATION FROM WATER: SUPPORTED LIQUID MEMBRANE TECHNOLOGIES
MARY FARAH

Chapter 1. Introduction

UNIVERSITAT ROVIRA I VIRGILI
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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 nanogram'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.

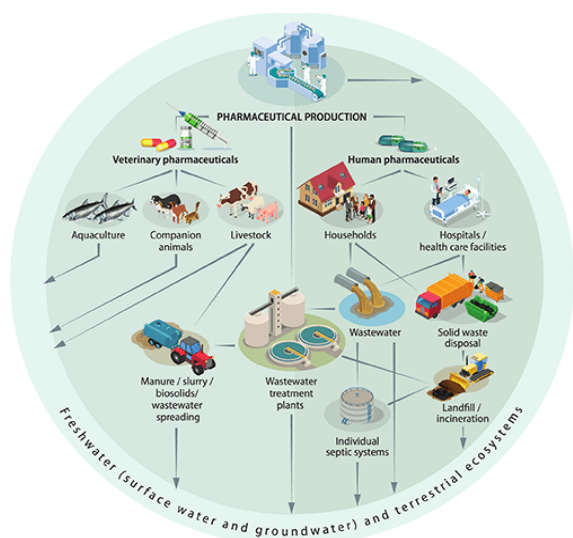


Figure1 Pharmaceutical contaminant pathway (*OECD (2019), Pharmaceutical Residues in Freshwater: Hazards and Policy Responses, OECD Studies on Water, OECD Publishing, Paris*)

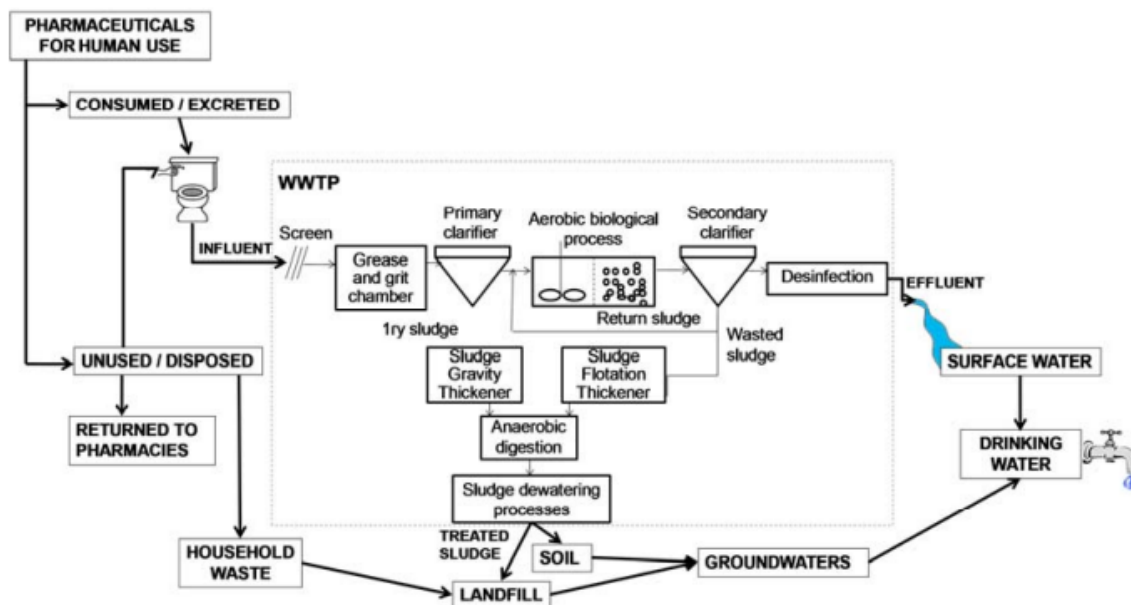


Figure 2. Routes of release of pharmaceutical contaminants for the use of humans into conventional wastewater Treatment

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 $\mu\text{g/L}$ 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 $\leq 50\%$, 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, | Greece | 8.02–132 | Wastewater | [27] |
| Naproxen, | | | | |
| Ibuprofen | | | | |
| Propranolol, | Italy | 0.001 -284 | River Water | [28] |
| Paracetamol | | | | |
| Diclofenac, | South Africa | 0.010–0.034 | Seawater | [29] |
| Sulfamethoxazole | | | | |
| Carbamazepine | | | | |
| Lamivudine | | | | |
| Caffeine, | | | | |
| Acetaminophen | | | | |
| Ketoprofen, | Spain | 0.3–324.7 | Wastewater treatment plants discharge | [30] |
| Naproxen | | | | |
| Fluoxetine | | | | |
| Carbamazepine, | Netherland | 0.91-0.9 | Sewage Treatment Plant effluents, surface water | [31]. |
| Erythromycin | | | | |
| Ibuprofen | France | 100 | Sewage Treatment Plants effluents, | [32] |
| Diclofenac | | | | |

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 µg/L⁻¹ in the sea water in South Africa and 1.51 µg/L⁻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 1 these 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 physicochemical 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].

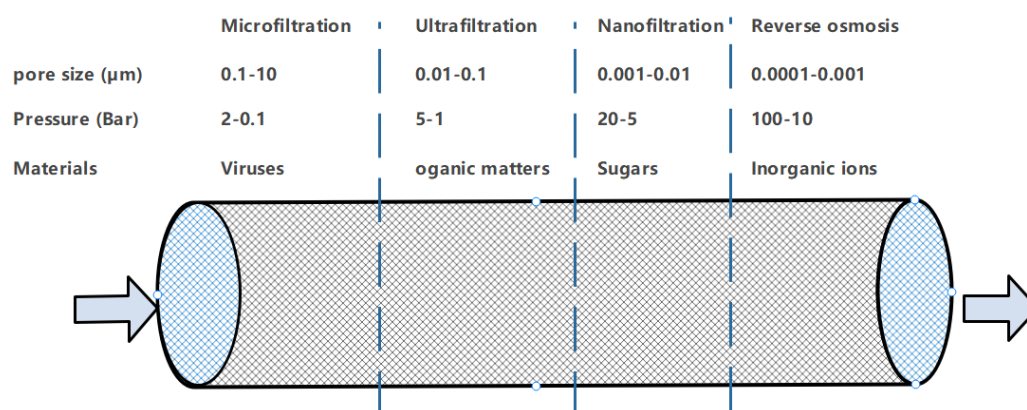


Figure 3 Classification of membranes according to pore size, driven force and removed materials.

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 ($\cdot\text{OH}$), 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 (O ₃ /H ₂ O ₂) | 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

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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.

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ENHANCED PHARMACEUTICAL ELIMINATION FROM WATER: SUPPORTED LIQUID MEMBRANE TECHNOLOGIES
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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 et 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.

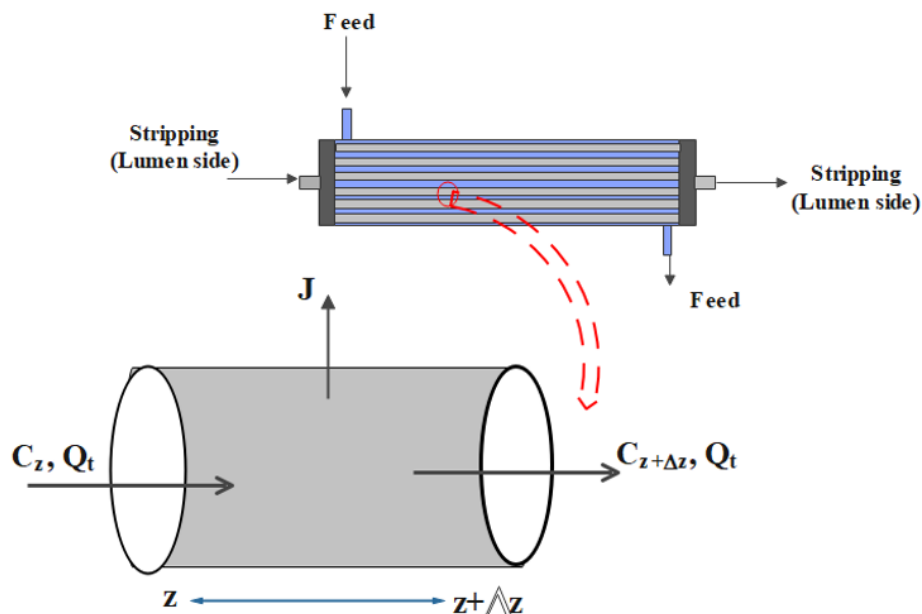


Figure 1 Mass balance of the cross-sectional area for a lumen side of the membrane.

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

Input = Output

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

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 $z+\Delta z$, 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, ($\text{mol}/\cdot\text{m}^2\cdot\text{s}$) 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) :

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

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):

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

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))

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

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:

$$Q_f = q_f \cdot N ; A = d \cdot \pi \cdot L \cdot N \quad (\text{with } N = \text{number of fibers})$$

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

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 (m²), 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)
 Input – Output = accumulation

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

With the V volume of the feed tank (m³), C_{fin} and C_{fout} are the inlet and outlet concentrations of the feed tanks (mol/L).

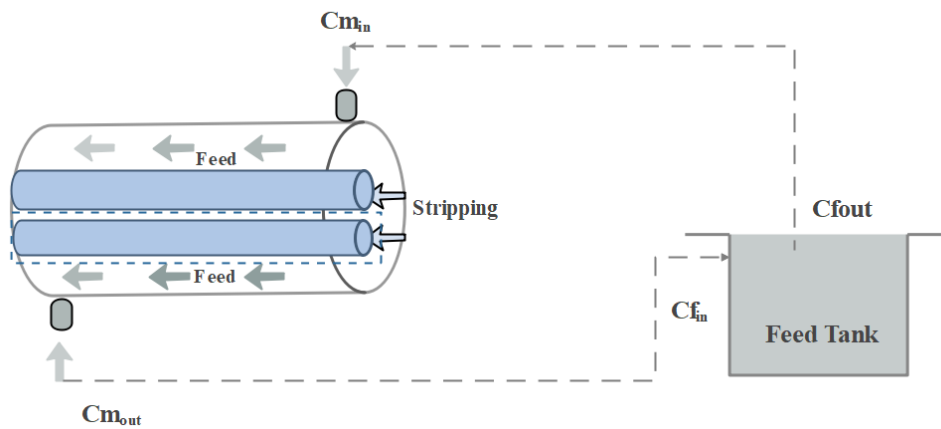


Figure 2. Mass balance in the feed tank of a HFSLM.

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 :

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

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, $\geq 98\%$), 4-Ethylbenzaldehyde (CAS No. 233633, $\geq 97.5\%$), 5-hydroxy diclofenac (CAS No.62248, $\geq 97\%$) 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™ (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 times 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 50 μ L. 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™)

| | |
|--|-----------------------------|
| Module diameter (cm) | 7.7 |
| Module length (cm) | 27.7 |
| Membrane Area (m ²) | 1.4 |
| Fibers OD/ID (μ m) | 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 |

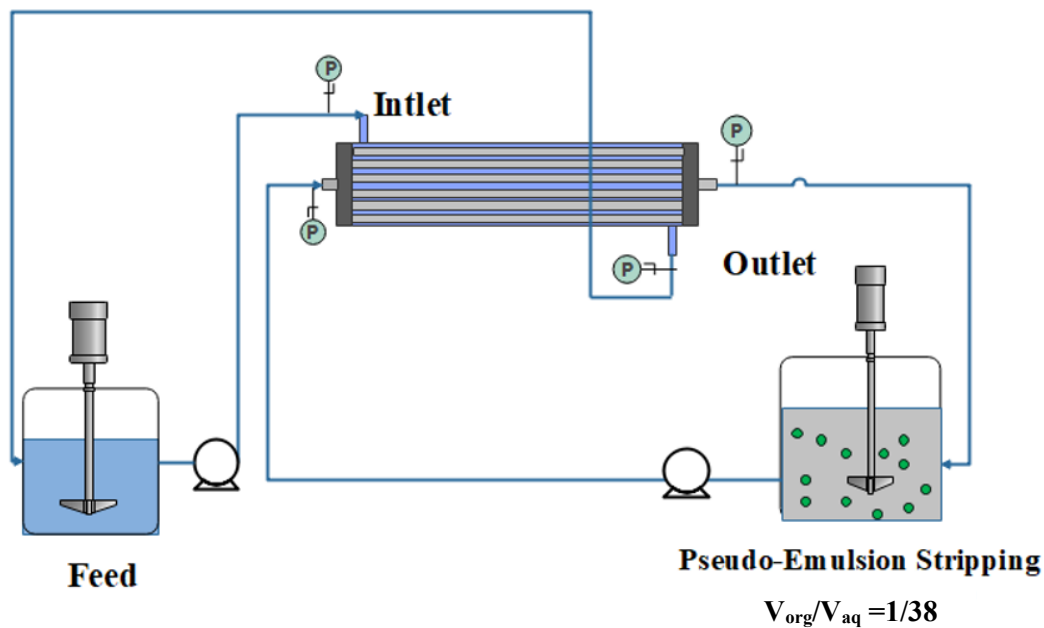


Figure 3. Experimental setup with pseudo-emulsion in the stripping phase

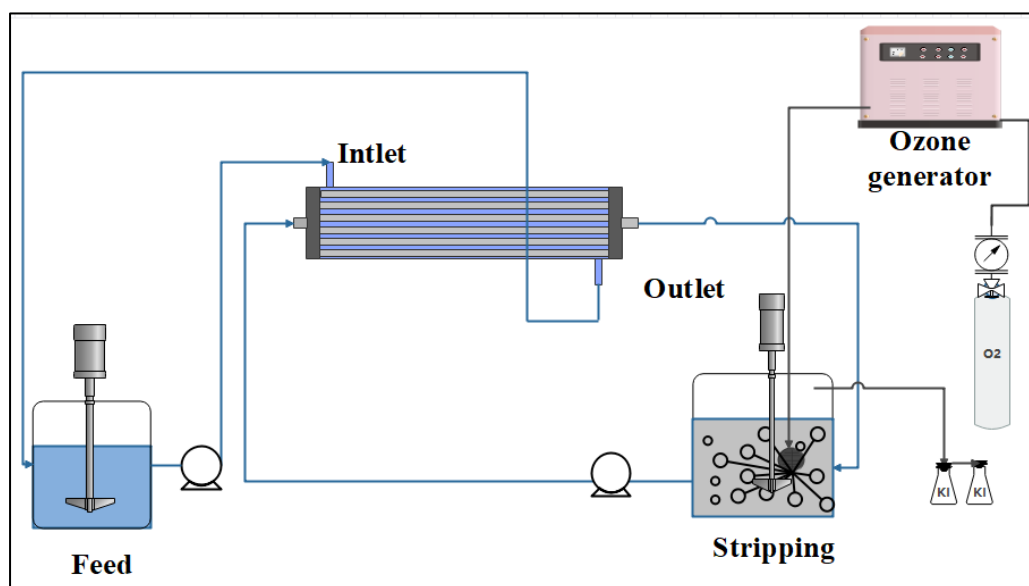


Figure 4. Experimental setup of HFSLM and ozonation

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**.

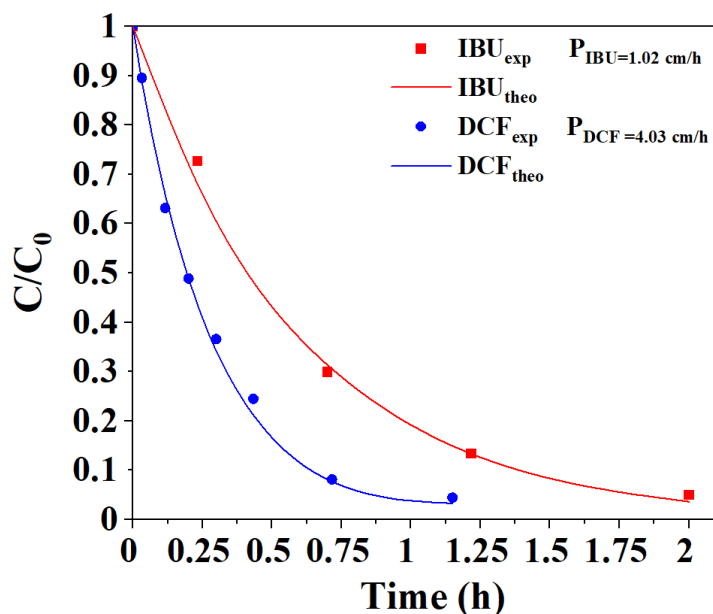


Figure 5. Pharmaceuticals concentration vs time in HFSLM. (Feed: $C_0=10$ mg/L, $pH = 5.5$; $Q= 47$ L/h; Organic extractant: 40% (v/v) Cy923/kerosene; Stripping phase: $Q=47$ L/h; $pH=11$).

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]:

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

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].

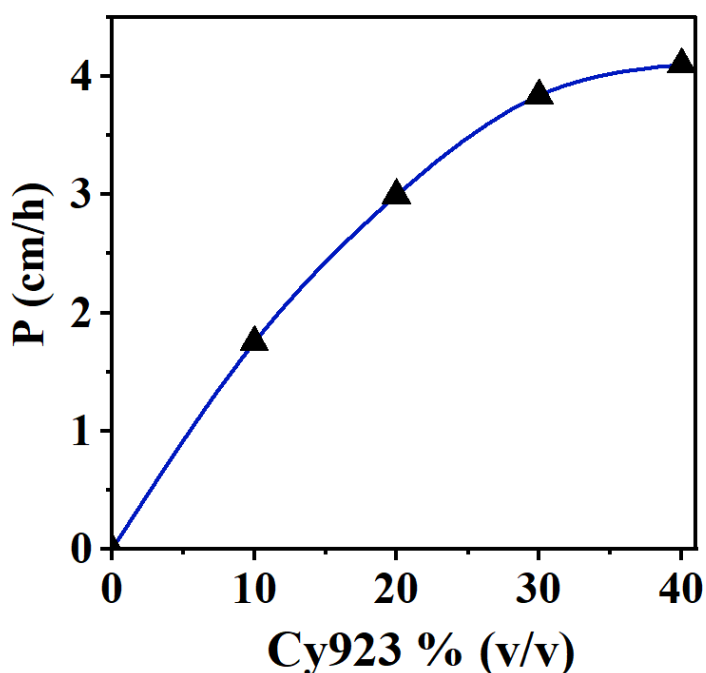


Figure 6. Effect of Cy923 concentration on the permeability in HFSLM (Feed: $C_0 = 10$ mg/L, pH = 5.5, $Q = 47$ L/h; Stripping phase: $Q = 47$ L/h; pH = 11).

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].

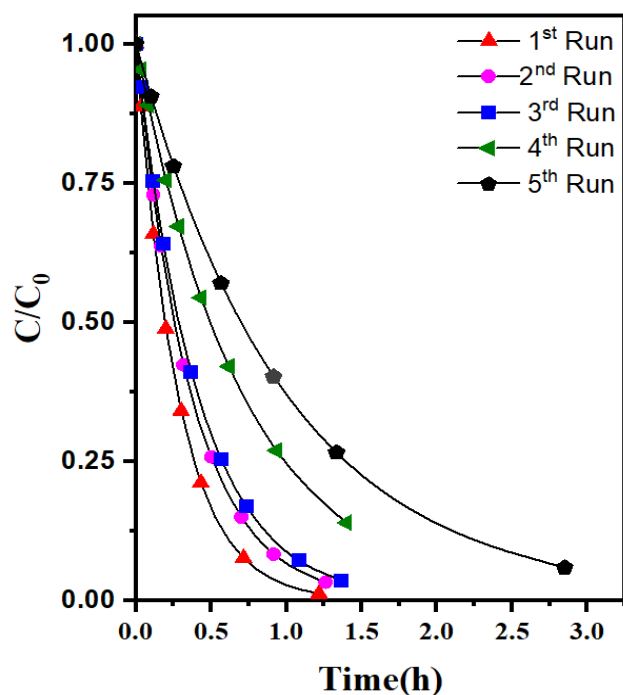


Figure 7. Concentration change of DCF for successive runs.(Feed: $C_0=10\text{mg/L}$; $\text{pH} = 5.5$; $Q=47\text{ L/h}$. Organic extractant: 40% (v/v) Cy923/kerosene. Stripping phase: $Q= 47\text{ L/h}$; $\text{pH} = 11$).

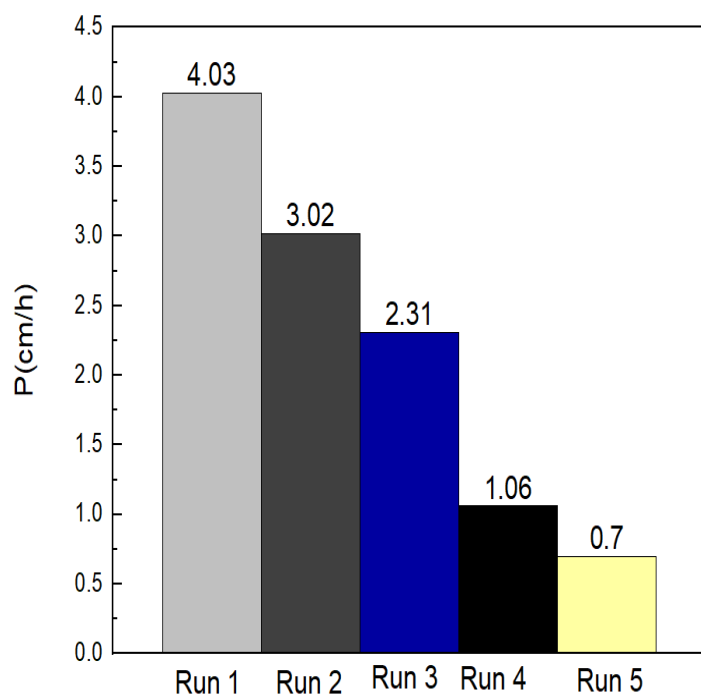


Figure 8. Permeability obtained for each consecutive run with HFSLM.

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].

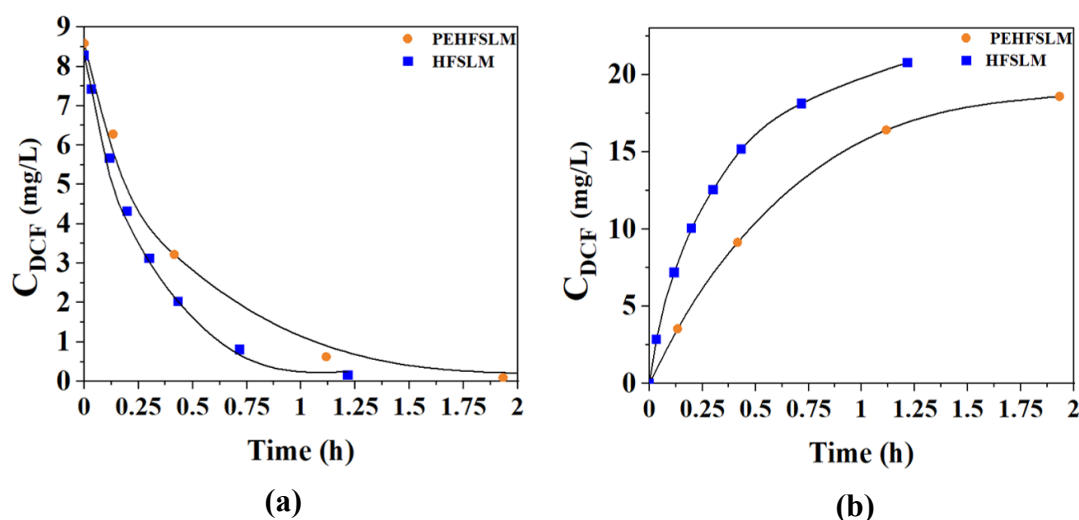


Figure 9 Comparison between HFSLM and PEHFSLM in (a) Feed phase: $C_0=10\text{mg/L}$, $\text{pH} = 5.5$, $V= 9 \text{ L}$, $Q=47 \text{ L/h}$. Organic extractant: 40% (v/v) Cy923/kerosene and (b) stripping phase: $V=3 \text{ L}$; $Q= 47 \text{ L/h}$; $\text{pH} = 11$).

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 pseudo-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.

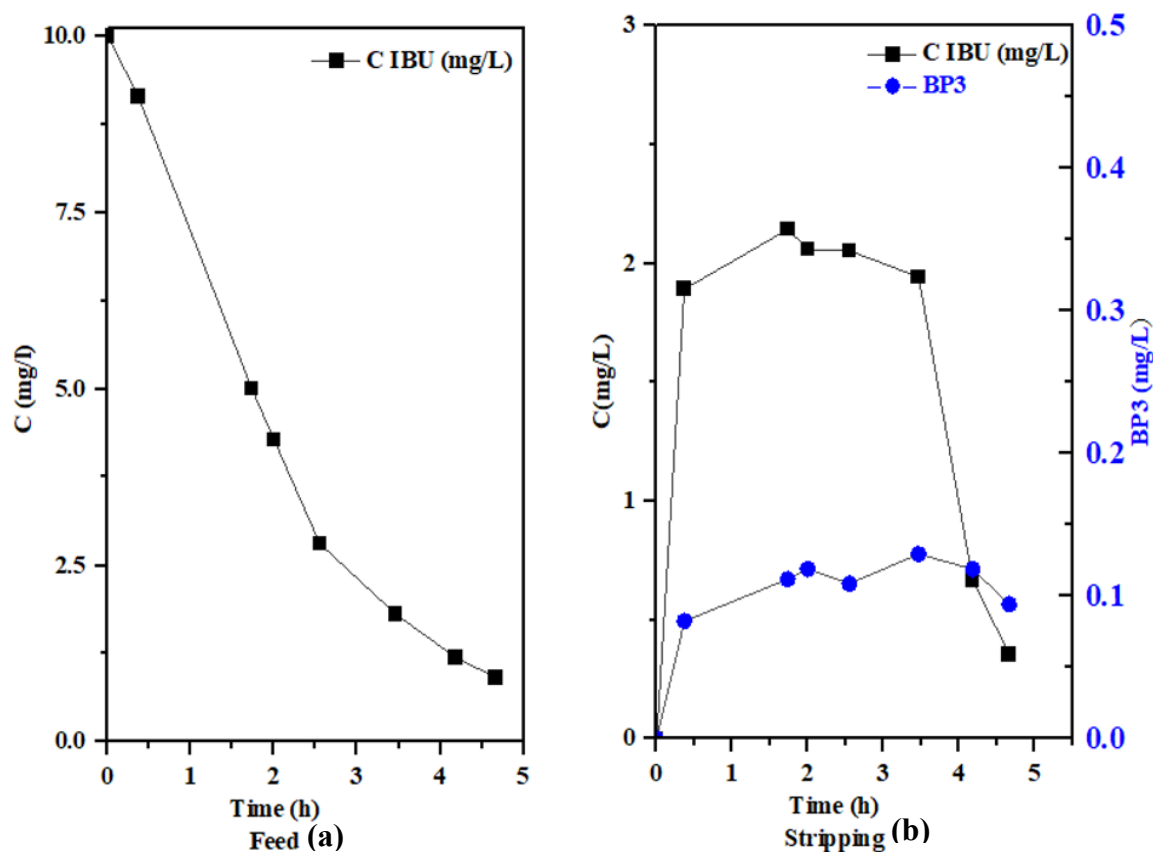


Figure 13. Concentration of IBU and by-product BP3 in (a) Feed: $C_0=10\text{mg/L}$, $V=9\text{L}$, $Q=47\text{L/h}$, $\text{pH}=5.5$; Organic extractant: 40% (v/v) Cy923/kerosene (b). Stripping phase: $V=2\text{L}$; $\text{pH}=11$; $Q=47\text{L/h}$; Inlet ozone concentration $10.2\text{mg O}_3/\text{L}$.

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-ethylbenzaldehyde, 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.

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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.

UNIVERSITAT ROVIRA I VIRGILI
ENHANCED PHARMACEUTICAL ELIMINATION FROM WATER: SUPPORTED LIQUID MEMBRANE TECHNOLOGIES
MARY FARAH

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 (SO₄^{•-}) 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, $\geq 99\%$) was used as the diluent, and Decanol (CAS 112-30, $\geq 99.9\%$) 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 °C) until use. The organic extractant solution was prepared by dissolving a specific concentration of Aliquat 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-CelTM) was selected, and its specifications are summarized in Table 2.

Table 1. Specifications of PTFE support (FluoroporeTM 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™).

| 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 assess 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 KH₂PO₄ 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 °C.

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 $\pm 5\%$ 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 $\pm 5\%$ error.

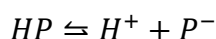
Table 3 Different concentrations of Aliquat 336 in decanol/kerosene used in experimental studies.

| Aliquat 336 (mol/L) | Viscosity (mPa·s) at 25 °C |
|---------------------|----------------------------|
| 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:



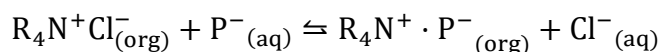
In the following study, the pH was kept at 6 ($pH > pK_a$) thus the dominant form in the solution is the anionic species (P^-). In this case, the ionic liquid, Aliquat 336 $[R_4N Cl^-]_{org}$ forms a complex with targeted compounds, P^- , in the feed phase, to obtain $[R_4N^+ \cdot P^-]$. These complexes 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:

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

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 ($\text{R}_4\text{N}^+\text{Cl}^-$)_{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:



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:

$$K_{\text{ext}} = \frac{[\text{R}_4\text{N}^+ \cdot \text{P}^-] \cdot [\text{Cl}^-]}{[\text{P}^-] \cdot [\text{R}_4\text{N}^+ \cdot \text{Cl}^-]}$$

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

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

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

4.2. Transport in FSSLM

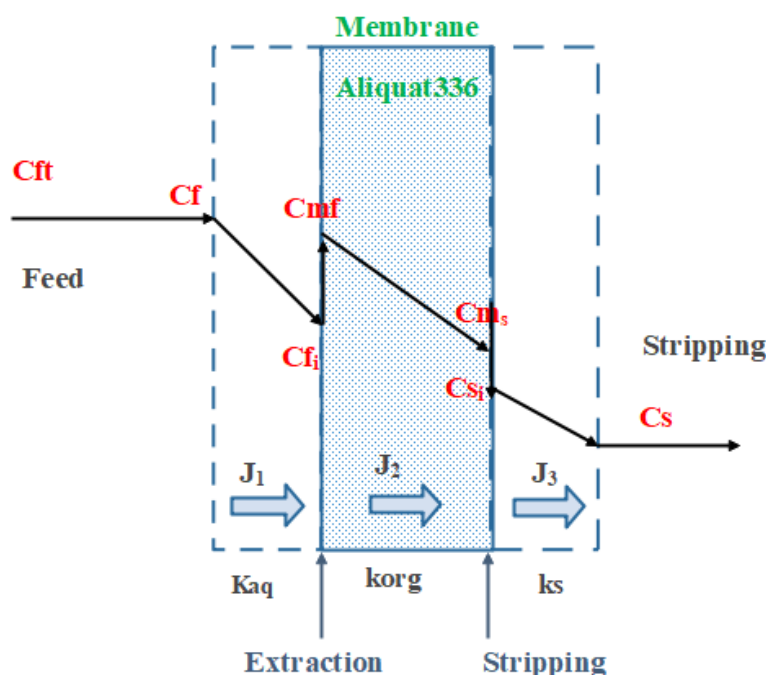


Figure 1. Concentration profile for the transport in liquid membrane considering the three different resistances (diffusion on feed and stripping sides and through the membrane).

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 ($\text{mol} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$); J_2 , flux through the liquid membrane diffusional film, ($\text{mol} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$); K_{aq} and K_{org} are respectively the mass transfer coefficients in the aqueous feed and organic membrane, ($\text{cm} \cdot \text{s}^{-1}$); 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 ($\text{mPa} \cdot \text{s}$) and K' , proportionality constant ($\text{mPa} \cdot \text{s})^{1/2} \cdot \text{cm/s}$)

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).

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

4.2.2. Solute Mass Balance

The mass balance in the feed tank is given by:

$$\text{Input} + \text{Generation} - \text{Output} + \text{Consumption} = \text{Accumulation}$$

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)

$$\text{Accumulation} = - \text{Output}$$

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

Where J , the molar flux J ($\text{mol} \cdot \text{cm}^{-2} \text{ s}^{-1}$), 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 , $C_{\text{fout}}=C_0$ and $C_{\text{Cl}}=0$

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 $z = 0$ $C_{\text{min}} = C_f$, and $z = L$ $C_{\text{out}} = C_{\text{fin}}$;

C_{out} and C_{in} are Pen-G concentrations in the inlet and outlet of the membrane and C_{fin} 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).

$$J = \frac{Q}{A} (C_{\text{min}} - C_{\text{out}}) \quad \text{Eq. (9)}$$

Where Q , is the volumetric flow rate ($\text{cm}^3 \cdot \text{s}^{-1}$); 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 ($\text{mol}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$), and $C_{m\text{ in}}$ and $C_{m\text{ out}}$ 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

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

Given V_f , the volume in the feed tank (cm^3); Q_f , volumetric flow rate ($\text{cm}^3\cdot\text{s}^{-1}$) and $C_{f\text{ in}}$, 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.

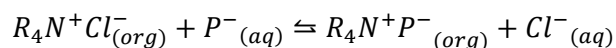
This study examined the impact of various parameters on the extraction efficiency, including the initial pH, concentration of the organic extractant, and stripping agent. The specifics of the experimental conditions are presented in Table 4. All experiments were carried out with a constant initial concentration 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, $T=25\pm^\circ\text{C}$).

| 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:



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 pK_a , 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].

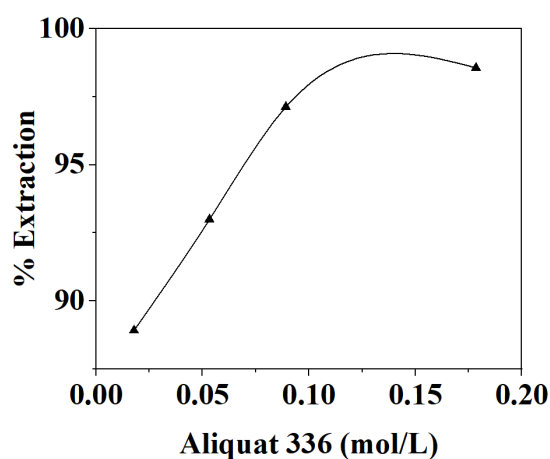


Figure 2 Influence of Aliquat 336 concentration on Pen-G extraction

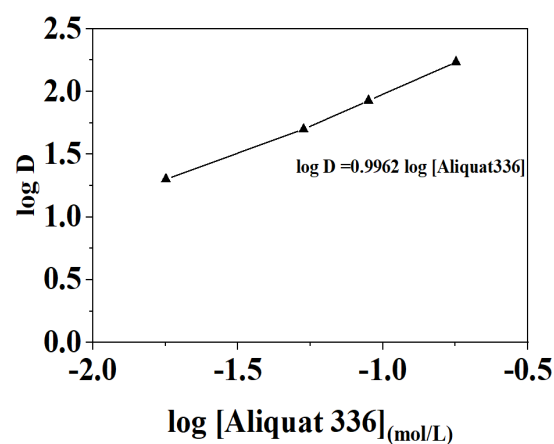


Figure 3 Log D vs. $\log [\text{Aliquat336}]$ to show 1:1 reaction mechanism.

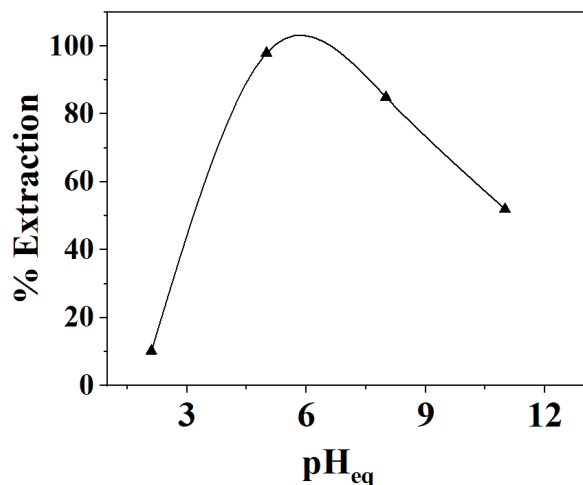


Figure 4. Influence of pH_{eq} on Pen-G extraction.

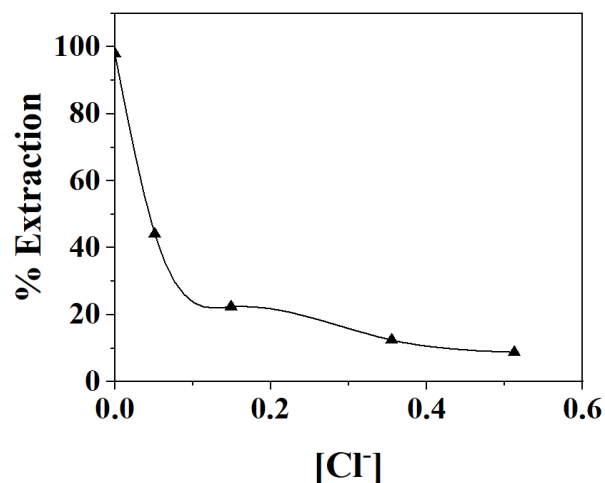


Figure 5. Influence of KCl concentration on Pen-G extraction.

To date, no prior research has reported the extraction constant (K_{ext}) for Pen-G) extraction using Aliquat 336. Consequently, $K_{\text{ext}} = 1.62$ 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) | $[\text{Cl}^-]$ (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.

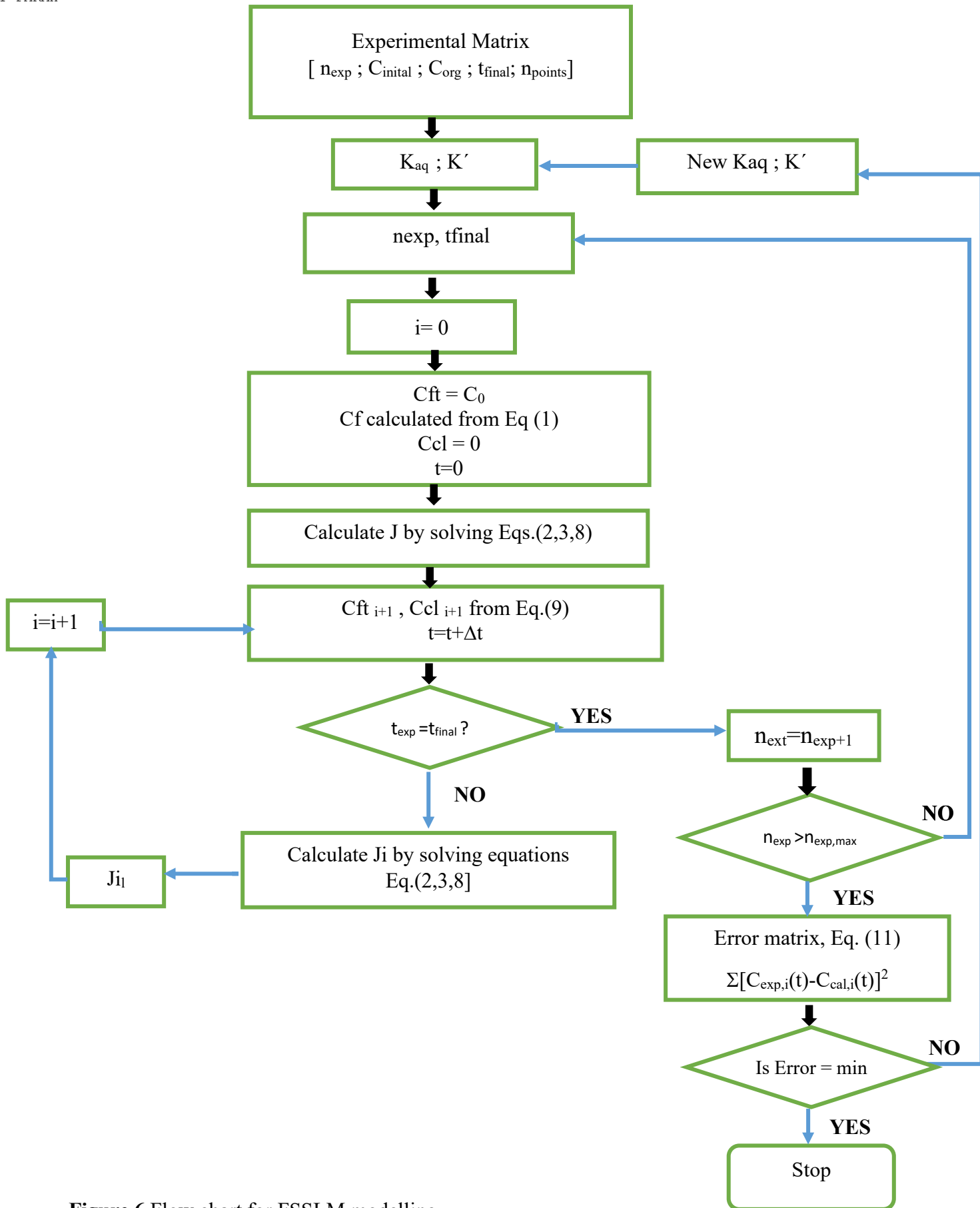


Figure 6 Flow chart for FSSLM modelling.

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 ($C_{f_{calc}}$) and experimental ($C_{f_{exp}}$) 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.

$$\text{Error}(i) = \sum_{i=1}^N (C_{f_{exp,i}} - C_{f_{calc,i}})^2 \quad \text{Eq.(11)}$$

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

Table 6 Optimization parameters values.

| $K_{aq} \times 10^{-2}$ (cm/s) | $K' \times 10^{-4}$ ($\sqrt{mPa \cdot s} \cdot \text{cm/s}$) |
|-----------------------------------|---|
| 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 Figure 7.

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 ($n_{\text{step}} = n_{\text{stepfinal}}$), 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

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

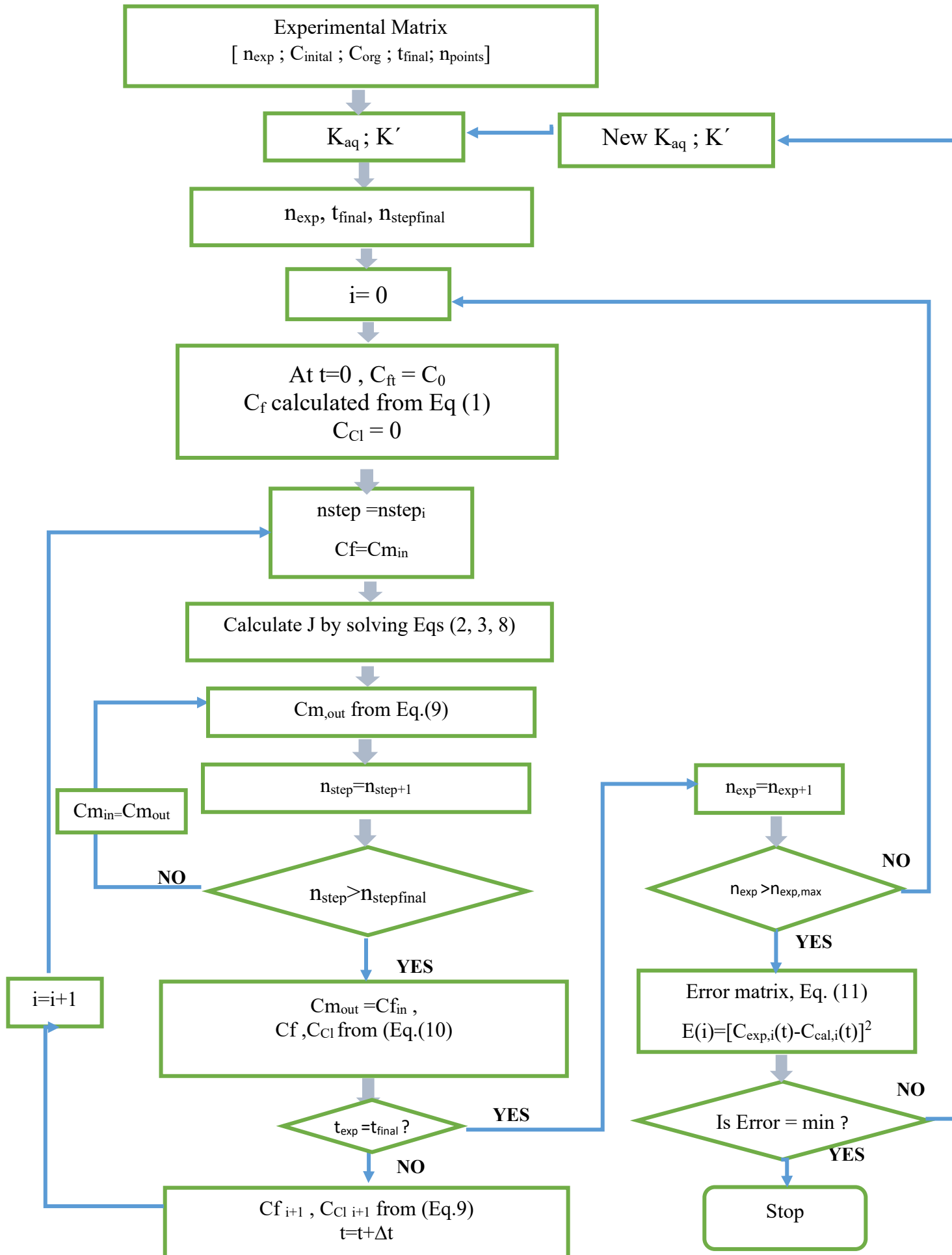


Figure 7. Model development Flow chart for HFM modelling.

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 ($K_{aq} = 0.48 \cdot 10^{-2} \text{cm/s}$), 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_m equal to $2.44 \cdot 10^{-7} \text{ cm}^2/\text{s}$ [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

Similar 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 $2.19 \cdot 10^{-9}$ cm²/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.

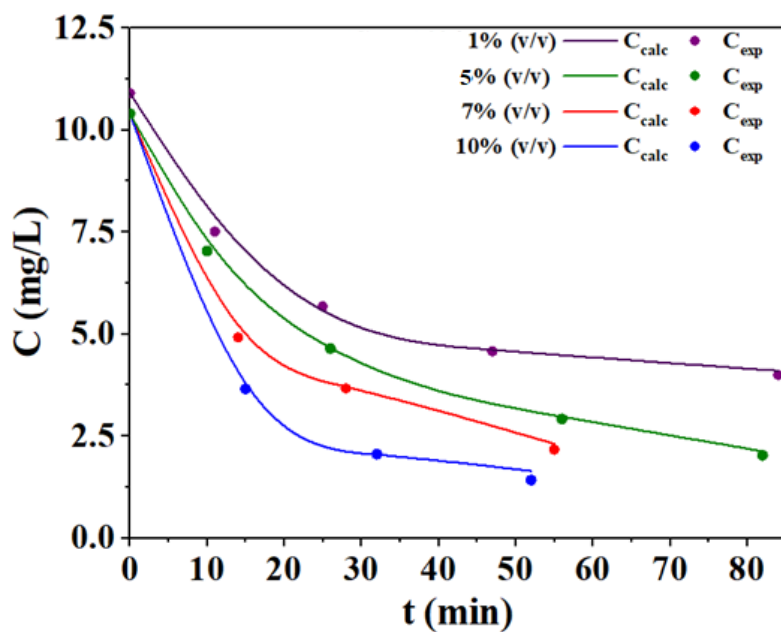


Figure 8 The evolution of Pen-G (mg/L) at different concentrations of Aliquat 336. (Feed: $C_0=30$ mg/L, pH=6.01, 1000 rpm. Stripping: KCl=0.1 mol/L, pH = 7.75, 1000 rpm).

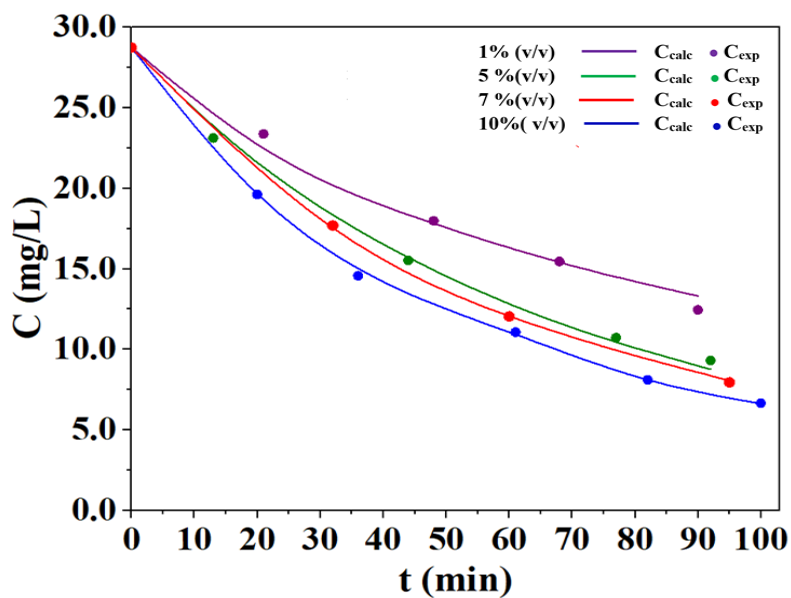


Figure 9 The evolution of pen-G (mg/L) at different concentration of Aliquat 336. (Feed: $C_0=13$ mg/L, pH=6.01, $Q=47$ L/h. Stripping: KCl=0.1 mol/L, pH = 7.75, $Q=47$ L/h).

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 .

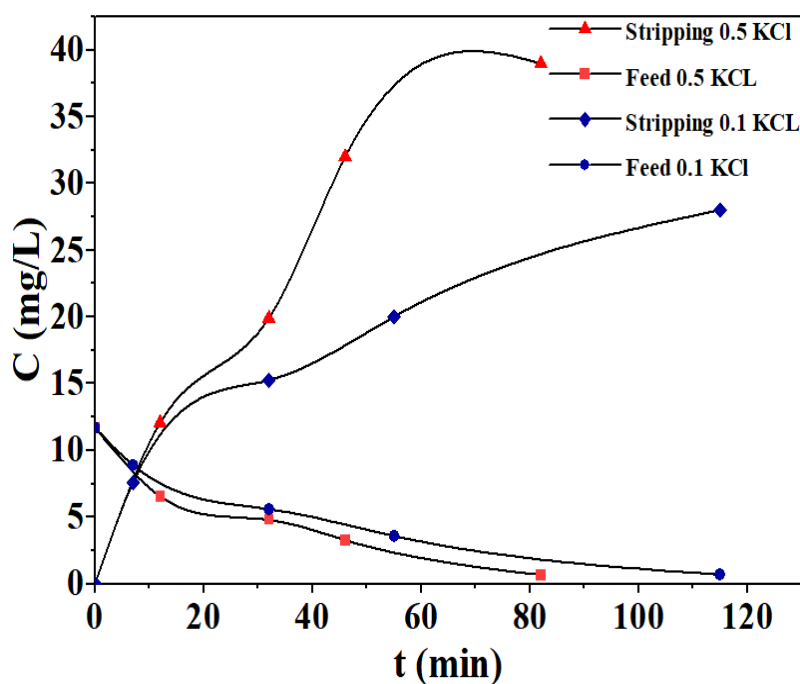


Figure 10 Effect of concentration of KCl on extraction and stripping of Pen-G. (Feed: $C_0=13$ mg/L pH=6.01 Q=47 L/h. Stripping pH=7.45, Q=47 L/h).

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 (K_{aq} , HFSLM: $7.76 \cdot 10^{-2}$ cm/s > K_{aq} , FSSLM: $0.36 \cdot 10^{-2}$ cm/s).

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Chapter 8 Conclusion and Recommendations

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ENHANCED PHARMACEUTICAL ELIMINATION FROM WATER: SUPPORTED LIQUID MEMBRANE TECHNOLOGIES
MARY FARAH

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.

