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Solvents and stabilisers for supported liquid membrane (SLM) extraction of key pharmaceuticals

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Abstract

Chiral amines are essential building blocks for the pharmaceutical industry. They can be synthesised either chemically or biochemically, of which the latter is preferred as the chemical route requires the use of heavy metal-based catalysts. The biochemical route involves the use of transaminase enzymes, leading to a theoretical yield of 100 %. However, this yield is only reached by employing *in-situ* product removal. The use of supported liquid membranes (SLMs) enables simultaneous extraction and stripping of the target amines. The lack of stability of the solvent immobilised in the membrane pores is the main challenge for the industrial deployment of this process. This work looks at less toxic alternatives to the benchmark organic solvent, undecane. Deep eutectic solvents (DESs), natural oils, and an ionic liquid (IL) were impregnated into the pores of different support materials for the extraction of α-methylbenzylamine (MBA) and 1-methyl-3-phenylpropylamine (MPPA). Stabilisers based on nanoparticles or a polydimethylsiloxane (PDMS) coating were used to improve the membrane stability. The DES trioctylphosphine oxide:thymol (TOPO:thymol), the IL trihexyltetradecylphosphonium bis(trifluoromethylsulfonyl)amide ([P6,6,6,14][N(Tf)2]), and the PDMS coating combined with a polytetrafluoroethylene (PTFE) membrane, achieved selective amine extraction comparable to the reference undecane. Stability for 48 hours was also demonstrated with the IL and PDMS coating.

Contents

1 Introduction

Chiral amines are key components of the pharmaceutical industry. These molecules are present at various stages in the production of pharmaceutical products, and therefore play a major role in public health. The synthesis of this type of compound is mainly carried out using toxic metal catalysts. Synthesis processes based on bio-catalytic enzymes have been developed to reduce the environmental footprint associated with catalysis. Among these bio-catalysts, ω-transaminases (ω-TAs) stand out as they allow a theoretical yield of 100 % for the production of chiral amines. This yield can be achieved by shifting the reaction equilibrium towards the products by various means. One of these methods, *in-situ* product removal (ISPR), involves continuously removing the products from the reactive medium, *i.e.*, selectively extracting the products. A supported liquid membrane (SLM), which consists of an extraction solvent immobilised in the pores of the membrane, enables the extraction and stripping of the target products to be combined in a single step. SLMs are therefore promising candidates for the continuous and selective extraction of chiral amines from their synthesis medium, and could be used to optimise their synthesis using ω-TAs.

The loss of solvent from the membrane pores during extraction is the main reason why SLMs are not yet used on a large scale in industry. When the solvent is lost, the membrane is said to be unstable, making it impossible to extract compounds selectively. Improving the stability of SLMs, by choosing solvents with suitable properties or by modifying the membrane surface, is crucial to the development of this separation technology.

In this work, different types of solvent are studied for use in SLMs, namely deep eutectic solvents (DESs), natural oils, and an ionic liquid (IL), with the aim of finding a less toxic alternative to the benchmark organic solvent, undecane. The amines studied are isopropyl amine (IPA), the amine donor, and the target amines α-methylbenzylamine (MBA) and 1-methyl-3-phenylpropylamine (MPPA). To be economically viable, the solvent has to be stable, selective towards the product amines, and less toxic than undecane while allowing a relatively efficient extraction. As the stability of the membrane is strongly linked to its surface hydrophobicity and as the feed and strip solutions are both aqueous, hydrophobic stabilisers are studied to enhance the solvent retention in the membrane. These stabilisers consist either of nanoparticles (NPs) or a hydrophobic polymer solution, deposited on the membrane surface prior to extraction. NPs of chitosan and silica, and a solution of polydimethylsiloxane (PDMS) are tested. The support in which the solvent is immobilised also has an impact on the stability and efficiency of the process. Different types of membrane, *i.e.*, membranes produced from different polymers, are studied for SLM applications. The influence of pore size is analysed for the polytetrafluoroethylene (PTFE) membrane, with pore sizes ranging from 50 to 450 nm.

This work first presents an overview of the literature associated with chiral amines and their production, while describing the membrane extraction process and the parameters that influence it. The techniques and materials used to characterise the solvents studied and to quantify the extraction capacity of SLMs are then described in chapter 3. Next, the membrane extraction results are presented in chapter 4, and the types of solvents and membranes are compared. The influence of stabilisers on extraction performance is also described, to finally select the systems that enable efficient, stable and selective extraction, potentially capable of competing with the reference solvent, undecane. Last, a conclusion and some future prospects are given in chapter 5.

2 Literature review

The aim of this literature review is to introduce chiral amines and discuss their applications in the industry. Then, chiral amine production will be discussed, distinguishing between standard processes and innovations that aim to make the process more environmentally friendly, using bio-catalysts in particular. The discussion will then focus on how to optimise this innovative production process by shifting the reaction equilibrium, detailing some techniques to achieve this objective. Among these techniques, the supported liquid membrane process will be discussed including the parameters influencing its efficiency.

2.1 Chiral amines

Chiral amines are essential components in the manufacturing of drugs, biologically active compounds, and many natural products, more specifically, chiral amine structures are found in 40 to 45 % of small pharmaceutical molecules, as well as in chemical and agrochemical products [1] (see Fig.1). For example, berberine is a molecule found in Chinese medicinal herbs. This amine, which acts on the intestinal barriers, is used to facilitate the assimilation of insulin after oral ingestion [2][3]. (R)-Fluoxetine serves as an antidepressant drug [4], sitagliptin is a molecule used in anti-diabetic treatments [5], pramipexole allows to treat Parkinson's disease [6], solifenacin is used to treat overactive bladder [6], formoterol is useful to treat asthma [7], suloxifen serves as a bronchodilator [8], and morphine and its derivatives are among the most powerful and common analgesics in use today [9]. The synthesis of these amine compounds suffers from various issues, such as the formation of large quantities of by-products, the use of toxic chemical reagents, and the need for a multi-step synthesis. However, these problems can be resolved by employing various cost-effective biocatalytic methods [10].

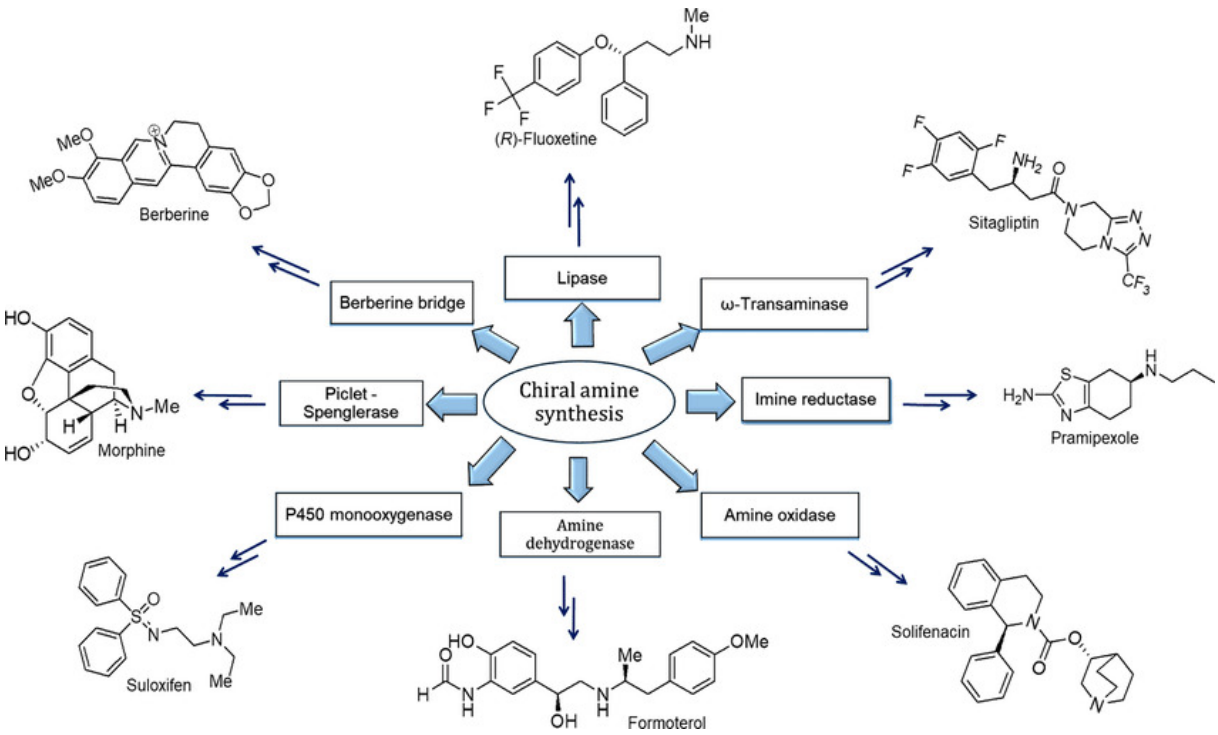

Figure 1: Overview of processes for the synthesis of various chiral amines, retrieved from Patil et al. [10].

A key property of chiral amines is their chirality, indicating that these molecules have two chemically identical enantiomers, which can be viewed as mirror images that cannot be superimposed. This chirality is due to the presence of an axis, a plane or a centre of chirality within the molecule [11]. The fact that these two chiral enantiomers have different pharmacological properties is a subtle point that should not be overlooked when developing, producing and commercialising chiral amines. It is necessary to separate the enantiomers or to know the composition of the chiral mixture at each stage, because if one of the enantiomers produces the desired pharmacological effect, the second may be inactive or even have undesirable effects [12][13].

Among these amines with a wide range of applications are α-methylbenzylamine (MBA) and 1-methyl-3-phenylpropylamine (MPPA). MBA, also known as 1-phenylethylamine, is a simple and inexpensive chiral molecule that can be used to prepare enantiomerically pure compounds, as a chiral ligand, or to develop organocatalysts. MPPA, on the other hand, is a precursor in the synthesis of dilevalol, an antihypertensive drug [14][15][16]. Efficient synthesis methods for MBA and MPPA are being studied, with the use of isopropyl amine (IPA) as the precursor.

2.1.1 Chiral amine synthesis

Given the importance of chiral amines in the manufacture of various drugs, several methods have already been studied for their synthesis, including the resolution method [13][17], transition metal-catalysed asymmetric hydrogenation [1], organocatalytic [18][19] and biocatalytic

asymmetric hydrogenation [20].

The classical resolution method, which dates from the 19th century and is still in use in industry today, involves mixing two enantiomers (R and S) with a stable chiral resolving agent (R'). This reaction creates two diastereomeric salts with different physical properties ($R-R'$, $S-R'$), which can be separated by precipitating the less soluble salt through the adjustment of the temperature and concentration. This process, which allows enantiomers to be separated, makes it possible to obtain pure chiral amines [13][17]. As this is a batch process, research is being carried out to transform it into a (semi-)continuous process in order to optimise production [13][21].

A second strategy for the production of chiral amines is to use hydrogenation, which is a chemical reaction between molecular hydrogen (H_2) and another compound in the presence of a catalyst, causing the reduction of an unsaturated double or triple bond by adding pairs of hydrogen atoms [22]. This hydrogenation is carried out asymmetrically, *i.e.*, the addition of hydrogen is done in such a way that the reaction product is an enantiomer of a chiral compound, while the stereoselectivity comes from the catalyst used for the reaction [23]. A schematic view of the process using a metal catalyst can be seen in Fig.2, *i.e.*, the synthesis of chiral amines bearing a stereogenic centre in the α, β or γ position with respect to the nitrogen atom. Ideally, a small amount of catalyst may be sufficient to produce enantiomerically pure compounds in large quantities from precursors that may or may not be chiral, this catalyst can also be tuned so that the enantiomer produced is either R- or S-type depending on the needs of the application [24].

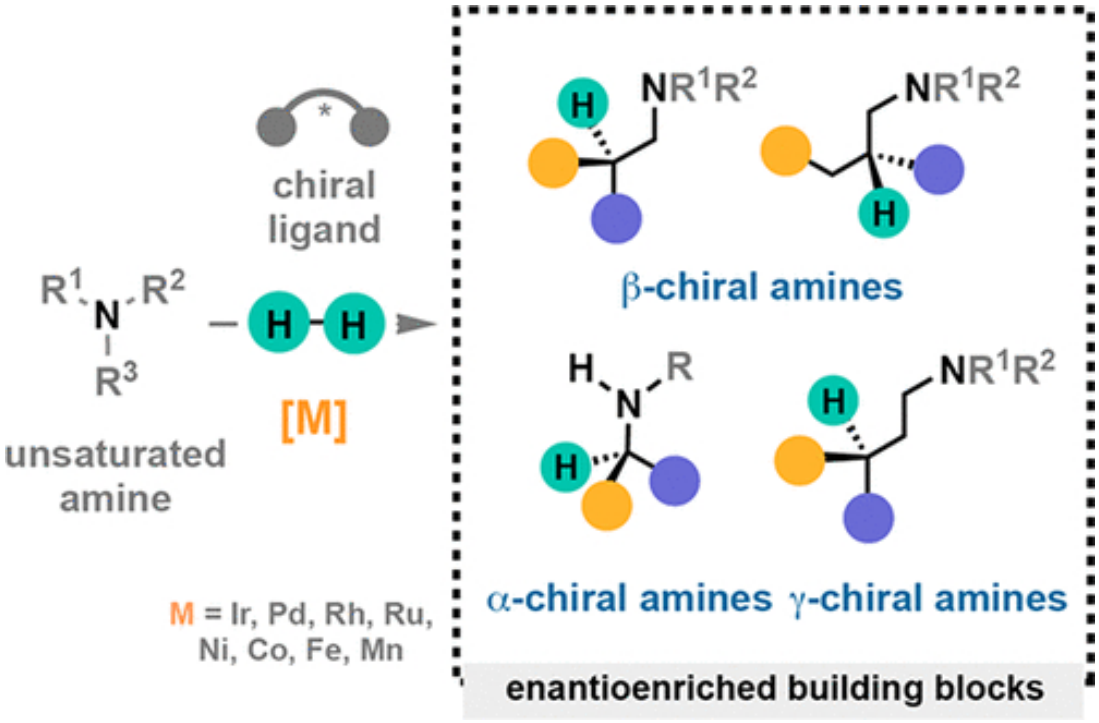

Figure 2: Synthesis of α, β and γ chiral amines by asymmetric hydrogenation using a metal catalyst, retrieved from Cabré et al. [1].

Transition metal-catalysed asymmetric hydrogenation is currently one of the most efficient strategies for chiral amine synthesis, offering high reactivity and selectivity as well as minimal by-product and waste production [1][24]. The main issue with this method is the type of catalysts used, as mainly precious metals are used, such as rhodium (Rh), iridium (Ir), and ruthenium (Ru). It is therefore necessary to look at the use of more accessible metals such as manganese (Mn), iron (Fe), cobalt (Co) or nickel (Ni) [1]. However, these heavy and toxic metals can lead to insufficient stereoselectivity for the amine synthesised, as well as products contaminated by the catalyst, requiring additional purification steps [14][25].

Organic catalysts have also been developed for asymmetric hydrogenation, this type of catalyst allows the synthesis of chiral compounds based on a biomimetic approach, unlike hydrogenation using metal catalysts. For example, 1,4-dihydropyridine (Hantzsch esters) can be easily oxidised to pyridine by aromatisation, the hydrogen anions produced in the process can be used for mild reduction of unsaturated compounds, like amines. The current difficulties in developing this type of catalyst are the fact that a stoichiometric amount of the hydrogen source is generally required, resulting in low atom economy, combined with the need to remove by-products [18][19].

Bio-enzymatic catalysts have also been developed to limit the difficult reaction conditions and the use of metals. These catalysts include lipases, transaminases, amine oxidases, ammonia lyases, imine reductases, and amine dehydrogenases for the synthesis of chiral amines. For

example, amine dehydrogenases enable the synthesis of chiral amines from ketones with H_2O as the only by-product [20][26]. Among the compounds mentioned above, transaminases and more particularly ω-transaminases can also be used as a tool for obtaining chiral amines, achieving a theoretical yield of 100 % [27].

2.1.2 ω-Transaminases for chiral amine synthesis

Transaminases are a class of enzymes that catalyse the transfer of an amino group from an amine donor. This class of enzymes can be divided into four sub-groups, simply named I, II, III and IV. Enzymes belonging to subgroups I, III and IV can only transfer an amino group if it is linked to an α-carbon of the amine donor, with the α-carbon being the carbon atom linked to the carboxyl group in the case of amino acids. These sub-groups can then be grouped together as α-transaminases. In contrast, sub-group II enzymes can transfer an amine group from a carbon that is not in the α-position. These subgroup II enzymes are therefore called ω-transaminases (ω-TAs), the Greek letter ω representing all the non-α positions [25][27][28].

The ω-TAs reaction scheme consists of two half-reactions, namely an oxidative deamination of an amine donor followed by a reductive amination of an amine acceptor. The first half-reaction involves transferring the amine group from the donor to a complex composed of the enzyme and pyridoxal-5'phosphate (PLP), as can be seen in Fig.3 (a). PLP is a derivative of the vitamin B6 molecule, acting as a reaction cofactor due to its capacity for electron delocalisation. The amine is then transferred to the enzyme-PLP complex (E-PLP), which is transformed into an enzyme complex composed of the enzyme and pyridoxamine-5' phosphate (PMP). The ketone corresponding to the donor amine is also produced [25][28].

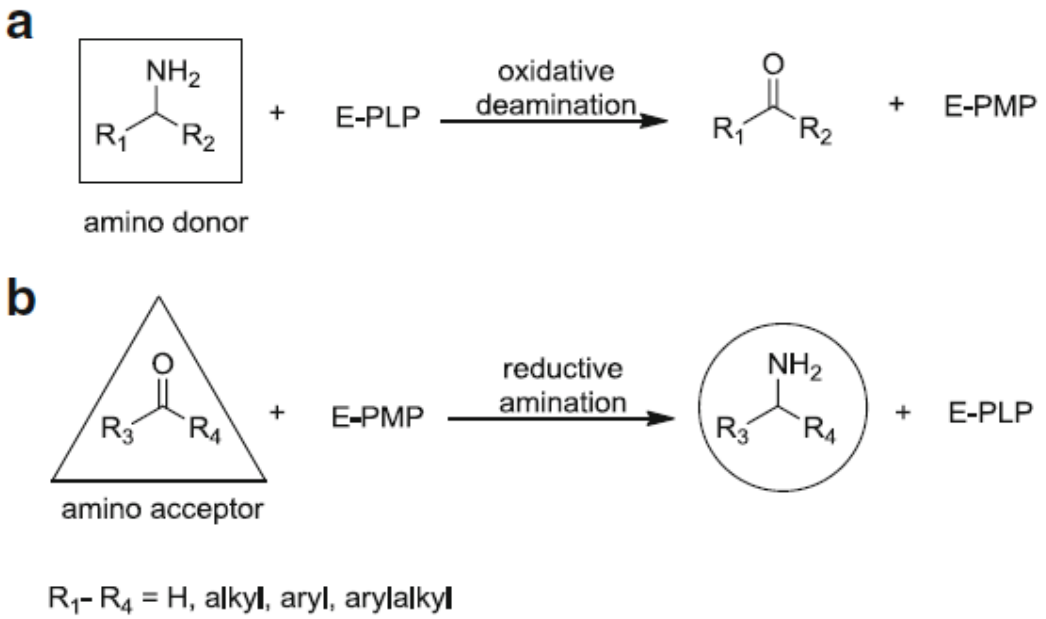

Figure 3: ω-TA reaction pathway consisting of oxidative deamination of an amino donor which converts E-PLP to E-PMP (a), and reductive amination of an amino acceptor which accompanies regeneration of E-PLP (b), retrieved from Malik et al. [25].

In the second part of the reaction, the enzyme-PMP (E-PMP) complex transfers its amine group to the amine acceptor (see Fig.3 (b)). A new amine is thus produced and the E-PLP is regenerated from the E-PMP. This regeneration implies that the reaction is reversible depending on the reactants present and that the PLP is not consumed by the reaction [25][28]. Furthermore, ω-TAs are potentially a ”green” alternative to conventional chemical methods. For example, they can be used to synthesise sitagliptin, a molecule used in anti-diabetic treatments, with a 19 % reduction in hazardous waste. However, there are still challenges to be overcome, such as the cost of enzymes, catalytic efficiency, and reaction time [5][26][29].

The chiral amines MBA and MPPA can be produced from acceptor amines using ω-TAs by the resolution method or by asymmetric hydrogenation, as can be seen in Fig.4. In this case, the donor amine is IPA, which is a low-cost molecule. The by-product of the reaction, acetone, is easily removed by evaporation. The resolution method can only achieve conversion rates of 50 %, while the asymmetric synthesis can reach a theoretical conversion rate of 100 %, as mentioned before [14].

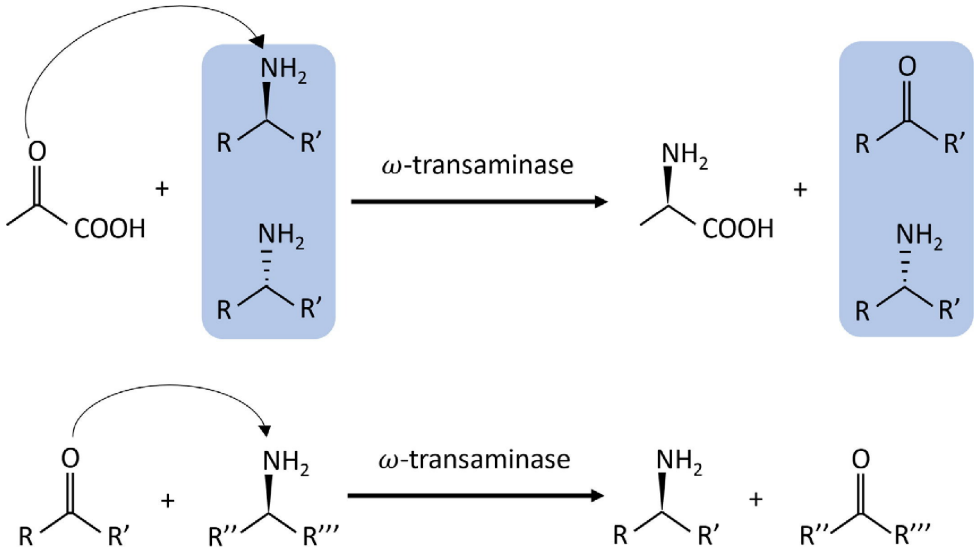

Figure 4: Synthesis of chiral amines using ω-transaminases by resolution method (top), and by asymmetric hydrogenation of a prochiral ketone (bottom), retrieved from Van Eygen et al. [14].

To achieve the highest possible yield in the synthesis of chiral amines, it is necessary to shift the reaction equilibrium to the product side, as the equilibrium is strongly in favour of the amine donor. This equilibrium shift can be achieved by different methods such as an excess of amine donor. *In-situ* product removal stands out as a particularly interesting method for amine synthesis by continuously removing the product from the reaction medium [14].

2.2 *In-situ* product removal

In-situ product removal (ISPR) is a method that aims to rapidly remove a product while the reaction is still progressing in order to avoid any subsequent interference with cellular or media components. The main aim of ISPR is to remove the product as it is formed near the cell, as opposed to batch processing, which leads to the accumulation of products [30] [31]. The increased yield and productivity is achieved by minimising product accumulation that causes interferences with the producing cell, by reducing product losses due to environmental conditions, and, by reducing the number of downstream processing steps. Different ISPR configurations can be seen in Fig.5.

The different ISPR configurations can be classified according to whether the product separation process takes place inside or outside the reaction medium or the vessel containing the solution to be separated. In addition, a distinction is made between direct contact processes, indirect contact processes using membrane technology, and vapour-liquid extraction processes using evaporation of volatile products. For direct contact extraction, the direct addition of solvent and the absorption process take place in an internal configuration (Fig.5 (A) and (B)), whereas separation in an external configuration can take place using a compact bed or absorption in an external tank (Fig.5 (D) and (E)). For indirect contact separation methods, a distinction can be

made between simple membrane extraction and supported liquid membrane extraction, which combine the separation and extraction stages into a single process (Fig.5 (C) and (F)). For liquid-vapour separations, ISPR can be performed using gas stripping and pervaporation (Fig.5 (G) and (H)) [32].

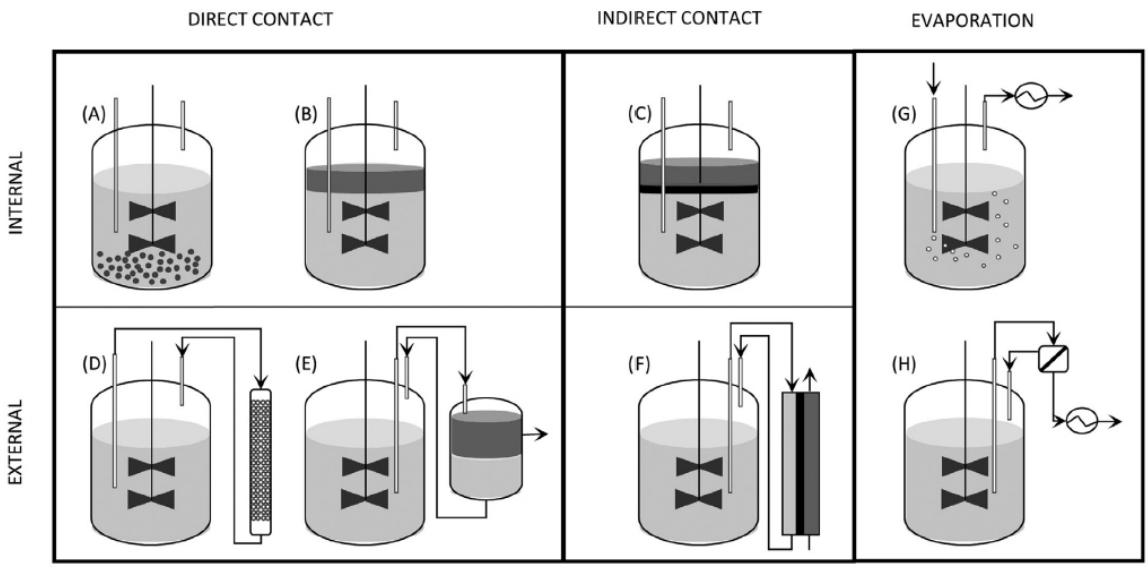

Figure 5: Different ISPR configurations: direct solvent addition (A), direct absorption (B), compact bed absorption (D), solvent extraction in an external tank with recirculation (E), membrane-assisted extraction with indirect contact with the extractant inside the reactor (C) and in an external loop (F), gas stripping (G) and pervaporation (H), retrieved from Santos et al. [32].

As a general rule, a strategy will be effective if it generates a significant driving force to separate the product from the other components. The most commonly used physico-chemical characteristics for ISPR are volatility, solubility, charge, hydrophobicity, and molecular size [33]. The current ISPR technologies include extraction and evaporation, electrodialysis, aqueous two-phase systems for biomolecules separation, adsorption, precipitation, complexation and membrane separation [30][32][34]. Liquid-liquid extraction and membrane extraction technology are discussed further below.

2.2.1 Liquid-liquid extraction

Liquid-liquid extraction (LLE) or partitioning, is a separation process that involves transferring a solute from one solvent to another. The two solvents used are immiscible or only partially miscible with each other. One of the solvents is generally an aqueous mixture, while the other is a non-polar organic liquid. Liquid-liquid extraction involves a mixing stage during which contact is made between solvents followed by a phase separation stage [35].

In the LLE process, the solute to be separated is distributed between the two immiscible phases, with the denser phase at the bottom. The efficiency of solute extraction from the aqueous phase

to the organic phase depends on two parameters, namely the equilibrium constant for solute partitioning between the two phases and any reaction involving the solute. One possible reaction for the solute is dissociation in the aqueous phase. For example, a weak acid HA decomposes into the ionic form A^- at a certain pH value. A schematic representation of the situation can be seen in the Fig.6 (a). The partition equilibrium constant K_D can therefore be defined as follows:

$$K_D = \frac{[HA_{org}]}{[HA_{aq}]} \tag{1}$$

with $[HA_{org}]$ the concentration of the weak acid solute in the organic phase, and $[HA_{aq}]$ the concentration in the aqueous phase. A high value of K_D indicates a favourable extraction in the organic phase. As the efficiency of the extraction depends on the total concentration of the solute in each phase, the dissociation of the species in the aqueous phase must be taken into account and a distribution ratio can be D defined as follows:

$$D = \frac{[HA_{org}]_{total}}{[HA_{aq}]_{total}} = \frac{[HA_{org}]}{[HA_{aq}] + [A^-_{aq}]} \tag{2}$$

with $[A^-_{aq}]$ the concentration of the ionic form of the weak acid. To simplify the distribution ratio expression, the dissociation constant of the weak acid K_a is defined as follows:

$$K_a = \frac{[H_3O^+_{aq}]\,[A^-_{aq}]}{[HA_{aq}]} \tag{3}$$

with $[H_3O^+_{aq}]$ the concentration of H_3O^+ ions. The distribution ratio can now be defined as a function of $[H_3O^+_{aq}]$, *i.e.*, the pH of the aqueous solution:

$$D = \frac{K_D\,[H_3O^+_{aq}]}{[H_3O^+_{aq}] + K_a} \tag{4}$$

This demonstrates the importance of pH for LLE applications, as the pH value determines the ionic or non-ionic form of many molecules. So, to favour the extraction of ionisable molecules, it is imperative to control the pH of the solution to be separated, as can be seen in Fig.6 (b) [35][36].

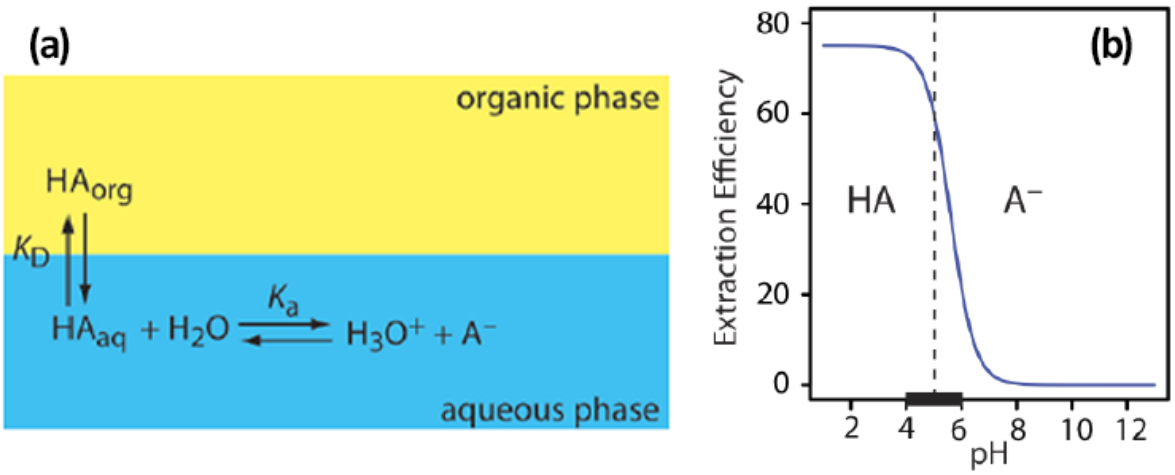

Figure 6: Liquid-liquid extraction of a weak acid HA dissociating in the aqueous phase (a), extraction efficiency versus pH of the aqueous phase for the extraction of the weak acid HA (b), retrieved from Harvey [36].

LLE technology is a common strategy for recovering a wide range of different amines downstream of the reaction. Enantioselective LLE combines enantiomeric recognition and solvent extraction in a single separation technique. If carried out under acidic or basic conditions, this extraction allows the amine product to be controlled if it is protonated, thus separating the amine from the other components of the product stream. The limitations of this separation technique are linked to the relative concentration of the reaction components and the selectivity of the solvent. Some by-products are also soluble and are extracted at the same time as the amines [33][37].

2.2.2 Membrane extraction

Membrane extraction involves the use of a membrane acting as an intermediary between a donor feed phase and a receiver phase in which the products are extracted. This transfer between the two phases requires the molecules to be separated to pass through the membrane [38]. Membrane extraction techniques can be divided into three categories, membrane-based solvent extraction (MBSE), polymer inclusion membrane (PIM) extraction and liquid membrane (LM) extraction.

Within MBSE, the feed phase and extraction phase are brought into contact through a porous membrane, of which the pores are filled with one of the two liquids, which allows for the diffusion of compounds from one phase to the other without phase mixing. Using a membrane to extract a given compound means that the phase separation step is no longer required, while keeping the interfacial area between the two liquids constant [39][40].

PIMs are composed of an extractant and a base polymer in which the extractant is entrapped, to ensure the mechanical stability of the membrane. A modifier or plasticiser can be added to mod-

ify the PIM properties, such as elasticity or solubility towards the species to be extracted. The basic polymers used are mainly poly(vinyl chloride) and cellulose triacetate. These membranes are gaining interest in many applications because of their greater stability compared with other types of liquid membrane, and their selectivity for the species to be separated [39][41][42].

Liquid membranes, like solid membranes, act as semi-permeable barriers between two liquid phases. The formation of such a membrane occurs when two miscible fluids are separated by a liquid that is immiscible with them, but allows mass transport between the fluids. There are several mechanisms by which solutes can be transported across the liquid-liquid interface or across a liquid membrane. These mechanisms can be based on differences in the physical solubility of the solutes, their solubilisation in the solvent or in reverse micelles, and the chemistry and rate of chemical or biochemical reactions occurring at the liquid-liquid interface. Liquid membranes can be classified into three groups depending on their formation step, namely bulk liquid membranes (BLMs), emulsion liquid membranes (ELMs) and supported liquid membranes (SLMs). A schematic view of these types of liquid membranes can be seen in Fig7 [39][43][44].

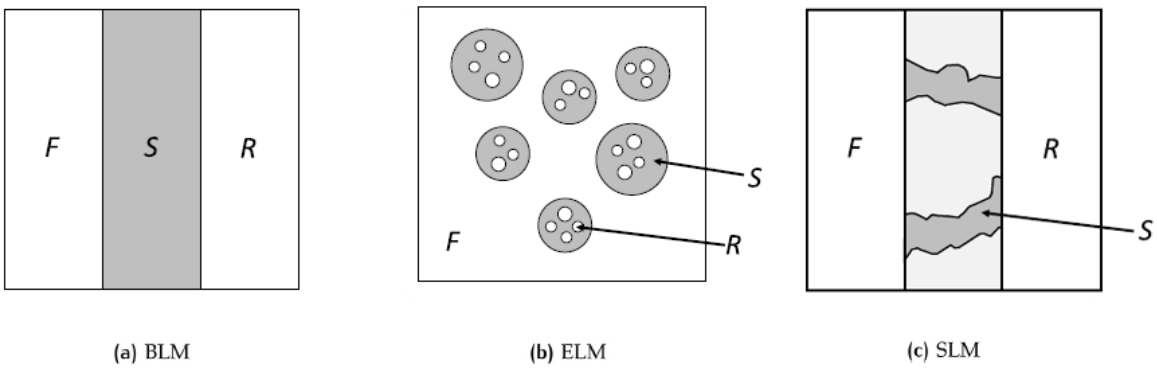

Figure 7: Types of liquid membranes, bulk liquid membrane (a), emulsion liquid membrane (b) and supported liquid membrane (c). F, S and R represent the feed, the solvent and the raffinate solution, retrieved from Van Eygen et al. [39].

BLMs (Fig7 (a)) consist of a bulk organic phase separating an aqueous feed phase and an aqueous receiving phase. This type of membrane, combining pre-concentration and product separation, is widely used for sample preparation for analytical purposes. The industrial potential of this type of membrane is nevertheless limited by the fact that the liquid membrane tends to be entrained during the extraction process and that the solvent can contaminate the feed phase [39][45].

In ELMs (Fig7 (b)), the product is recovered via droplets of a stripping solution, which are dispersed in an organic extractant. This solvent is then dispersed in the aqueous feed phase from which the product is to be extracted. The main advantages of this technique are energy savings, low cost, and high mass transfer rates due to the large interfacial area between the two aqueous phases. Once again, the poor stability of this type of membrane explains the difficulty

of using ELMs on a large scale [39][46].

Last, within SLMs (Fig7 (c)), an extractant is immobilised within a porous membrane by capillary forces. It can be used in three configurations depending on the separation application, namely gas feed/gas permeate, liquid feed/liquid permeate, and liquid feed/gas permeate [47]. SLMs for liquid-liquid separations and their characteristics are described in more detail below.

2.2.3 Supported liquid membranes

In an SLM process, the target product in the feed solution is extracted into the LM using an extractant held in the pores of the membrane. The product is simultaneously removed by the strip solution, enabling the extraction and stripping process to be combined. This advantage, together with the fact that the amount of extractant is reduced, makes SLMs particularly attractive compared with conventional LLE [14].

To better understand how SLMs work, the species transport mechanism through the LM needs to be explained. The driving force for transporting the species from the feed to the strip is the concentration difference of the species. There are three different transfer mechanisms, as shown in Fig.8. Simple uphill transport (Fig.8 (a)) occurs when an irreversible chemical reaction of type A+B $\rightarrow$ AB takes place in the stripping solution, while species A is the species to be transported. The reaction creates a concentration gradient favourable to the transport of species A across the membrane. As the product AB is insoluble in the LM, the latter is accumulated in the strip phase [47].

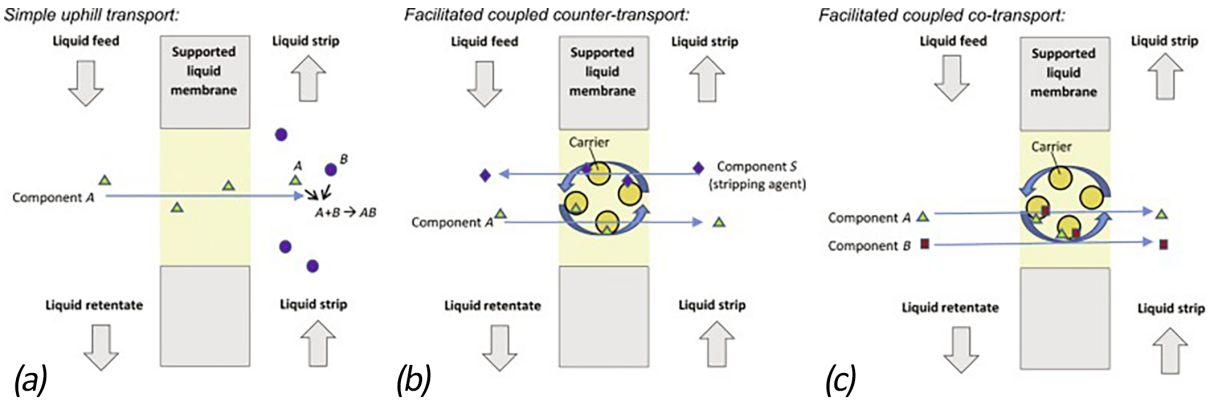

Figure 8: Transfer mechanisms controlling the removal and concentration of a species through a supported liquid membrane for liquid-liquid separation: simple uphill transport (a), facilitated coupled counter-transport (b), and facilitated coupled co-transport (c), retrieved from Luis [47].

Facilitated coupled counter-transport (Fig.8 (b)) allows the removal of charged ions A from the feed solution, while maintaining the electrical neutrality of the system. This neutrality is maintained by transporting species S carrying the same charge as species A from the strip to the feed. Transfer across the membrane is achieved by a transporter forming a complex with the

species transported. In the third case, facilitated coupled co-transport (Fig.8 (c)), positively and negatively charged species A and B are transported to the strip via the transporter. This process is useful for removing metals such as copper or zinc [47].

Now that the transport mechanisms have been discussed, it is useful to quantify the mass transfer of the species to be separated across the membrane and thus determine the solute flux. Given the SLM configuration (Fig.9), mass transfer is defined by the feed-membrane interface and the membrane-strip interface. This mass transfer can therefore be defined as follows: (1) convective transport from the feed bulk to the feed-membrane interface, (2) partitioning between the feed and liquid membrane phase, (3) diffusion across the liquid membrane due to the presence of a concentration gradient, (4) partitioning between the liquid membrane phase and the strip bulk, and (5) convective transport from the membrane-strip interface to the strip bulk [39].

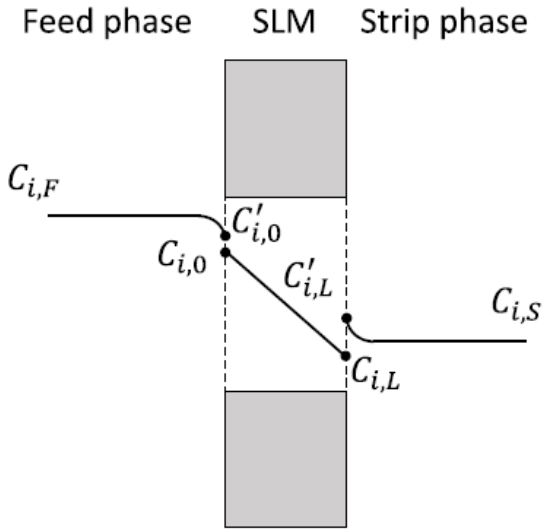

Figure 9: Concentration profile of a species through a supported liquid membrane, retrieved from Van Eygen et al. [39].

Using the concentration profile in Fig.9, it is possible to define the solute flux J_i through the SLM :

$$J_i = \frac{K_i D_i}{L} (C_{i,F} - C_{i,S}) \tag{5}$$

where K_i is the partition coefficient of solute i, $C_{i,F}$ and $C_{i,S}$ are the concentration in the bulk feed and strip phases, D_i is the diffusivity of solute i, and L is the membrane length [39].

As explained above, the driving force for species transport through SLMs is the concentration difference between the feed and acceptor phases. One of the keys to keeping this concentration gradient constant is to prevent reverse transfer of the species to be separated, *i.e.*, from the strip to the feed. In simple uphill transport, the species that has passed through the membrane reacts to become a species that is no longer soluble in the LM. This principle can be applied to ionisable solutes, which will exist in two different forms depending on their position in the

SLM system. The species to be transported are therefore in their non-ionic deprotonated form in the feed phase. This allows them to be extracted by the solvent present in the LM. On the strip side, the elements to be separated are in their ionic, protonated form. These compounds are thus trapped because the solvent is unable to dissolve compounds that are too polar. This protonation of the compounds is controlled by the pH of the three-phase system and by the pK_a of the species. By adjusting the pH of the different phases, it is thus possible to fine-tune the overall selectivity of the system, *i.e.*, to trap only the desired molecules in the strip phase. Neutral molecules, which are insensitive to changes in the pH of the system, are distributed evenly between the phases without enrichment in any particular phase [48]. A diagram showing the conditions for separating ionisable, organic compounds by SLMs according to their pK_a can be seen in Fig.10, with the protonated forms on the strip phase side. Three conditions are defined for transporting either a carboxylic acid RCOOH or a basic primary amine RNH_2 across a membrane, to enrich the acceptor phase with the chosen compound. The first condition is that the compound to be separated must be in deprotonated form so that it can be dissolved in the solvent contained in the membrane. This is achieved by defining a pH value of the donor solution equal to the pK_a-2 for the acid or the pK_a+2 for the base. The third condition is the opposite of the first, and consists of having the molecules in protonated form in the acceptor phase, preventing their re-dissolution by the solvent, as the molecules are too polar. The second condition concerns the octanol-water partition coefficient (K_{OW}), a measure of a compound's hydrophilicity/lipophilicity. Since extraction by SLM is effective for compounds with moderate hydrophobicity, a log(K_{OW}) value of between 2 and 4 is required for the compounds to be extracted [49][50].

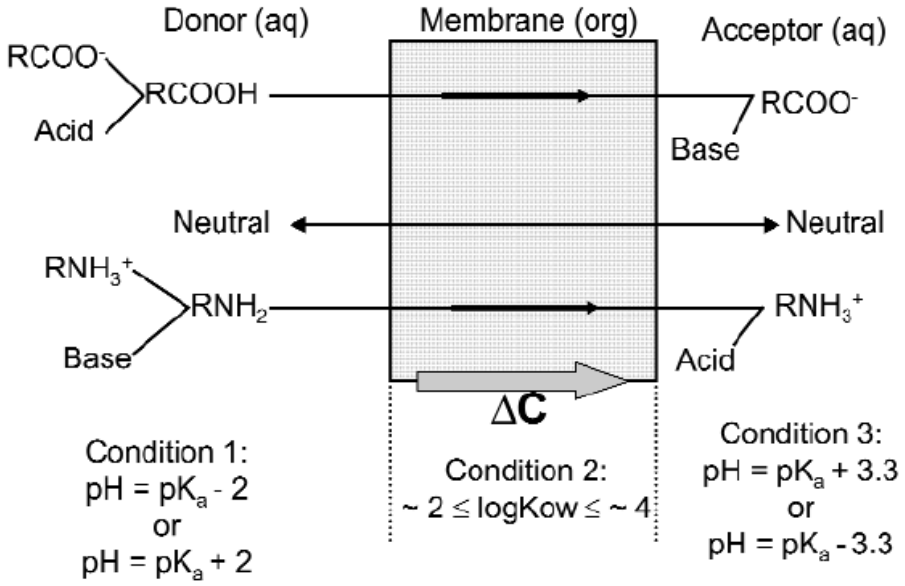

Figure 10: pH conditions for SLM separations of ionisable organic compounds, retrieved from Chimuka et al. [48].

As amines are ionisable organic molecules, the process described above is perfectly applicable

to separation applications. Fig.11 shows that it is possible to separate amines selectively by maintaining the feed under alkaline conditions and the strip under precise acidic conditions. In this case, the product amine MBA is protonated on the strip phase side, which enables it to be enriched because back extraction in the solvent is prevented [39][51].

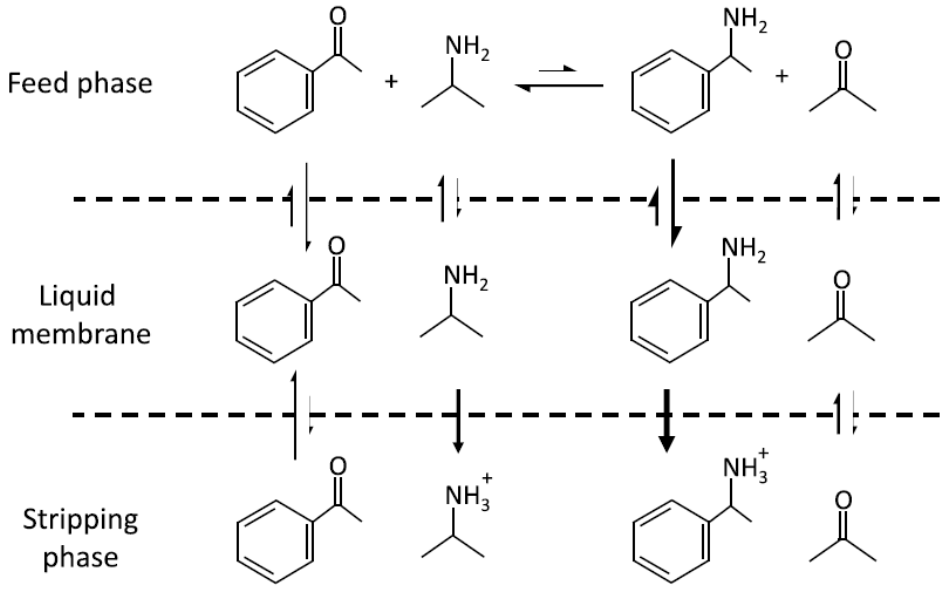

Figure 11: Schematic representation of amine extraction using an SLM with deprotonated compounds on the feed side and the protonated product on the strip side, retrieved from Van Eygen et al. [39].

Moreover, SLM as an ISPR process was already used by Rehn et al. [51][52] to separate MBA and MPPA from IPA. The amines were produced by asymmetric synthesis catalysed by ω-transaminases, whose reaction equilibrium is not in favour of the products (See section 2.1.2). The SLM consisted of undecane held in the pores of a polypropylene hollow fibre membrane contactor. This enabled the product to be removed, thereby shifting the reaction equilibrium towards the formation of MBA and MPPA. The system remained stable for more than 30 hours and demonstrated high selectivity for amine products [14]. The membrane used for this application is one of two possible membrane types for SLM that are discussed below. The organic solvent used for extraction is also discussed further (See section 2.4), and the problems inherent in its use and alternatives are also addressed.

2.3 Membranes suitable for SLM extraction

In SLMs, the liquid membrane is immobilised in the pores of a solid porous polymer. This support is generally made up of a hydrophobic microporous polymer. The support polymer is not active in the separation, but provides a structural support for the liquid membrane phase, which enables the separation to take place [53]. The liquid membrane remains inside the membrane pores due to capillary forces [39]. It is possible to differentiate between two membrane types, depending on their size, shape, surface area, and field of application. These are flat sheet sup-

ported liquid membranes (FSSLM) and hollow fibre supported liquid membranes (HFSLM), which are illustrated in Fig.12.

For FSSLM (Fig.12 (a)), a microporous membrane impregnated with an extractant is held and clamped between two half-cells using seals. The membrane then separates two mechanically mixed phases, namely the feed and the strip solution [53]. In HFSLM (Fig.12 (b)), a module using hollow fibres wetted with an extractant is used. The feed phase is pumped through the fibres, while the receiver phase circulates along the outer wall [53][54].

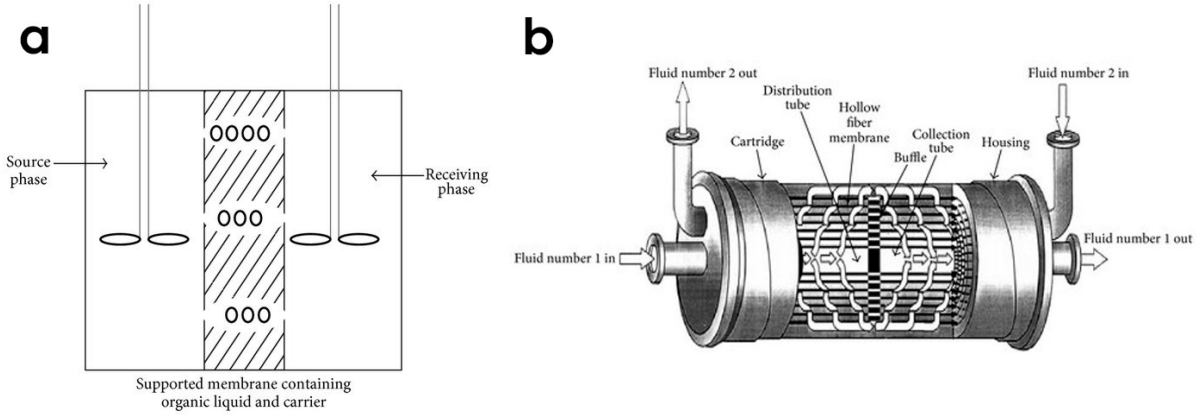

Figure 12: Flat sheet supported liquid membrane (a), and hollow fibre supported liquid membrane (b), retrieved from Parhi [53].

The material used as a support to contain the LM phase is crucial for SLM applications. The support is a polymer that can be (a)symmetrical in structure, neutral or charged, heterogeneous or homogeneous, and hydrophilic or hydrophobic. For SLM applications, the support must be hydrophobic to retain the solvent inside the pores and create a barrier between the two aqueous phases to be separated. It must also be thermally and chemically stable so that it does not deteriorate during use. Numerous materials are commercially available for SLM applications, either in a flat sheet or tubular form [53]. This work focused on the use of three flat sheet, polymeric membranes with different pore sizes, namely polytetrafluoroethylene (PTFE), polyvinylidene fluoride (PVDF) and polyethersulfone (PES). The chemical structures of the three polymers are shown in Fig.13

PES is an amorphous thermoplastic polymer and is the most temperature-resistant transparent thermoplastic resin commercially available. PES membranes are widely used in membrane bioreactors. PES is a hydrophilic molecule due to its molecular structure, which facilitates hydrogen bonds with water molecules, as both the ether and sulphone groups are polar. It is therefore necessary to choose an appropriate solvent for SLM applications [55][56]. PVDF is a semi-crystalline polymer with hydrophobic properties. Chemically, PVDF is based on C-F and C-H bonds. PVDF membranes have a very uniform pore size distribution, as well as being resistant to a wide range of chemicals. Thermal resistance is also superior to that of PES

[55][56]. PTFE, also know as Teflon, is a highly hydrophobic molecule due to its chemical structure based on C-F bonds. PTFE is also chemically inert and has relatively good mechanical properties, making it an ideal material for a range of membrane technology applications [57][58].

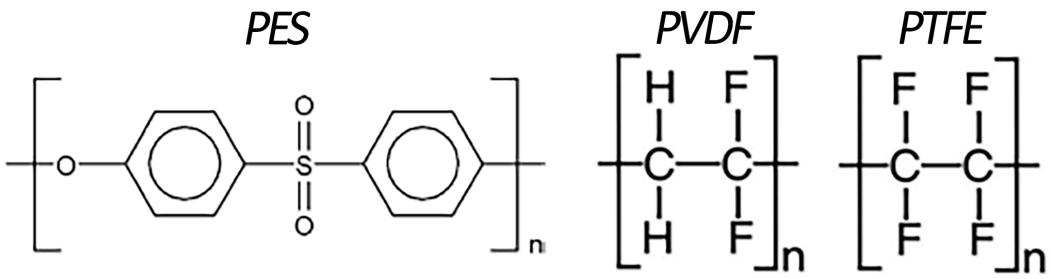

Figure 13: Molecular structure of polyethersulfone (PES), polyvinylidene fluoride (PVDF) and polytetrafluoroethylene (PTFE), modified from McKeen [55] and Hawach Scientific [59].

2.4 Extractants suitable for SLM extraction

To separate compounds efficiently using SLMs, it is essential to select an appropriate liquid membrane, which determines stability and species transport. The most important property to take into account is the solubility of the species to be extracted in the liquid membrane. The higher the solubility of a compound, the easier its transport across the membrane [60]. The viscosity of the liquid membrane must also be taken into account, as a low viscosity is needed to easily immobilise the liquid in the membrane. On the other hand, this low viscosity might impair the stability of the SLM [60][61]. The volatility of the liquid membrane must be as low as possible to reduce evaporation of the liquid membrane. The liquid membrane must also have a low surface tension to avoid surface tension gradients that reduce the stability of the SLM. Thus, the contact angle between the liquid solvent and the membrane should be zero or close to zero [60][62].

The majority of solvents used for SLM applications are organic solvents. This type of solvent is generally considered as toxic, so it is necessary to look for environmentally friendly alternatives for these extractants, while maintaining sufficient extraction rates. Different types of solvents that could potentially be used for SLM applications are discussed below, ranging from conventional organic solvents, to ionic liquids, and natural oils.

2.4.1 Organic extractants

Organic solvents, or carbon-based solvents, are mainly volatile organic compounds produced by fractional distillation of petroleum sources. The main advantage of using these solvents is their low production cost, given their petroleum origin. Their chemical properties are also important, including their ability to solubilise many molecules. This type of solvent is used in a wide

range of industrial applications, from chemical synthesis to the food industry. This massive use, coupled with their volatility and toxicity, means that organic solvents represent a health risk for human populations [63][64].

When they are used for SLM applications, several selection criteria need to be taken into account. It is necessary that the solvent is liquid at room temperature, to be able to be impregnated in the LM. The boiling point of the solvent must be relatively high to avoid its evaporation during the extraction. Moreover, the price of the solvent must be as low as possible for the application to be economically valid. Finally, the solvent must be immiscible in water to avoid its dissolution in the aqueous phases adjacent to the LM [65]. As explained in section2.2.3, the standard extraction of the amines MBA and MPPA by SLM uses undecane, an organic solvent. It is therefore necessary to find less toxic alternatives for the production of these amines.

2.4.2 Ionic liquids

Traditional organic solvents have significant drawbacks due to their natural volatility and toxicity. Their volatility leads to losses and makes SLMs less stable. In addition, the toxicity associated with these solvents is clearly undesirable. It is therefore imperative to find environmentally friendly solvents to ensure the potential of SLM processes [66]. Room temperature ionic liquids are characterised by their thermal stability, their liquid state at room temperature and their ability to solvate a variety of organic and inorganic compounds. These organic salts are a combination of mostly cations and anions or short-lived ion pairs, with a melting point below 100°C. Their high asymmetry prevents crystallisation at room temperature, and they are stable in air and water. In addition, ionic liquids offer the possibility of tailoring their physicochemical properties by careful selection of the cation, its substituents and the anion [60][66]. In addition, ionic liquids do not mix with various organic solvents, have relatively high viscosities and interfacial tensions, and exhibit reduced solubility in water. These characteristics make them attractive alternative green solvents for obtaining stable supported liquid membranes [67].

2.4.3 Deep eutectic solvents

Deep eutectic solvents (DESs) represent a significant advance in the field of green solvents, offering alternatives to traditional ILs. They have emerged as an alternative for common ILs, which are characterised by a higher toxicity, non-biodegradability, complex synthesis and high cost of raw materials. DESs are obtained by mixing two or more components which form a eutectic mixture [68].

The term ”DES” was introduced to differentiate them from ILs and to reflect the significant reduction in the freezing point of the eutectic mixture, often by several hundred degrees. At a given pressure, the eutectic point is an invariant and corresponds to the situation where a minimum melting temperature is reached. Liquid mixtures of two compounds A and B with

a certain composition C (see Fig.14) have parts that begin to solidify out when reaching the liquidus line (point D) towards the corresponding region (B + saturated solution), if the temperature decrease is slow enough. As the temperature approaches the eutectic, the remaining liquid is forced to reach the eutectic composition. This implies that, whatever the initial composition of the mixture, the last liquid drops will be at the eutectic composition [69].

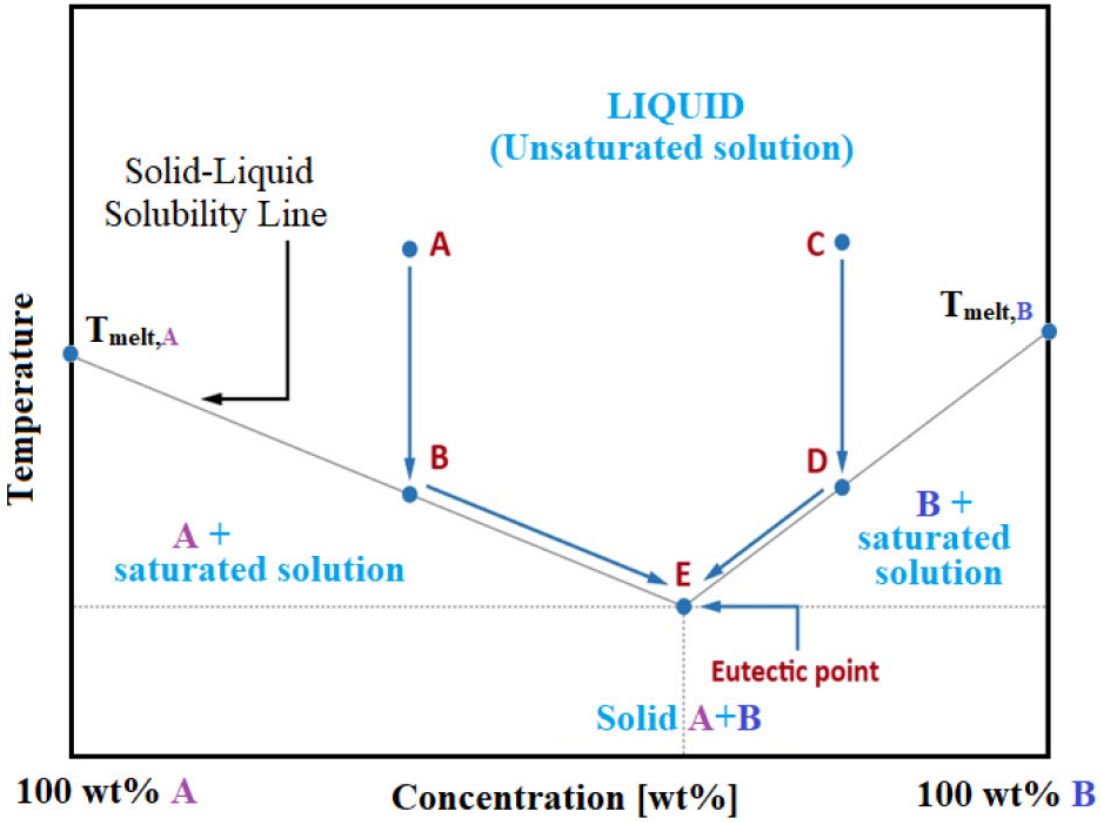

Figure 14: Binary phase diagram for eutectic mixtures. Deep eutectic solvents follow the same general trend, but exhibit deep melting point depressions, retrieved from Benworth et al. [69].

The formation of DESs requires a hydrogen bond donor (HBD), such as urea, glycerols, carboxylic acids, or polyols, in addition to a hydrogen bond acceptor (HBA). A common HBA is choline chloride, a low-cost, biodegradable and non-toxic quaternary ammonium salt. Apart from using salts or ionic species for DESs preparation, they can also be derived from non-ionic species. DESs are now recognised as an emerging class of ILs analogues, attracting increased interest over the last two decades. They share many characteristics with ILs, such as thermal stability, low volatility, low vapour pressures and adjustable polarity. Although DESs share similarities with ILs, it is essential to emphasise that they are two distinct solvent types [69][70]. DESs are formed from a eutectic mixture of Lewis or Brønsted acids and bases, while ILs are composed primarily of a distinct anion and cation type. DESs are generally obtained by complexing a quaternary ammonium salt with a metal salt or a HBD. The delocalisation of the charge through the hydrogen bond contributes to lowering the melting point of the mixture, thus offering unique properties to deep eutectic solvents [71].

2.4.4 Natural oils

The use of edible natural oils as a solvent for extraction applications is not widely documented in the literature. However, the search for less toxic solvents for extracting hydrophobic contaminants from soils has led some studies to turn to natural oils. The potential of these oils for the extraction of hydrophobic contaminants is based on the presence of these same contaminants in the lipid tissues of fish and aquatic animals. For example, peanut oil can be used as a natural, non-toxic, cost-effective and biodegradable extraction agent to extract polycyclic aromatic hydrocarbons from soils [72]. Natural oils can also be used as liquid membranes in SLM processes for the extraction of phenols in aqueous solution and the recovery of dyes produced by the textile industry [73][74][75][76].

2.5 Stabilisers for SLM extraction

The main challenge for the use of supported liquid membranes on a large scale is the short membrane lifetime due to its instability [48][77]. This instability means that SLMs cannot be used for certain commercial applications. The fact that the membrane becomes unstable is caused by the loss of solvent from the membrane phase. This degradation of the LM leads to a loss of selectivity of the elements to be transported, and even to a total loss of selectivity if the membrane is completely broken and the two phases to be separated are in contact. This solvent loss can be due to various factors: a pressure difference across the membrane, solubility of the solvent in the adjacent feed and strip solutions, wetting of the support pores by the aqueous phases, blocking of the support pores by precipitation or by water, presence of an osmotic pressure gradient across the membrane, or formation of an emulsion of the LM phase in water induced by lateral shear forces. The stability of an SLM system depends on the type and characteristics of the support, the solvent, the aqueous phases, and the operating parameters. For example, the stability of SLMs decreases with an increasing pore size of the support material. Other techniques to improve the stability include re-impregnation of the support, use of membranes in a sandwich configuration or gelation of the SLM [77][78]. It is also possible to tune the hydrophobicity of the LM to reduce the harmful effects of the aqueous phases surrounding the LM. Certain techniques can be used to make a surface hydrophobic or hydrophilic, including the use of nanoparticles or the deposition of a polymer coating.

2.5.1 Nanoparticles

Nanoparticles (NPs) are not simple molecules but nanomaterials with a size between 1 and 100 nm. These NPs are composed of three layers: the surface layer, which can be functionalised using different molecules; the envelope layer, which is chemically different from the core; and the core itself, which is the central part of the NP. NPs can be classified according to their properties, shape and size. Their high surface area and relatively small size imply that NPs have

unique physico-chemical properties. These specific characteristics have prompted a great deal of effort to synthesise NPs in a controlled manner. NPs are suitable for a wide range of applications, including catalysis, imaging of biological compounds and cells, and precise delivery of drugs. In addition to these significant advantages, NPs have certain disadvantages, including their possible toxicity. Given their size, they are able to penetrate the human body by inhalation or ingestion. Data is still lacking to quantify the toxic effect of NPs on the environment and organisms, but it is certain that they are or will be a problem in the future, given their increasing use [79].

If NPs are to be used for SLMs, it is useful to classify them according to their affinity with aqueous media. The two categories are hydrophilic and hydrophobic NPs [80]. Hydrophilic NPs are used for ultrafiltration membrane applications. For example, the hydrophobic nature of ultrafiltration membranes means that they are contaminated by the adsorption of hydrophobic contaminants. This surface fouling can be reduced by including hydrophilic NPs in the membranes [81]. On the other hand, hydrophobic NPs make it possible to transform a hydrophilic PES membrane into a hydrophobic membrane by dip coating in a solution of hydrophobic NPs for use as an SLM, while retaining the advantages of the PES membrane [82]. Mahdavi et al. [83] tested the effect of adding hydrophilic or hydrophobic NPs in an SLM application for the pertraction of cationic dyes. It was concluded that the addition of hydrophobic NPs to the membrane improved the pertraction efficiency, while the opposite effect was observed with hydrophilic NPs.

There are various methods for including NPs in the LM phase and thus modifying its surface properties. The membrane can be manufactured using the NPs themselves, or the NPs can be added into the membrane phase at the same time as the solvent, or a solution can simply be deposited on the surface in one step. It is thus possible to obtain a membrane with a superhydrophobic surface with water-repellent and self-cleaning functions by immersion coating in a solution of fluoro-containing silica nanoparticles [84].

2.5.2 Polymer coatings

Polymer coatings can be used for a variety of applications, as they are easy to apply, inexpensive and may offer enhanced performance. A polymer coating can have superhydrophobic, superhydrophilic or self-cleaning properties. The fundamental objective of a polymer coating is to protect a substrate from undesirable effects caused by water, oxygen or other harmful fluids. Polydimethylsiloxane (PDMS) is one such polymer that can be used in various forms for different extraction or separation applications [85][86]. PDMS can be used directly as a separation membrane, but it can also be used to prepare new membranes by gelation, or it can be deposited as a coating to modify the properties of the support. For example, PDMS was used as a membrane support, after addition of NPs or metallo-organic structures in processes for ex-

tracting phenol from aqueous media [87]. An extraction gel membrane has been produced using PDMS, providing improved stability and extraction efficiency by preventing loss of the extracting solvent. The synthesised membrane was then used in an SLM setup for metal ions recovery showing improved long-term stability [88]. PDMS, as a coating, can therefore be deposited by heat treatment on mesoporous silica particles to make its surface superhydrophobic. This makes it possible to adsorb various chemical agents under very humid conditions [89]. Finally, it can be applied to a membrane by simple dip coating to improve thermal and chemical stability in gas and hydrocarbon separation applications [90].

2.6 Scope of work

Chiral amines are essential molecules for the pharmaceutical industry. Their synthesis by asymmetric hydrogenation catalysed by ω-transaminases makes it possible to limit the toxicity of the manufacturing process while maintaining a high yield. The chiral amines MBA and MPPA can be synthesised by this method using IPA as the reagent. Shifting the reaction equilibrium towards the products can be achieved by ISPR, *i.e.*, by continuously removing the products from the reaction medium. SLMs make it possible to combine the extraction and product stripping stages using solvent immobilised in the membrane pores, and therefore have major potential for optimising the production of chiral amines. The choice of the type of membrane, the solvent to be impregnated into the pores of the membrane, and any coatings to be applied to the membrane is essential to ensure the stability of the LM while maintaining sufficient amine flux. This thesis therefore focused on the selective extraction of MBA and MPPA by SLM. Different types of membranes, solvents and stabilisers were tested for ME. The aim of this work was to examine the alternatives to the toxic organic solvents used in the literature, and to determine whether these alternatives make it possible to achieve effective amine extraction while reducing the overall toxicity of the process.

3 Materials and methods

3.1 Use of AI tools

During the writing of this thesis, the ChatGPT artificial intelligence tool was used, mainly to reformulate sentences, but also to obtain a better understanding of certain concepts. The translation tool DeepL was also used to ensure that syntax and spelling were as correct as possible.

3.2 Chemicals

The following natural oils were used: olive oil (Ph. Eur., virgin, Carl Roth), coconut oil (pure, refined, Thermo Fisher Scientific), sunflower oil (extra pure, refined, Carl Roth), palm oil (analytical standard, Merck Life), corn oil (Acros Organics), peanut oil (refined, Carl Roth), and castor oil (Acros Organics). Their density and viscosity are given in Tab.1.

Oil	**Density** $\left[\frac{g}{mL}\right]$	**Viscosity** $[mPas]$
Olive oil	0.93	85.75
Coconut oil	0.87	58.90
Sunflower oil	0.92	60.70
Palm oil	0.98	103.00
Corn oil	0.92	53.68
Peanut oil	0.91	53.00
Castor oil	0.96	485.00

Table 1: Density and viscosity of the oils used for membrane impregnation [8][74][75][91][92].

For the DESs, the following chemicals were used: trioctylphophine oxide (TOPO, 98 %, Sigma-Aldrich), octanoic acid (98 %, Alfa Aesar), nonanoic acid (97 %, Thermo Fisher Scientific), decanoic acid (99 %, Acros Organics), dodecanoic acid (98%, Sigma-Aldrich), p-toluenesulfonic acid (99 %, Acros Organics), oleic acid (T.R., Carl Roth), hexylene glycol ($>$ 99 %, VWR), lidocaine ($>$ 99 %, TCI Europe), menthol ($\geq$ 95 %, Sigma-Aldrich), and thymol ($>$ 99 %, VWR). Their molar mass and melting point are given in Tab.2.

Chemical	Molar mass $\left[\frac{g}{mol}\right]$	Melting point [°C]
Trioctylphosphine oxide (TOPO)	386.645	50-54
Octanoic acid	144.214	16.7
Nonanoic acid	158.241	12.5
Decanoic acid	172.268	31.6
Dodecanoic acid	200.322	43.8
Oleic acid	282.468	13-14
P-toluenesulfonic acid	172.20	38
Hexylene glycol	118.17	-40
Lidocaine	234.343	68
Menthol	156.15	36-38
Thymol	150	49-51

Table 2: Molar mass and melting point of the chemicals used for the DESs preparation [8].

The following ionic liquid (IL) was used for membrane impregnation: trihexyltetradecylphosphonium bis-(trifluoromethylsulfonyl)amide ([P6,6,6,14][N(Tf)2], ≥98 %, Iolitec). For the silica NPs synthesis, the following chemicals were used: tetraethyl orthosilicate (TEOS, Sigma-Aldrich), tridecafluorooctyl triethoxysilane (FAS, Fluorochem), ethanol (≥99.8 %, Fisher Chemical) and ammonium hydroxide (25 %, Fluka Chemie GmbH). The chitosan NPs synthesis was done using the following chemicals: high molecular weight chitosan flakes (Sigma-Aldrich), thiophene-2-acetyl chloride, acetic acid (3 % w/v), a sodium hydroxide solution (40 w/w%) diluted from sodium hydroxide (NaOH, ≥98.5 %, VWR), acetone, and methanol (≥99.9 %, Sigma-Aldrich). The PDMS coating solution was prepared using the following chemicals: hexane (≥ 98%, ROTISOLV HPLC), tetraethyl orthosilicate (TEOS, Sigma-Aldrich) and poly(dimethylsiloxane) (PDMS, Sigma-Aldrich) in liquid form.

The feed and strip buffers for the membrane extraction experiments were prepared using the following chemicals: phosphoric acid (H_3PO_4, 85 %, VWR), sodium dihydrogen phosphate (NaH_2PO_4, ≥98 %, VWR), sodium carbonate (Na_2CO_3, ≥99.9 %, Merck Life), and sodium bicarbonate ($NaHCO_3$, A.R., Fisher Scientific). The following amines were used: methylbenzylamine (MBA, 98 %, Merck Life), 1-methyl-3-phenylpropylamine (MPPA, 98 %, Sigma-Aldrich) and isopropyl amine (IPA, ≥99.5 %, Sigma-Aldrich). The GC samples were prepared using the following chemicals: triethylamine (TEA, ≥99.5%, Sigma-Aldrich), and 25 w/w% NaOH solution diluted from sodium hydroxide (NaOH, ≥98.5%, VWR)

3.3 Solvents and coatings

Three types of solvents were used for membrane impregnation, namely, edible natural oils, deep eutectic solvents (DESs) based on trioctylphophine oxide (TOPO) as a hydrogen bond acceptor (HBA), and an ionic liquid (IL) that already demonstrated its potential as a selective solvent for chiral amines [14]. The oils used were: olive oil, coconut oil, sunflower oil, palm oil, corn oil, peanut oil, and castor oil. The DESs used were: TOPO:octanoic acid, TOPO:nonanoic acid, TOPO:decanoic acid, TOPO:dodecanoic acid, TOPO:oleic acid, TOPO:p-toluenesulfonic acid, TOPO:hexylene glycol, TOPO:menthol, and TOPO:thymol. Two coating types were used, coating with polydimethylsiloxane (PDMS) and coating with hydrophobic nanoparticles (NPs). Silica and chitosan NPs were used.

3.3.1 Natural oils

The oils were impregnated into the pores of the membrane as described in section 3.4.2. However, it was necessary to heat the coconut oil and palm oil to 45 °C for a few minutes before impregnation, as these oils are solid at room temperature. As a result, after impregnation, these two oils solidified again. Since membrane extraction takes place at room temperature, this type of experiment could be described as supported solid membrane extraction. It should be noted that impregnation with castor oil, which has interesting properties for SLMs due to its high viscosity (see Tab.1), was not possible with the vacuum pump (MPC 201E, ILMVAC GmbH). An attempt was also made to impregnate the membrane by dip coating using gentle heat for a duration of several hours, but this did not give a satisfactory impregnation.

Liquid-liquid extraction (LLE), as explained in section 2.2.1, is a separation process that consists of transferring a solute from one solvent to another, the two solvents being partially or immiscible with each other. This extraction takes place in two stages, mixing the two solvents and then separating the two phases. The aim here was to determine whether the selected natural oils are good extractants for amines. A feed solution at a pH of 10 containing the considered amines was prepared (refer to section 3.5.1). To carry out the tests, 3 mL of each oil was added to a laboratory test tube using a pipette, together with 3 mL of the feed solution. For each oil, three repetitions were carried out. The test tubes were placed in a lab shaker for 24 hours at 120 rpm and 30 °C. After shaking, the samples were taken out of the shaker and were left unattended for 24 hours to let the phases settle. Afterwards, samples of 1 mL were taken from the aqueous phase for HPLC and GC analysis (refer to section 3.5.3).

3.3.2 DESs

For the DESs preparation, a 1:2 molar ratio of the HBA (TOPO) to the HBD was applied. Using the molar mass data in Tab.2, it was possible to determine the mass of TOPO and the mass of HBD to be mixed to give a total mass of the DES of 10 or 20 g (see appendix A). First, the

two solid reagents (except hexylene glycol) were weighed using an analytical balance (SE 422, VWR). They were then placed in a vial with a stirring rod. The vial was placed in a beaker filled with demineralised water for improved heat distribution. The beaker is set on a stirring hotplate (VMS-C7, VWR), under continuous stirring and at 80 °C. The setup used can be seen in Fig.15. The vial was removed when the mixture was a homogeneous liquid. If the DES remained liquid at room temperature, it was used for the membrane impregnation (see section 3.4.2).

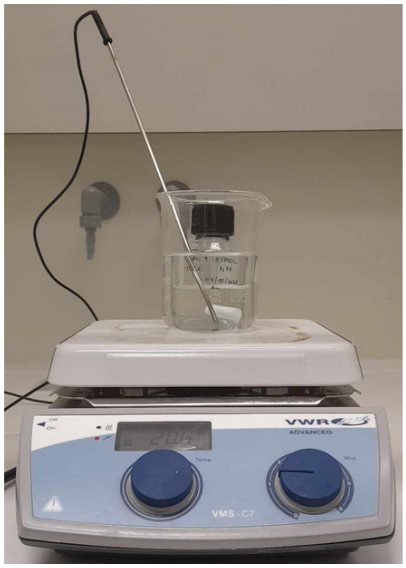

Figure 15: Setup for the preparation of DES.

Other molar ratios were tested to prepare certain DESs that did not remain stable at room temperature. For example, molar ratios of 3:1, 2:1, 1:1, 1:2 and 1:3 were tested to prepare a DES from TOPO and lidocaine. None of these molar ratios gave a liquid DES mixture. It should also be noted that the DES TOPO:p-toluenesulfonic acid could only be impregnated into a membrane once. The second impregnation, several days after the first, was not possible.

The hydrophobic nature of a solvent is extremely important for SLM applications in the aqueous phase as explained in section 2.5. Indeed, it is important that the LM does not dissolve in the aqueous feed or strip phases. To verify the hydrophobicity of the DESs, 1 g of each DES and 3 g of ultrapure water were added to a centrifuge tube. The tube was then sealed with laboratory film (PARAFILM "M", Bemis) and placed in an orbital shaker (IKA-VIBRAX-VXR, JANKE&KUNKEL) for over a day. The separation between the DES phase and the aqueous phase was then determined visually. This experiment also allowed to compare the DES and water density.

3.3.3 NPs

First, the synthesis of iron oxide NPs according to the report by Jamilpanah et al. [93] and the synthesis of zeolitic imidazolate framework (ZIF-8) NPs according to the article by Cravillon

et al. [94] were considered. These syntheses were not carried out in view of the toxicity of the products. The synthesis of gold NPs based on the work of Shen et al. [80] was also undertaken, but it was impossible to complete it and obtain NPs.

The silica NPs synthesis was done according to Wang et al. [84]. TEOS and FAS were added in a 10:1 molar ratio to a beaker containing 25 mL of ethanol and the solution was mixed. 6 mL of the 25 % ammonium hydroxide solution were added to a second beaker also containing 25 mL of ethanol. This second solution was then poured into the first and the resulting mixture stirred for 12 hours at room temperature. The solution was then ultrasonicated in an ultrasonic cleaner for 30 minutes before being used for dip coating membranes (see section 3.4.1). After dip coating, the membrane is dried with paper and heat treated in an oven for one hour at 110 °C.

The chitosan NPs synthesis was based on Jothimani et al. [95]. To 200 mL of the aqueous acetic acid solution were added 2.5 g of chitosan, and the solution was stirred for 30 minutes at room temperature. The pH of the solution was adjusted to 7.3 using the sodium hydroxide solution. 11.2 g of thiophene-2-acetyl chloride was then added to the solution over 30 minutes. During this period, the pH of the solution was maintained between 7.3 and 7.5 using the sodium hydroxide solution. This pH adjustment was continued for an additional two hours. The mixture was then poured into 600 mL of acetone to precipitate. The precipitated product was filtered and washed with 200 mL of methanol before being dried under vacuum for two hours until a powder was obtained. The obtained product was ground and sieved, and then several ball milling steps were performed to obtain NPs. The chitosan NPs were then dispersed in the ionic liquid (IL) at a concentration of 2 mg/mL before impregnation into the membrane (see section 3.4.2).

Transmission electron microscopy (TEM) is a powerful tool used to observe matter at a scale of 1 to 100 nm. The term ‘transmission’ refers to the method by which electrons pass through a sample to create an image. In TEM, a beam of electrons is transmitted through an ultrathin sample and the interactions of the transmitted electrons with the sample are used to form an image. This method provides a high-resolution image of the internal structure of samples at the atomic level [96]. Since TEM allows to observe particles of the order of a few nanometres in size, it was used to observe the chitosan NPs that were synthesised. This observation was used to determine the size and shape of the NPs produced. The ball-milled chitosan NPs were dispersed in acetone or ethanol to be observed with a TEM (CM30, Philipps).

3.3.4 PDMS coating

The PDMS coating solution was prepared according to Suleman et al. [90]. The PDMS-based coating solution was prepared by adding 20 w/w% PDMS and 1 w/w% TEOS to 100 mL of

hexane solvent. The solution was mixed until a homogeneous mixture was obtained. The solution can then be used for dip coating membranes (see section 3.4.1). After dip coating, the membrane was blotted with paper and heat treated in an oven at 120 °C for 45 minutes.

3.4 Membrane preparation

The different flat sheet membranes used for the membrane extraction experiments are given in Tab.3.

Material	Pore size [nm]	Supplier
Polytetrafluoroethylene (PTFE)	50	Donaldson
Polytetrafluoroethylene (PTFE)	100	Donaldson
Polytetrafluoroethylene (PTFE)	200	Donaldson
Polytetrafluoroethylene (PTFE)	450	Donaldson
Polyvinylidene difluoride (PVDF)	100	Synder Filtration
Polyethersulfone (PES)	90	Synder Filtration
Polydimethylsiloxane (PDMS)	dense	VITO NV

Table 3: Type and pore size of the membranes used for the membrane extraction experiments.

The membranes were cut in a circular shape, approximately 6 cm in diameter. The pristine membranes were then weighed using an analytical scale. If the membranes underwent heat treatment for the coating procedure, they were cut in a slightly larger shape, as they shrank during the heating stage.

3.4.1 Dip coating

For the dip coating method, the coating was added to a beaker and mixed using a stirring plate (VMS-C7, VWR) at room temperature. The membrane was then simply placed in the gently stirred solution for a period of 30 min. This optimal time period to ensure maximum hydrophobicity of the membrane surface was determined experimentally by contact angle measurements (see section 4.2). This coating method is represented in Fig.16.

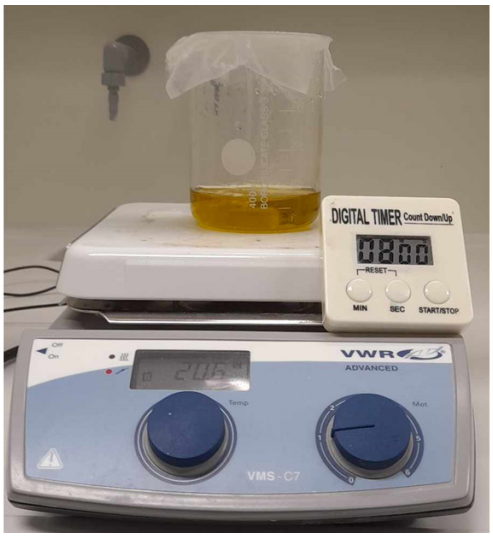

Figure 16: Setup for membrane coating.

3.4.2 Vacuum impregnation

For the membrane impregnation, a set-up with a Büchner funnel and a vacuum flask connected to a vacuum pump (MPC 201E, ILMVAC GmbH) was required, of which the set-up can be seen in Fig.17. A filtration paper was first placed in the Büchner funnel to prevent mechanical degradation of the membrane. The circular membrane was then placed on the filtration paper and spread out evenly. The vacuum pump was switched on and the solvent was gradually applied to the membrane using a pipette. The solvent was spread over the entire membrane surface with a lab spatula. The impregnation time, depends on the type of membrane-solvent system, but for reasons of consistency, a period of 45 minutes and between 1 and 2 mL of solvent were used. At the end of this period, the vacuum pump was switched off and the membrane was dried using paper to remove any residual solvent.

Figure 17: Setup for membrane impregnation.

For certain solvents with a higher viscosity, the use of a more powerful pump may be necessary (MD 4C NT, VACUUBRAND). Some solvents, such as coconut oil and palm oil, were slightly heated before impregnation, as they are solid at room temperature [97].

The membranes were weighed with an analytical scale (AE 260, METTLER TOLEDO) at each stage, namely pristine after cutting, after coating of the membrane, after impregnation with the solvent, and after the membrane extraction experiment. These measurements make it possible to quantify the amount of solvent or coating present in the pores or on the surface of the membrane before and after the experiment.

3.4.3 Water contact angle measurements

When a droplet of liquid is deposited on a surface, the contact angle can be defined as the angle formed by intersecting the liquid-solid interface and the liquid-vapour interface. A small contact angle means that the liquid spreads on the surface, while a large contact angle means that the liquid beads on the surface. A surface is said to be hydrophilic if the water contact angle is less than 90°. Hydrophobic and superhydrophobic surfaces have contact angles greater than 90° and 150°, respectively. The contact angle is hence the thermodynamic property that characterises the wettability of solid surfaces [98][99]. The hydrophobic or hydrophilic properties of the membranes and solvents used for SLM applications are crucial. When the liquid phases adjacent to the membrane are aqueous, it is essential that the LM is hydrophobic, otherwise instability will occur. The membranes used for the membrane extraction experiments were analysed using a drop shape analyser (DSA 10 Mk2, KRÜSS) to determine their hydrophobicity.

The following pristine membranes were tested: PTFE-50, PTFE-100, PTFE-200, PTFE-450,

PVDF-100, PES-90. Both sides of the PES and PVDF membranes had to be analysed because they were prepared on a support material. The membranes were cut into a rectangle measuring 1 cm wide and 3 cm long. After cutting, the membrane was impregnated or coated as described above, and then taped to the platform of the drop shape analyser using double-sided tape. Then, a droplet of ultrapure water was deposited on the surface of the membrane and the contact angle was measured. Three repetitions were performed on each membrane to obtain a statistical mean value. The aim was to determine whether the impregnation or coating procedure improved the hydrophobic properties of the membrane.

3.5 Membrane extraction

During the course of this thesis, 78 membrane extraction experiments were carried out and 34 different SLM systems were tested. The DESs and oils tried for ME with a PTFE-50 membrane are shown in Tab.4. The experiments to determine an effective and selective coating procedure along with long-term stability tests are given in Tab.5. The membranes tested with silica (Si) NPs coating combined with IL ([P6,6,6,14][N(Tf)2]) impregnation, and with PDMS coating are shown in Tab.6.

Solvent: DES	**ME**	**Solvent: oil**	**ME**
TOPO:thymol	3	olive oil	3
TOPO:p-toluenesulfonic acid	1	peanut oil	2
TOPO:menthol	2	sunflower oil	3
TOPO:octanoic acid	2	corn oil	2
TOPO:nonanoic acid	2	coconut oil	3
TOPO:decanoic acid	1	palm oil	2
TOPO:dodecanoic acid	2	castor oil	0
TOPO:oleic acid	1		
TOPO:hexylene glycol	2		

Table 4: Solvents tested for SLM extraction with a PTFE-50 membrane, with the number of ME experiments tried.

Membrane	Coating	Solvent	Time	ME
PTFE-50	Si	IL	24h	3
	PDMS	N/A	24h	2
	N/A	IL	48h	2
	PDMS	N/A	48h	2
	PDMS	IL	48h	2
PTFE-100	N/A	IL	24h	1
	Si	N/A	24h	3
	Si	IL	24h	3
	PDMS	N/A	24h	2
	PDMS	IL	24h	2
	N/A	Chitosan + IL	24h	2

Table 5: Systems tested to determine an efficient coating procedure and for long-term stability, with the number of ME experiments tried.

Si + IL		PDMS	
Membrane	**ME**	**Membrane**	**ME**
PTFE 50	3	PTFE 50	2
PTFE 100	3	PTFE 100	2
PTFE 200	3	PTFE 200	3
PTFE 450	3	PTFE 450	2
PVDF 100	3	PVDF 100	2
PES 90	3	PES 90	2
		PDMS (pristine)	2

Table 6: Membranes tested for SLM extraction with a silica NPs coating, or a PDMS coating, with the number of ME experiments tried.

3.5.1 Feed and strip solutions preparation

The synthesis of MBA and MPPA by asymmetric hydrogenation catalysed by ω-transaminases is carried out using the donor amine IPA, as explained in section 2.1.2. To simplify the membrane extraction experiment, conditions similar to these synthesis conditions need to be recreated. The objective of the membrane extraction experiment is to transfer MBA and MPPA from the feed buffer to the strip buffer via the SLM, while IPA should remain in the feed buffer. To achieve this objective, as explained in section 2.2.3, it is necessary for MBA and MPPA to be deprotonated in the feed phase and in the protonated form in the strip phase so that they accumulate there. IPA must remain in the protonated form in the feed phase. Since the predicted pK_a

values for MBA, MPPA and IPA are 9.04 $\pm$0.10, 10.0 $\pm$0.35 and 10.63 respectively [8][91], the pH value of the feed phase was set at 10. For the membrane extraction experiments, a feed buffer and a strip buffer were prepared with a pH of 10 and 3 respectively.

The feed buffer was prepared by adding 7.58 g of Na_2CO_3 and 10.76 g of $NaHCO_3$ to 1000 mL of ultrapure water. The solution was stirred until complete dissolution, then, the amines were added using a pipette. 500 mg of MBA, MPPA, and IPA were added to the solution. The strip buffer was prepared by adding 21.98 g of NaH_2PO_4 to 1000 mL of ultrapure water. The solution was stirred until complete dissolution, then, 1724 µL of H_3PO_4 was added using a pipette. A table resuming the mass of amines added in the feed buffer is available in appendix B.

3.5.2 Membrane extraction experimental procedure

A picture of the membrane extraction setup can be seen in Fig.18. First, the membrane was put in the membrane contactor, *i.e.*, the membrane was placed between two rubber O-rings and held in the Teflon cell, which is connected to the pumps for contact with the feed and strip solutions. A schematic view of the setup can be seen in Fig.19, the Teflon cell and a O-ring can also be seen with the spiral pattern for the solution flow. Next, 250 mL of feed and strip buffer were added to the appropriate containers. A thermometer was used to monitor the temperature of the two solutions at all times. It should be noted that the setup was supposed to be accompanied by a thermostatic bath (KISS K6, Huber) but the latter was not operational during the period when this thesis was being carried out. The pumps were then started at a flow rate of 10 L/h, corresponding to a setting of 20.7 and 40.2 on the feed and strip frequency drives, respectively. The solutions were continuously mixed using a magnetic air stirrer, and the whole experiment was carried out under a fume hood to avoid the risk of dangerous fumes.

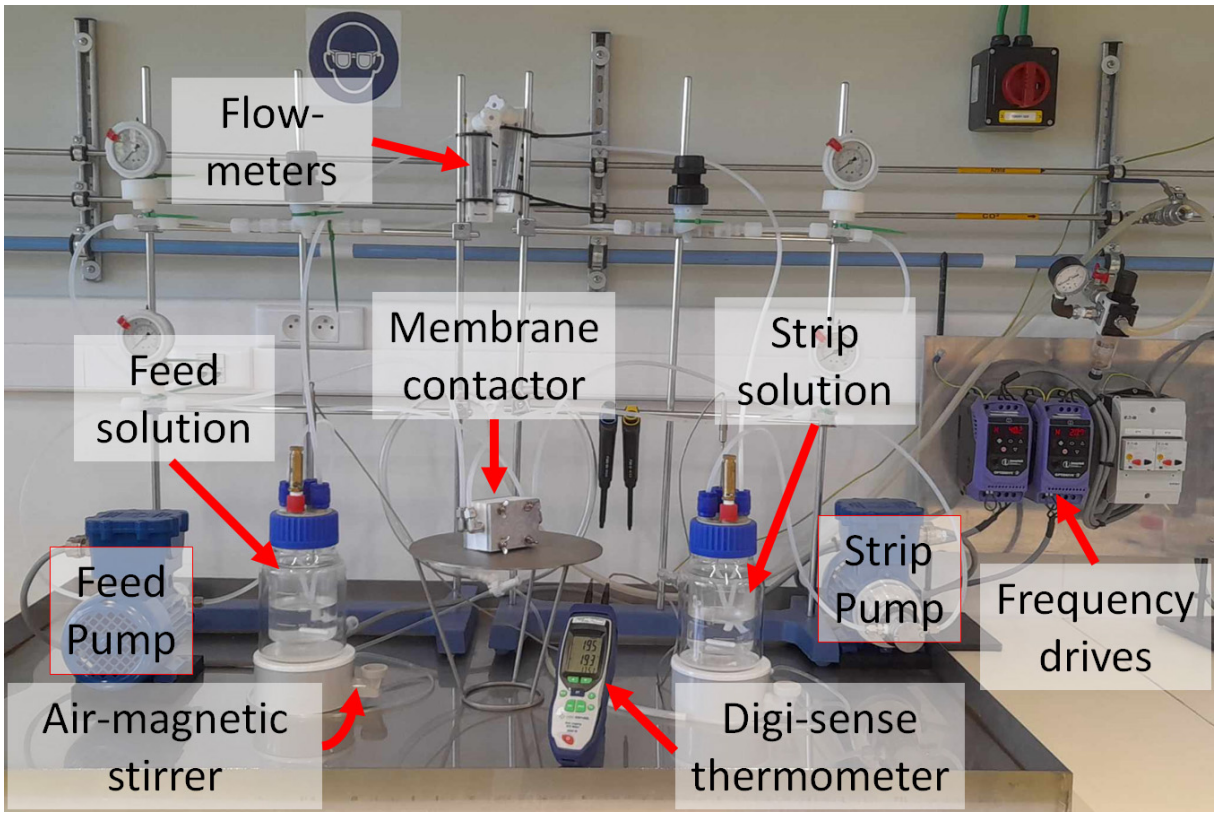

Figure 18: Membrane extraction setup showing all the essential components.

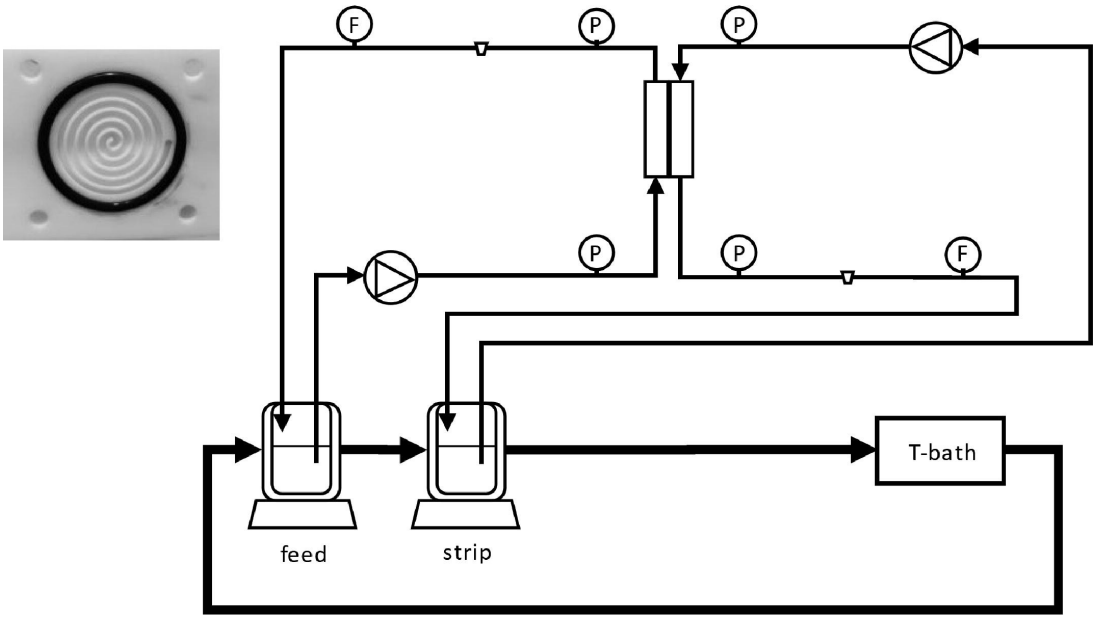

Figure 19: Schematic view of the membrane extraction setup and indication of the spiral pattern (top left), retrieved from Van Eygen et al.[14]

During each experiment, samples were taken using a pipette at start-up, after 1, 3, 6, and 24 hours, the temperature of the solutions was also recorded. 1 mL of each solution was taken for both high performance liquid chromatography (HPLC) and gas chromatography (GC). The experiment ended either after 24 hours or earlier, if a failure was detected. Generally, a failure

resulted in a visible difference in solution level between the feed and the strip, indicating a channelling between the two phases. The containers of the solutions were systematically weighed at the end of the experiment, to confirm the volume difference between the two solutions. The pH was also determined at the start and end of the experiment using a pH meter (Metrohm). The membrane was removed from the contactor after the experiment and left to dry at room temperature for at least a day before being weighed, which enabled to determine the mass of solvent/coating lost during the experiment.

As explained in section 2.5, the medium- and long-term instability of SLMs is an obstacle to their development. Thus, three promising SLM systems, regarding stability, were tested over a period of 48 hours. The experimental procedure was similar, however, samples were taken at start-up, after 6, 24, 30, and 48 hours.

3.5.3 HPLC and GC

High-performance liquid chromatography (HPLC) was used to determine the concentration of MBA and MPPA in the samples. The machine used was an HPLC-UVVIS (Schimadzu Prominence-I LC-2030C 3D) employing a gradient elution with acetonitrile and phosphoric acid (H_3PO_4, 0.1 vol%) as the mobile phases.

Gas chromatography (GC) was used to detect the IPA concentration in the samples. Prior to analysis, 15 µL of TEA and 200 µL of a 25 w/w% NaOH solution were added to the feed and strip samples. A headspace GC-FID Autosystem XL (PerkinElmer) was used for the analysis. Helium served as the mobile phase and an Rtx-5 Amine column (30 m length, 0.25 mm diameter, 0.50 µm particle size) was used.

4 Results and discussion

This chapter discusses the results of the experiments carried out in the context of this work. First, the liquid-liquid extraction (LLE) performance of natural oils is discussed and compared with that of reference solvents. Next, the hydrophobicity of different pristine membranes is studied. The influence of coating and impregnated solvent is considered. Then, the membrane extraction (ME) results are discussed. DESs and natural oils are analysed to determine which solvents are effective and stable. The effect of coatings on the ME stability and efficiency is then considered and long-term stability tests are finally evaluated.

4.1 Liquid-liquid extraction using oil

The extraction efficiency E_a for a given amine was defined as follows:

$$E_a = \frac{C_{a,i} - C_{a,raff}}{C_{a,i}}[-] \tag{6}$$

with $C_{a,i}$ [mg/L] the initial amine concentration and $C_{a,raff}$ [mg/L] the amine concentration in the raffinate.

The selectivities $S_{MBA/IPA}$ and $S_{MPPA/IPA}$ were defined as follows:

$$S_{a/IPA} = \frac{E_a}{E_{IPA}}[-] \tag{7}$$

with E_a the MBA or MPPA extraction efficiency and E_{IPA} the IPA extraction efficiency.

The extraction properties of the natural oils were compared with those of three references: undecane, the ionic liquid (IL) [P6,6,6,14][N(Tf)2], and Aliquat-336, a reference ionic liquid for solvent extraction applications [100]. The LLE results are shown in Fig20. The oils extracted more MBA and MPPA than undecane (26.6 % MBA, 52.4 % MPPA), but less than [P6,6,6,14][N(Tf)2] (91.9 % MBA, 99.3 % MPPA) or Aliquat-336 (95.0 % MBA, 97.9 % MPPA). The best natural oils for extraction are castor oil (76.0 % MBA, 98.0 % MPPA) and palm oil (64.6 % MBA, 88.0 % MPPA). Peanut oil extracted only 42.9 % of MBA, while olive oil extracted 61.9 % of MPPA. The oils extracted between 8.8 % and 13.3 % of IPA. These results are similar to undecane (10.3 % IPA) but much lower than [P6,6,6,14][N(Tf)2] (31.9 % IPA) and Aliquat-336 (71.3 % IPA). In terms of selectivity towards MBA and MPPA (see Fig.21), castor oil (MBA/IPA = 7.98, MPPA/IPA = 10.30) and palm oil (MBA/IPA = 6.63, MPPA/IPA = 9.05) again performed best. All the oils were more selective towards MBA and MPPA than [P6,6,6,14][N(Tf)2], undecane and Aliquat-336. The only exceptions were olive oil and sunflower oil, which were less selective towards MPPA than undecane.

Natural oils, which were more efficient than undecane, are therefore promising candidates for the extraction of MBA and MPPA, particularly castor oil and palm oil. Although the oils extracted less MBA and MPPA than the IL [P6,6,6,14][N(Tf)2], their low IPA extraction made these solvents more selective.

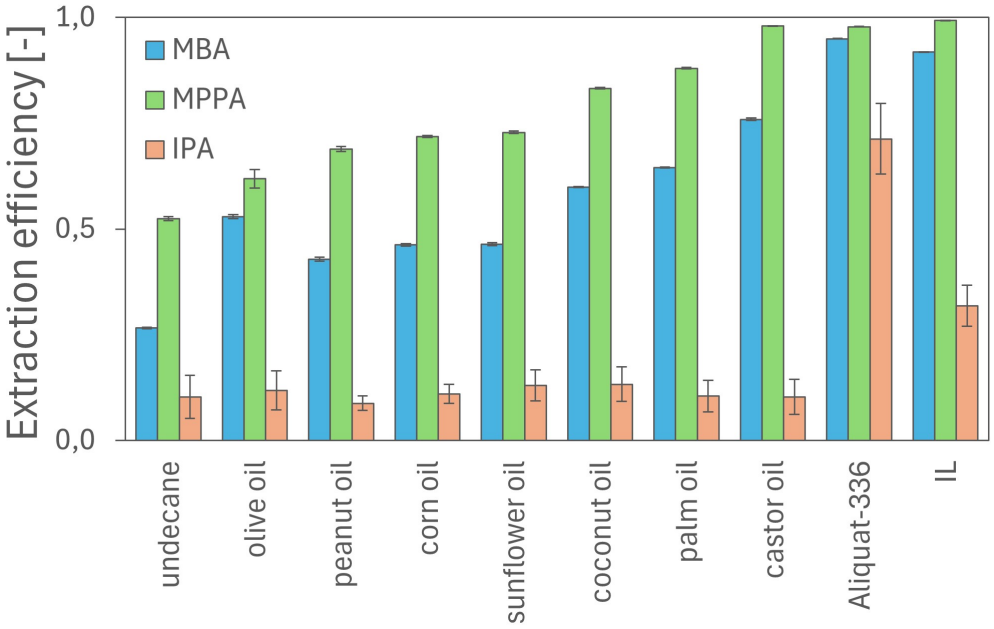

Figure 20: Extraction efficiency of amines using natural oils, compared with the IL [P6,6,6,14][N(Tf)2], undecane and Aliquat-336.

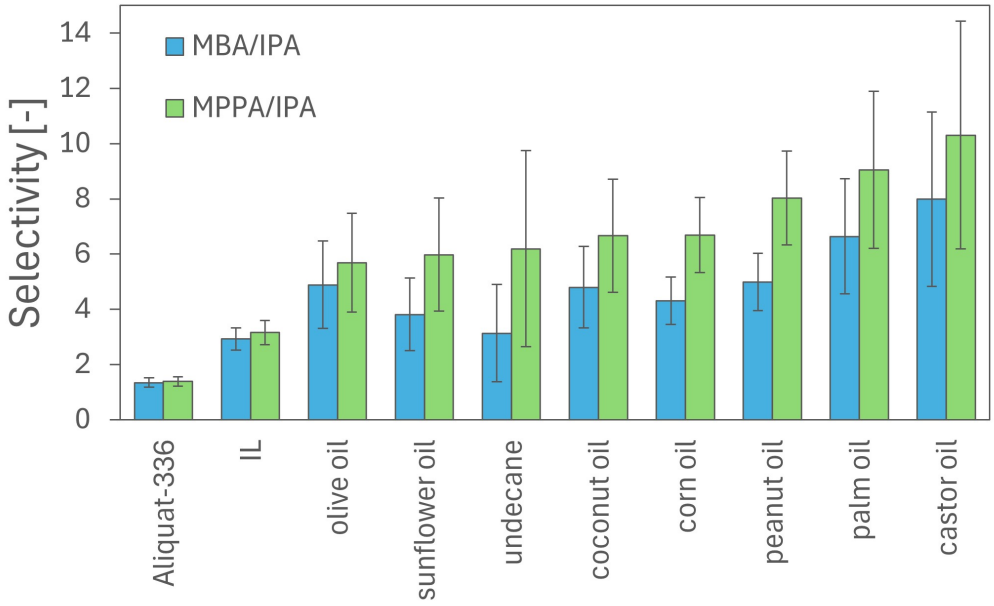

Figure 21: Selectivity of amines using natural oils, compared with the IL [P6,6,6,14][N(Tf)2], undecane and Aliquat-336.

4.2 Contact angle measurements

To determine the optimal coating time for the silica nanoparticles, water contact angle measurements were performed on a PTFE-100 membrane coated with silica NPs for various coating times (see Fig.22). The contact angle for a pristine PTFE-100 membrane is also given. The pristine membrane was already hydrophobic (118°) without silica NPs, but the NPs addition made the membrane more hydrophobic. A maximum surface hydrophobicity (134°±3.85) was reached after 30 minutes of coating, and a decrease in the contact angle was observed after 60 minutes. For the PDMS coating, Suleman et al. [90] observed a maximum water contact angle for their membrane after 30 min of dip coating in the PDMS solution. The longer the coating time, the thicker the hydrophobic layer of PDMS.

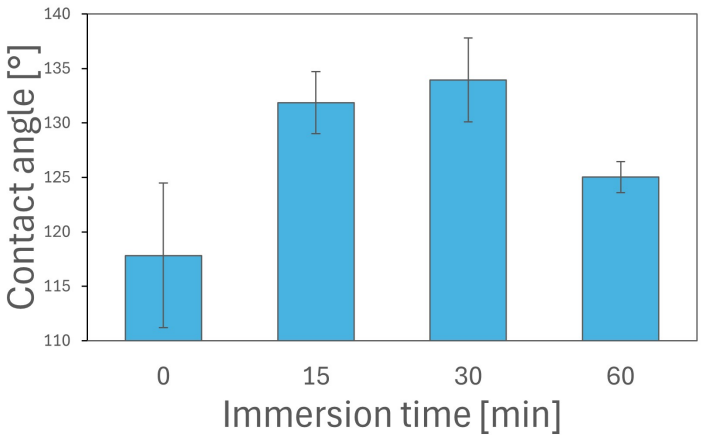

Figure 22: Water contact angle measurements of a PTFE-100 membrane coated with silica NPs for different immersion times.

The contact angle data for different types of pristine membrane can be seen in Fig.23. Both the PES-90 and the PVDF-100 membrane were not hydrophobic, as their water contact angle was equal to around 73° and 87°. In addition, there were no significant differences between the two sides. PTFE membranes, on the other hand, are hydrophobic. A water contact angle of around 124° was measured for all PTFE membranes [14].

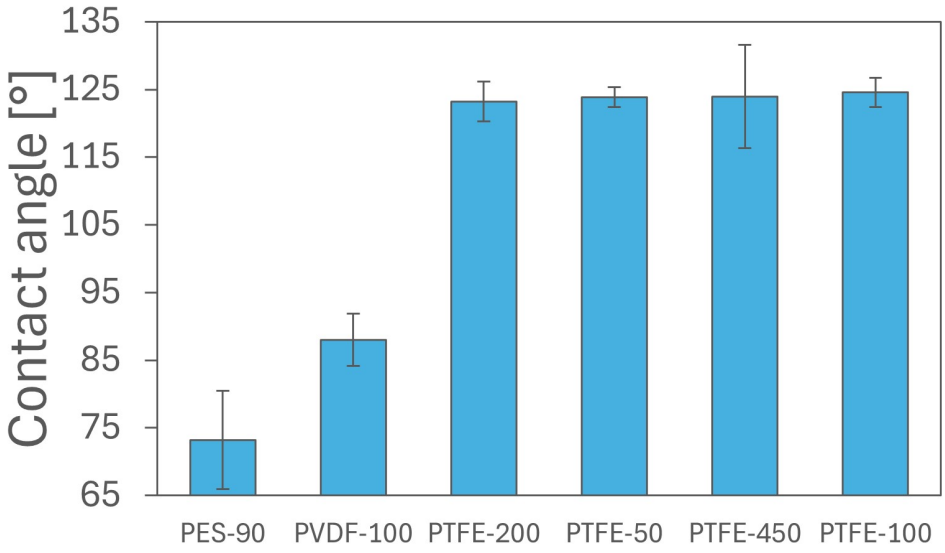

Figure 23: Water contact angle measurements of pristine membranes [14].

The coating or impregnation effect on the PTFE-100 membrane can be seen in Fig.24. For the NPs deposition, it was found that after 30 min of dip coating, the PTFE-100 membrane had an increased contact angle up to 134°±3.85. However, such an increase in the contact angle was not observed for the repetition of the experiment after a couple of months. Instead, the measured contact angle decreased to 116°. This difference could be explained by the fact that the dip coating was carried out at two different times. The coating solution was sealed using laboratory film only, and it was visually observed that the appearance of the coating solution had changed with the passage of time. This was also true for the PDMS solution. The hydrophobicity of the PTFE-100 membrane decreased following application of the silica NP coating (116°) or the PDMS coating (100°). The [P6,6,6,14][N(Tf)2] impregnation involved the highest decrease in hydrophobicity (92°), whilst impregnation of [P6,6,6,14][N(Tf)2] in a PDMS-coated or silica-coated membrane resulted in a similar decrease of the contact angle (97°). These results indicate that by using the coating procedure, the PTFE membrane is actually made less hydrophobic.

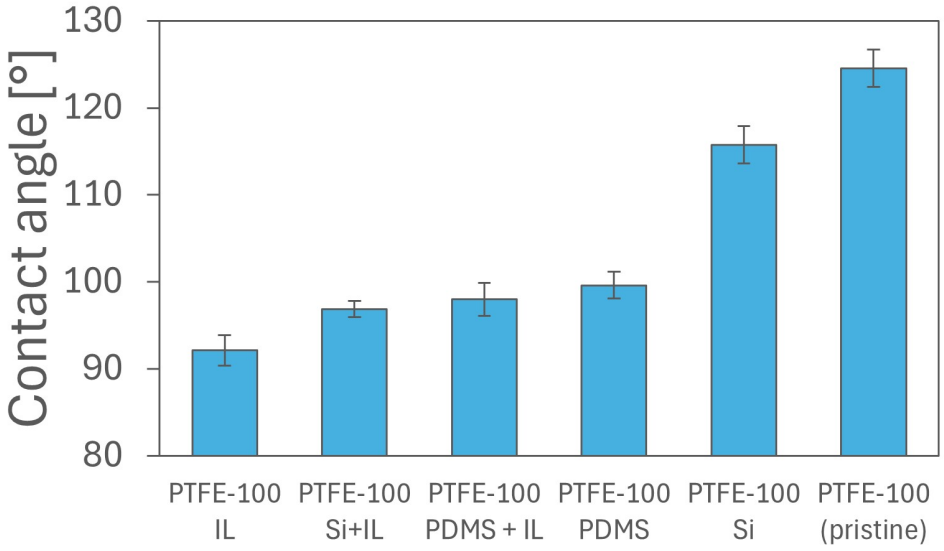

Figure 24: Water contact angle measurements of a PTFE-100 membrane, either pristine or with a silica (Si) or PDMS coating, and with or without ionic (IL) impregnation.

4.3 Membrane extraction

To analyse the ME results, several parameters were defined. The wetting efficiency W_{eff} was defined as follows:

$$W_{eff} = \frac{m_{impreg,after} - m_{impreg,before}}{A} \left[\frac{g}{m^2}\right] \tag{8}$$

with $m_{impreg,after}$ the mass of the membrane after impregnation, $m_{impreg,before}$ the mass of the membrane before impregnation, and A the membrane area. The diameter of the membrane was equal to 46 mm.

Similarly, the coating efficiency C_{eff} was defined as:

$$C_{eff} = \frac{m_{coating,after} - m_{coating,before}}{A} \left[\frac{g}{m^2}\right] \tag{9}$$

with $m_{coating,after}$ the mass of the membrane after coating, $m_{coating,before}$ the mass of the membrane before coating, and A the membrane area.

The mass residual M_{res} allowed to quantify the loss of solvent/coating during ME experiments:

$$M_{res} = \frac{m_{test,after} - m_{dry}}{m_{test,before} - m_{dry}} [-] \tag{10}$$

with $m_{test,after}$ the mass of the membrane after ME experiment, $m_{test,before}$ the mass of the membrane before ME experiment, and m_{dry} the mass of the pristine membrane.

The solute flux through the membrane for a given amine J_a was defined as follows:

$$J_a = \frac{10^{-3}\Delta C_a}{\Delta t}\frac{V}{A_{eff}}\left[\frac{g}{m^2 h}\right] \tag{11}$$

with ΔC_a [mg/L] the variation in the given amine concentration given by HPLC or GC analysis, Δt [h] the time variation, V the volume of the feed or strip solution (0.25 L), and A_{eff} the effective contact area between the SLM and the feed or strip solution (0.0005607 m^2).

Similarly to LLE experiments, the selectivities $S_{MBA/IPA}$ and $S_{MPPA/IPA}$ were defined as follows:

$$S_{a/IPA} = \frac{J_a}{J_{IPA}}[-] \tag{12}$$

with J_a the MBA or MPPA flux through the membrane and J_{IPA} the IPA flux through the membrane.

These parameters were used to define the optimum solvent or coating procedure for SLM extraction of MBA and MPPA from a solution containing MBA, MPPA and IPA. High fluxes of MBA and MPPA indicated an efficient solvent, and low fluxes of IPA relative to the fluxes of MBA and MPPA indicated a selective solvent. The wetting and coating efficiencies reflected the compatibility between the solvent/coating and the membrane. A high wetting efficiency indicated that the solvent had penetrated well into the pores of the membrane and, similarly, a high coating efficiency signified that the coating was deposited well on the membrane surface. The residual mass, which takes into account the mass after ME, gave an indication of the stability of the solvent/coating. A stable solvent would remain in the pores of the membrane during the ME tests. The ideal solvent or coating would therefore be both effective and selective, while being compatible with the membrane and stable during ME. The aim of this work is to find an alternative to undecane, the benchmark organic solvent which is able to extract 17.58 g/m^{2}h of MBA and 24.01 g/m^{2}h of MPPA.

A summary describing the success or failure of the different ME experiments is available in appendix C. The residual mass data, and solute flux and selectivity data are available in appendix D and appendix E, respectively. It should be mentioned that some experimental results were unavailable due to difficulties with the analysis. This was particularly true for the IPA fluxes obtained by GC, where values had to be selected to obtain a coherent analysis. This also had an impact on the selectivity results, which depend directly on the IPA flux. Moreover, only data from the feed solution were used for the flux calculation, as they were more complete and consistent.

4.3.1 DES selection

The hydrophobic nature of the DESs prepared can be seen in Fig.25. The separation between the aqueous phase and the solvent phase was visually confirmed, with the solvent phase on top. In addition, this experiment showed that the DESs prepared are less dense than ultrapure water.

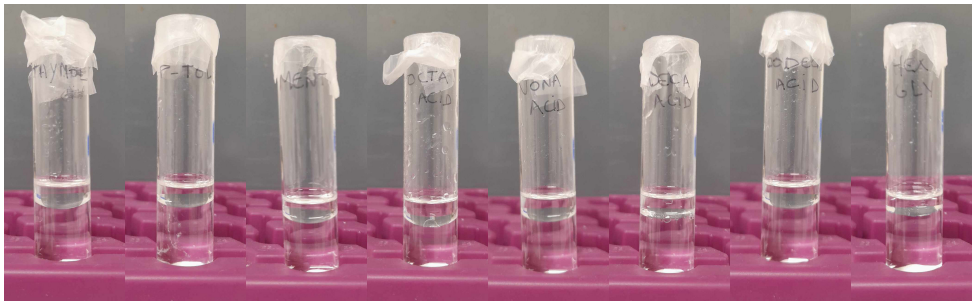

Figure 25: Hydrophobic nature of the DESs, from left to right: TOPO:thymol, TOPO:p-toluenesulfonic acid, TOPO:menthol, TOPO:octanoic acid, TOPO:nonanoic acid, TOPO:decanoic acid, TOPO:dodecanoic acid, TOPO:hexylene glycol.

First, the wetting efficiency and residual solvent mass after ME were compared for the considered DESs, as can be seen in Fig.26. It should be noted that only TOPO:thymol allowed more than one stable extraction, while TOPO:p-toluenesulfonic acid allowed only one stable extraction during the period covered by this report.

TOPO:thymol was found to be by far the most stable DES, with 81.70 % of the solvent mass remaining in the membrane pores following complete ME. However, the values showed a very large variation of the mass residual, making the process not robust. The other DESs retained between 38.43 % (TOPO:oleic acid) and 57.62 % (TOPO:octanoic acid) of the impregnated solvent mass. This low solvent mass did not allow the membrane stability to be maintained, which led to the failure of these experiments. Even more surprising was the very low residual mass of TOPO:p-toluenesulfonic acid (27.98 %), despite the fact that the experiment was successful. The high wetting efficiency value (29.24 g/m^2) compared with other DESs could explain this. This DES is highly compatible with the PTFE-50 membrane, *i.e.*, it was easily incorporated in the pores of the membrane. However, it was not stable and was lost during the ME process. The relatively large quantity of solvent present in the membrane would have therefore made it possible to postpone the moment when the SLM became unstable by a few hours.

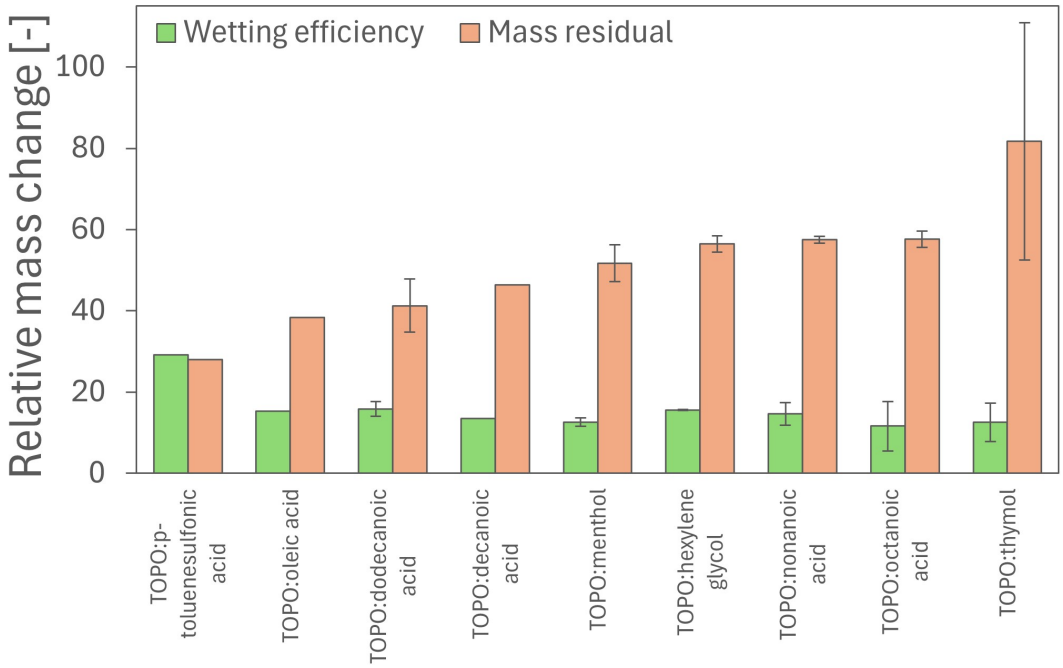

Figure 26: Relative mass change for the membrane extraction using PTFE-50 membranes impregnated with various TOPO-based DESs.

The solute flux and selectivity for the DESs are shown in Fig.27 and Fig.28. It should be noted that the values for TOPO:p-toluenesulfonic acid, TOPO:menthol, and TOPO:octanoic acid are from experiments carried out prior to this thesis. The results of the TOPO:p-toluenesulfonic acid experiment carried out this year were not available. TOPO:octanoic acid had the highest MBA (10.06 g/m^{2}h) and MPPA (21.13 g/m^{2}h) fluxes. The selectivities were similar, with the MBA/IPA and MPPA/IPA selectivity being around 4-6 and 8-10, respectively. The large standard deviation of the selectivity values for TOPO:thymol is due to the large variation in the IPA flux, because of analysis difficulties. The values for TOPO:p-toluenesulfonic acid, TOPO:menthol, and TOPO:octanoic acid should be interpreted with caution as they are the result of a single experiment.

To conclude this section on DESs, it was found that TOPO:octanoic acid is the most effective DES for MBA and MPPA extraction. Although, all the selectivities of the DESs were similar. However, TOPO:thymol was the most stable DES for ME. Further experiments with TOPO:p-toluenesulfonic acid, TOPO:menthol, and TOPO:octanoic acid would be necessary to better quantify their extraction efficiency. The instability of these three DESs for ME is an obstacle to their use in SLMs. Using membrane stabilisers or attempting to impregnate these DESs in other types of membrane could enable their amine extraction properties to be studied more fully.

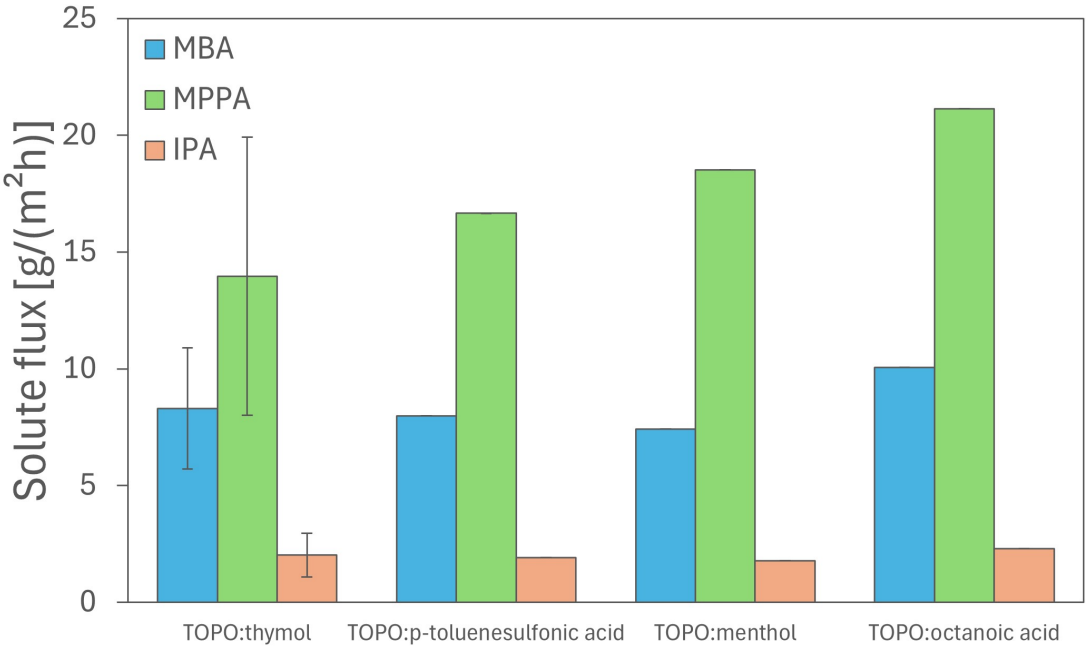

Figure 27: Solute flux during membrane extraction for PTFE-50 membranes impregnated with a DES.

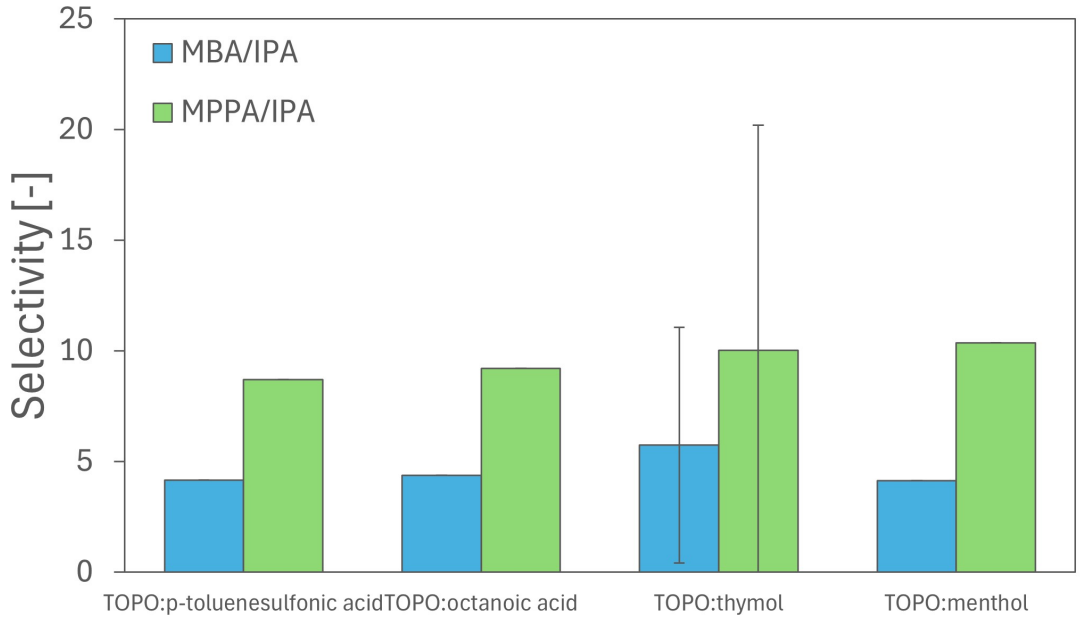

Figure 28: Selectivity towards MBA and MPPA during membrane extraction for PTFE-50 membranes impregnated with a DES.

4.3.2 Natural oil selection

The various natural oils used as solvent in the PTFE-50 membrane were compared with each other for residual solvent mass and wetting efficiency in Fig.29. Approximately 80 % of olive oil, coconut oil and sunflower oil were retained in the membrane following ME, these solvents only allowed stable extraction once. Only 58.94 % of peanut oil was retained following an

unsuccessful ME, this value rose to 82.82 % for corn oil. Palm oil was retained at 73.96 %. This solvent stood out for its high wetting efficiency value (40.52 g/m^2), with the other oils obtaining values below 21 g/m^2. This wetting efficiency value for palm oil can be justified by its density, which is higher than that of the other oils (see Tab.1).

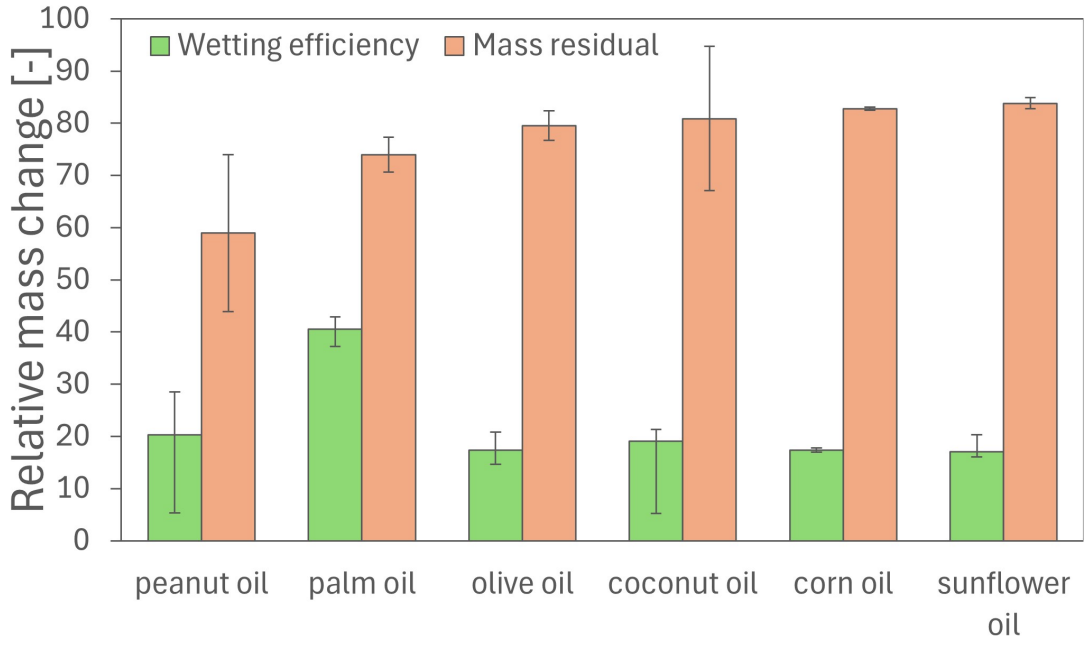

Figure 29: Relative mass change due to membrane extraction for PTFE-50 membranes impregnated with a natural oil.

The solute fluxes and selectivity of the natural oils that enabled successful ME are shown in Fig.30 and Fig.31, respectively. It is immediately noticeable that palm oil had the lowest MBA (0.73 g/m^{2}h) and MPPA (1.13 g/m^{2}h) fluxes of all the oils. The IPA flux was higher than those of MBA and MPPA and was the highest of all the oils. As a result, palm oil had extremely low selectivity values, below unity. Coconut oil was the most selective towards MBA (11.50) and MPPA (20.87) due to its very low IPA flux (0.11 g/m^{2}h). However, this oil was less efficient than olive oil or sunflower oil for MBA and MPPA extraction.

To conclude on natural oil as solvents for ME, olive and sunflower oil were the most efficient for MBA and MPPA extraction. Coconut oil was the most selective, while palm oil was the most stable of the oils tested, despite other oils obtaining higher residual mass values. Despite their low stability, oils remain attractive solvents for SLM extraction applications because of their non-toxicity and natural origin. As with DESs, the stability of SLMs using oil as a solvent needs to be improved. This would make it possible to fully determine the extraction capabilities of oils for SLM applications, bearing in mind that oils were effective and selective for the extraction of amines by LLE, as explained in section 4.1.

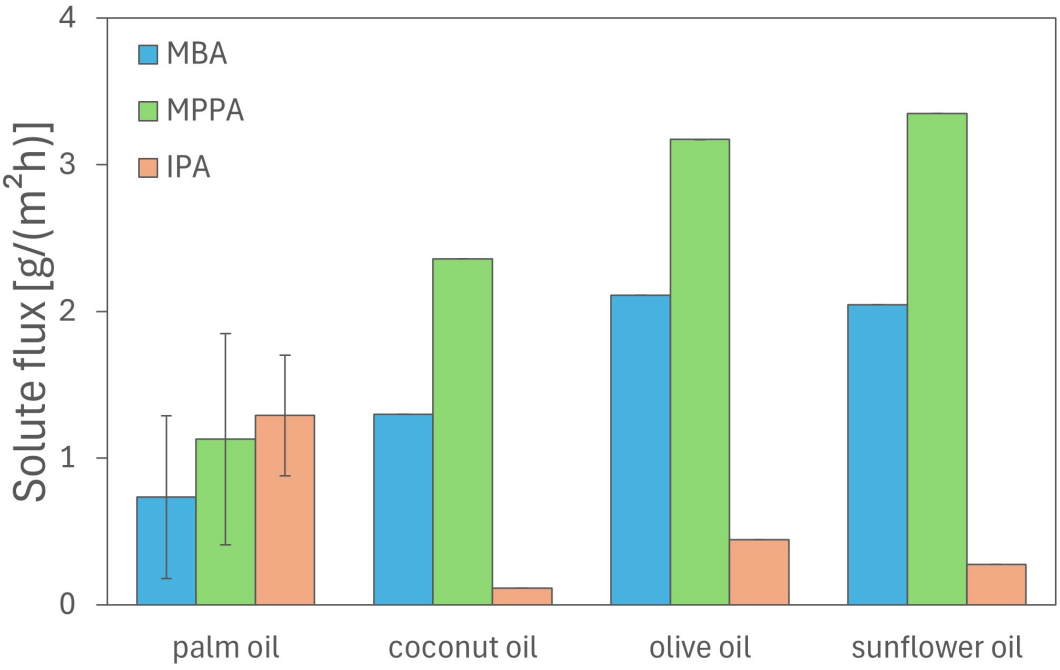

Figure 30: Solute flux during membrane extraction for PTFE-50 membranes impregnated with a natural oil.

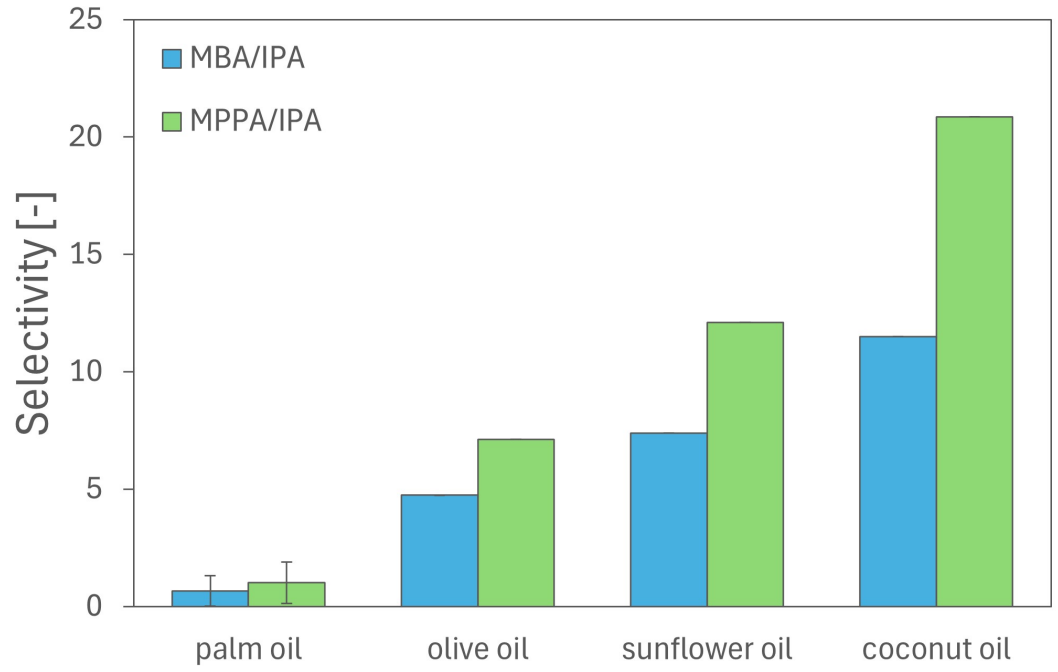

Figure 31: Selectivity towards MBA and MPPA during membrane extraction for PTFE-50 membranes impregnated with a natural oil.

4.3.3 Selection of stable and selective coatings

To improve the stability and selectivity, a coating procedure was used on the PTFE-100 membrane, namely a PDMS coating, silica NPs coating, and with or without ionic liquid ([P6,6,6,14]

[N(Tf)2]) impregnation. The combination of the IL and chitosan NPs was also used, and was considered as a solvent for the discussion because the chitosan NPs were dispersed at a low concentration of 2 mg/mL in the IL before impregnation. An analysis of the morphology of chitosan NPs is available in appendix F.

As can be seen in Fig.32, the highest residual mass was obtained for the PDMS coated membrane (92.96 %), while the value decreased slightly when [P6,6,6,14][N(Tf)2] was impregnated after the PDMS coating (89.88 %). The residual mass of silica NPs was relatively low, with only 51.33 % of the coating mass remaining after ME. The coating efficiency of PDMS was between 25.69 g/m^2 and 30.57 g/m^2, while that of silica NPs was between 16.80 g/m^2 and 31.96 g/m^2. The wetting efficiency for the IL (44.04 g/m^2) and for the chitosan-dispersed IL (41.18 g/m^2) were similar. Their residual mass was also similar and around 85 %.

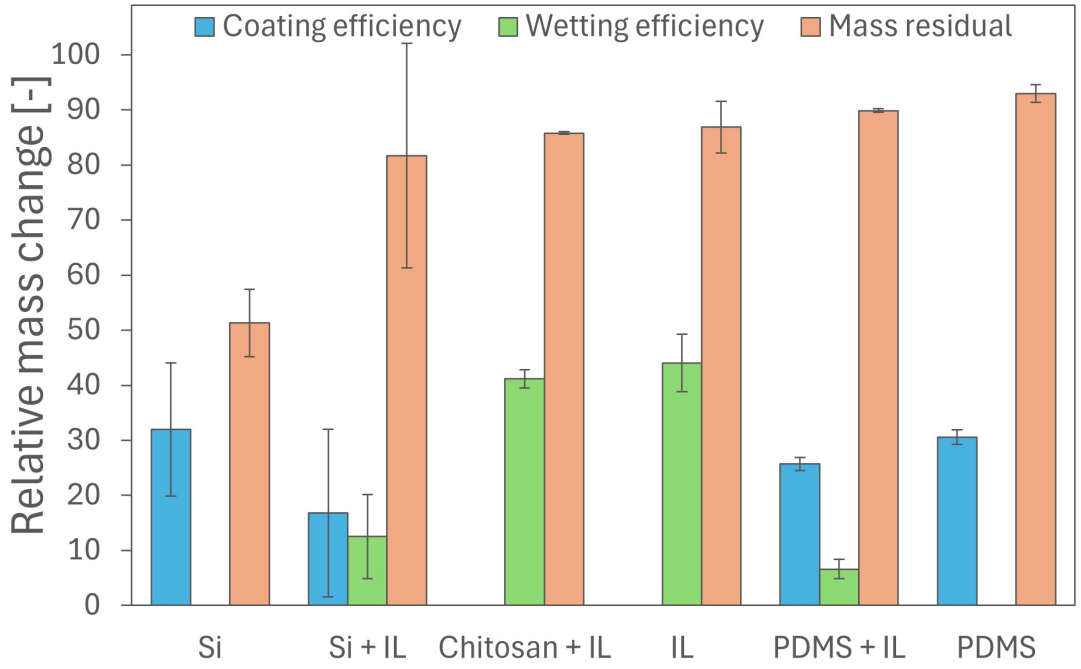

Figure 32: Relative mass change due to membrane extraction for a PTFE-100 membrane, either with chitosan NPs or with a silica (Si) or PDMS coating, and with or without ionic liquid (IL) impregnation.

The solute fluxes and the selectivity are shown in Fig.33 and Fig.34, respectively. The PDMS coating involved the highest MBA (0.89 g/m^{2}h) and MPPA (1.41 g/m^{2}h) fluxes. These flux values decreased slightly when the PDMS was impregnated with [P6,6,6,14][N(Tf)2]. The selectivity towards MBA and MPPA remained practically unchanged. The ME experiments with the silica coated membrane showed little or no selectivity at all, as the flux of IPA was greater than MBA and MPPA fluxes. The addition of [P6,6,6,14][N(Tf)2] to the silica NPs again led to an overall flux reduction. Membranes impregnated with chitosan NPs and [P6,6,6,14][N(Tf)2] showed a very large variation on the IPA flux, making the process not robust. The extraction results for the IL were similar to those obtained with chitosan NPs. This could mean that the

effect of chitosan NPs is negligible for extraction results. No IPA flux data were available for the experiments with only [P6,6,6,14][N(Tf)2] impregnation.

To conclude this section on coatings, the PDMS coating was the most efficient for the amines extraction, as it was more efficient than [P6,6,6,14][N(Tf)2]. The membranes containing silica NPs were the least efficient for extraction and the silica NPs tended to be strongly removed from the membrane during ME. It is difficult to make a quantitative statement about selectivity, as IPA flux results were not very stable. However, it can be said that silica coated membranes were not selective and PDMS coated membranes were relatively selective. Based on the extraction results, it seemed that chitosan NPs had no impact on the properties of SLM when combined with [P6,6,6,14][N(Tf)2]. Increasing the concentration of dispersed chitosan NPs in the IL before impregnation could make it possible to observe the impact of these hydrophobic NPs on the ME experiment. It was also found once again that the addition of the IL to an already coated membrane resulted in a reduction in the flux of amines to be extracted.

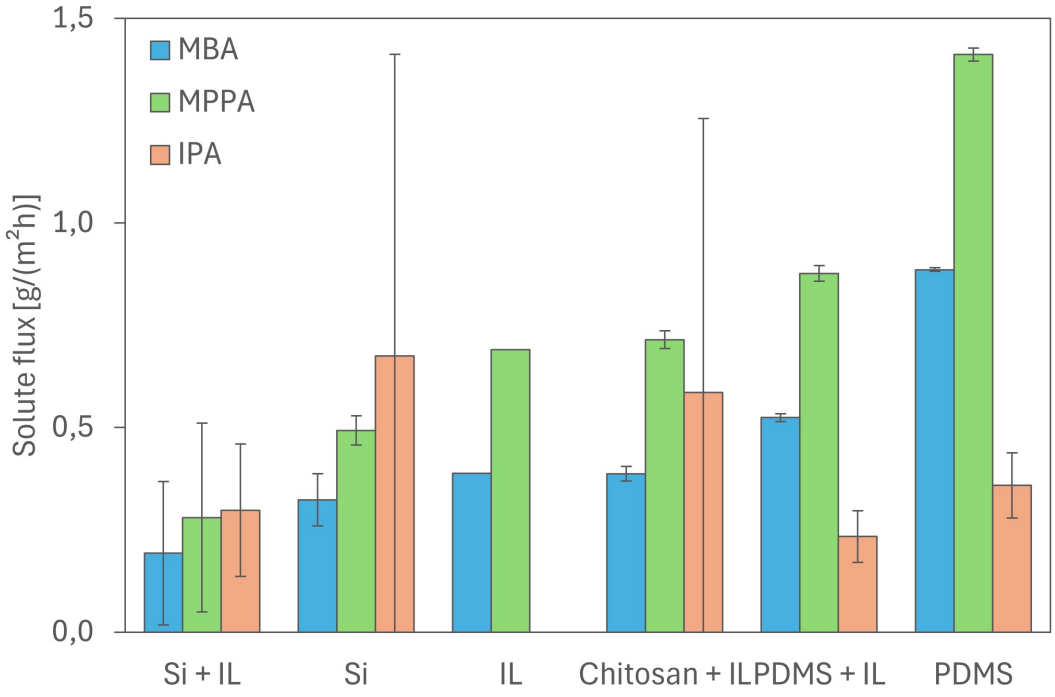

Figure 33: Solute flux during membrane extraction for a PTFE-100 membrane, either with chitosan NPs or with a silica (Si) or PDMS coating, and with or without ionic liquid (IL) impregnation.

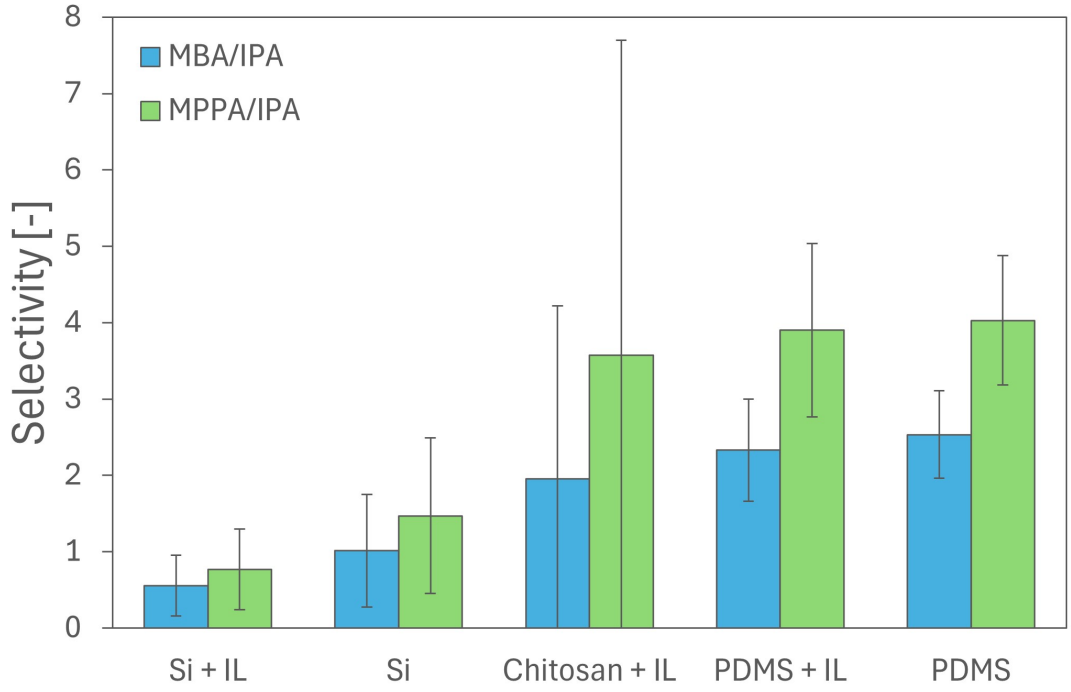

Figure 34: Selectivity towards MBA and MPPA during membrane extraction for a PTFE-100 membrane, either with chitosan NPs or with a silica (Si) or PDMS coating, and with or without ionic liquid (IL) impregnation.

4.3.4 Silica NPs coating

Different types of membrane coated with silica NPs and then impregnated with [P6,6,6,14][N(Tf)2] were compared. The influence of the pore size for PTFE membranes was also discussed.

As can be seen in Fig.35, the residual masses for PTFE membranes were similar, between 81.70 % and 87.77 % of mass was retained during ME. The results were similar for PVDF-100 (80.86 %) and slightly lower for PES-90 (75.72 %). For PTFE membranes, the coating efficiency increased with increasing pore size, while the opposite occurred with wetting efficiency. The values for coating efficiency (167.23 g/m^2) and wetting efficiency (-50.22 g/m^2) for PTFE-450 were removed from the graph for clarity. The larger the pores, the easier it was for the solution containing the silica NPs to be deposited on the surface or even to enter the membrane pores. When the IL was impregnated after the coating step, the NPs were already inside the pores. The negative wetting efficiency value for PTFE-450 could therefore be explained by the fact that the IL removed the NPs in the pores of the membrane during the impregnation step. This caused a decrease in the total mass of the membrane. This phenomenon was not, or only slightly, visible for smaller pores, as it requires more energy to force the NPs out.

It can also be seen that silica NPs were deposited with difficulty on the PVDF-100 membrane. The PES-90 membrane showed a mass loss due to the coating step, which could be explained by the heat treatment applied to the membranes after the coating. The mass loss is such that part

of the membrane must have been consumed during the heat treatment stage. PVDF-100 and PES-90 membranes were also very compatible with [P6,6,6,14][N(Tf)2] impregnation, given the wetting efficiency values achieved.

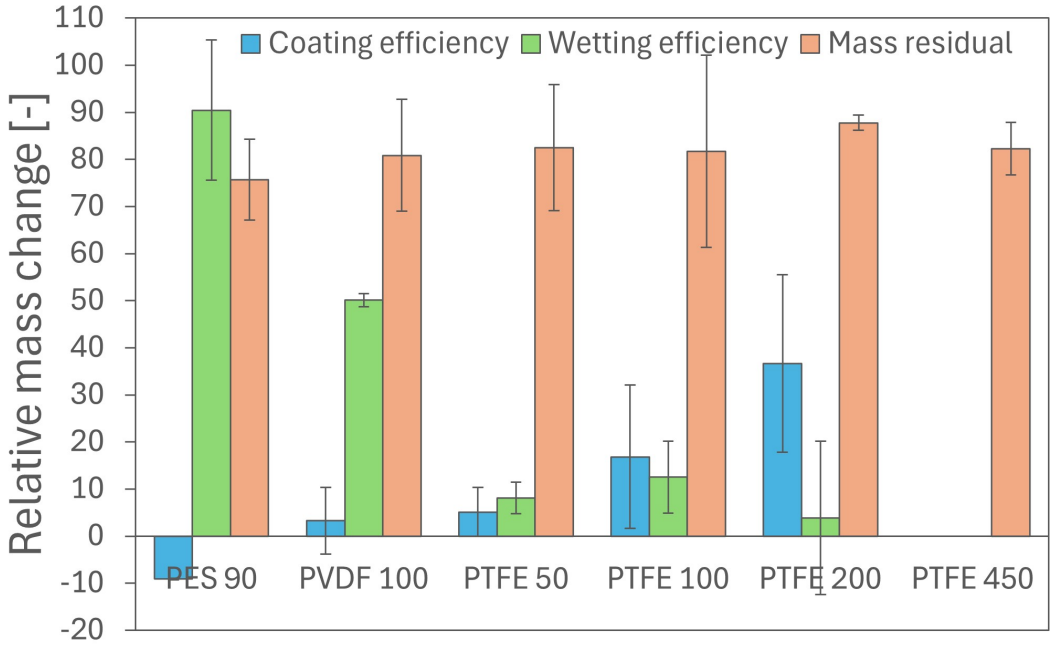

Figure 35: Relative mass change due to membrane extraction for silica coated membranes impregnated with IL ([P6,6,6,14][N(Tf)2]).

The amine extraction and selectivity results can be seen in Fig.36 and Fig.37. First, the silica coating with [P6,6,6,14][N(Tf)2] impregnation resulted in membranes that were non-selective towards MBA and MPPA. The highest MBA and MPPA fluxes were obtained with PVDF-100, although these fluxes remained relatively low. The MBA and MPPA fluxes were similar for PTFE-50 and PTFE-100, and an increase was observed for PTFE-200. This increase in flux was not replicated for the PTFE-450 membrane, the flux decreased sharply with the increasing pore size. This could be explained by the coating loss during the impregnation step. The PES-90 membrane showed similar MBA and MPPA extraction results to PTFE-50 but appeared to be less selective.

Finally, the coating of silica NPs combined with [P6,6,6,14][N(Tf)2] impregnation resulted in membranes that were non-selective. In addition, solute fluxes were extremely low. The increase in pore size implied difficulties to impregnate the membrane, without losing the previously deposited coating layer. It was also found that [P6,6,6,14][N(Tf)2] was compatible with PVDF-100 and PES-90 membranes. The coating with the silica NPs, on the other hand, was not. The coating of silica NPs coupled with [P6,6,6,14][N(Tf)2] impregnation, is not an effective alternative for the extraction of MBA and MPPA by SLM. However, the experiments carried out were stable, even with a high pore size. Reducing the quantity of NPs deposited on the membrane surface, by shortening the duration of the dip coating step, could allow an increase

in the flux of amines through the membrane while maintaining the stability of the system.

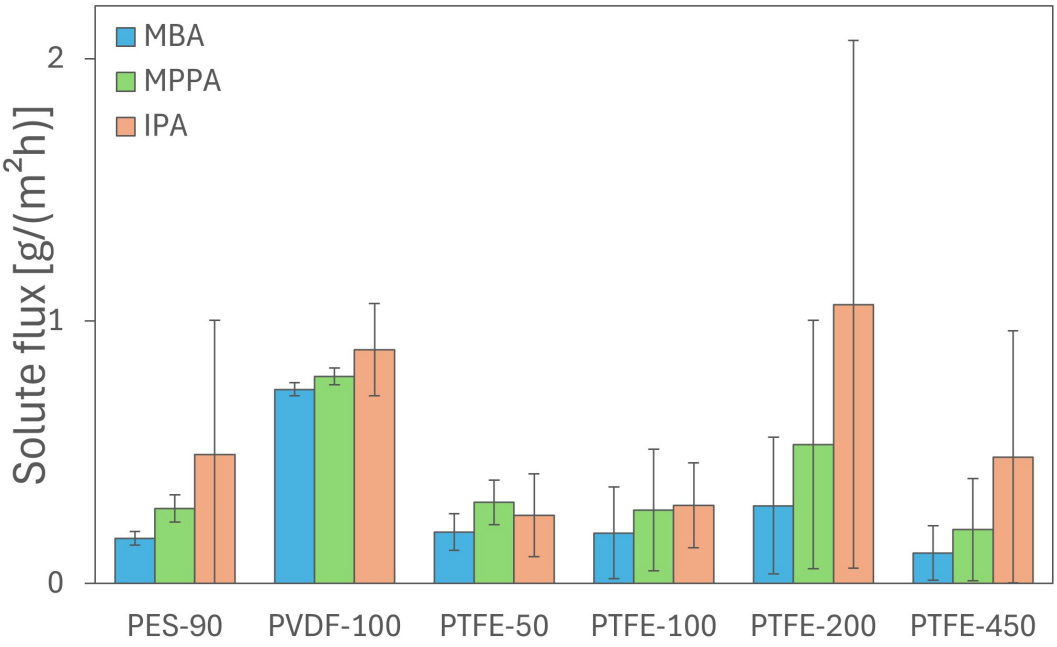

Figure 36: Solute flux during membrane extraction for silica coated membranes impregnated with IL ([P6,6,6,14][N(Tf)2]).

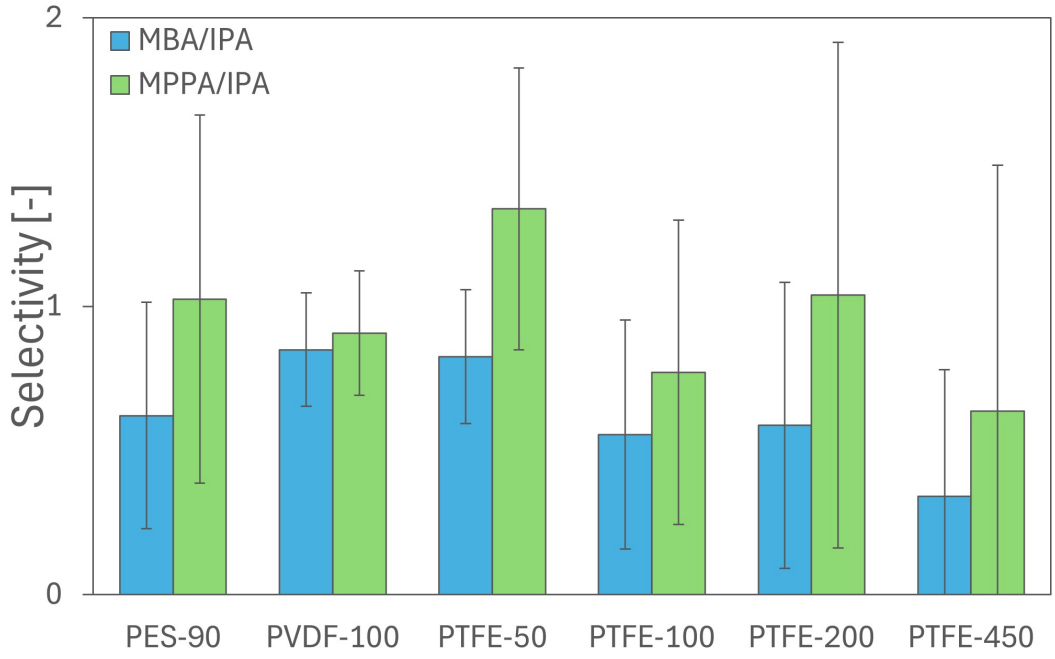

Figure 37: Selectivity towards MBA and MPPA during membrane extraction for silica coated membranes impregnated with IL ([P6,6,6,14][N(Tf)2]).

4.3.5 PDMS coating

Different types of membrane coated with PDMS were compared, the influence of the pore size for PTFE membranes was also discussed. The extraction results of the dense PDMS membrane were also used for discussion.

As can be seen in Fig.38, the residual mass for the PTFE-50 (92.10 %) and PTFE-100 (92.96 %) membranes were similar. The coating efficiency was lower for the PTFE-50 membrane, probably because of the smaller pores. Coating efficiency increased for PTFE-200 and then decreased for PTFE-450. It can be assumed that the larger pore size no longer allowed PDMS to be retained as strongly. It should be noted that PVDF-100 retained very little PDMS (42.55 %), which could explain the ME failures. More surprising was the very low residual mass in the PES-90 membranes (14.14 %) while the experiment remained stable. In addition, the coating efficiency value was low, which implies that the coating mass applied to the membrane was low.

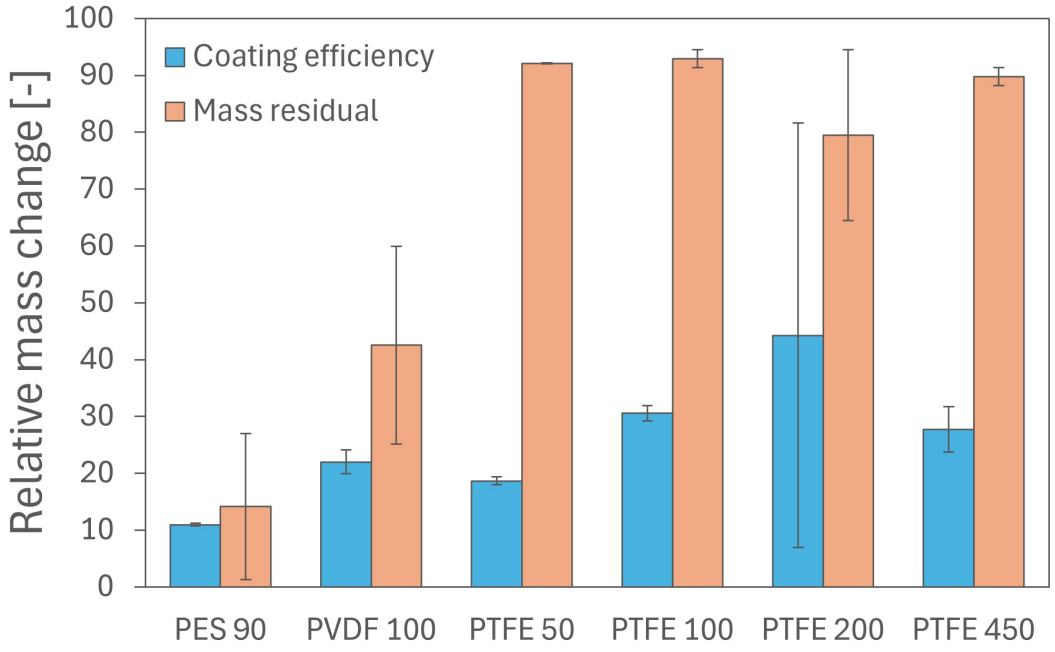

Figure 38: Relative mass change due to membrane extraction for PDMS coated membranes.

First, the dense PDMS membrane results are discussed. This membrane extracted more amines than the PDMS coated membranes. It should be noted that the experiments with the dense PDMS membrane resulted in failures between 6 and 24 hours of ME. However, the MBA (6.64 g/m^2h) and MPPA (8.10 g/m^2h) fluxes were three times higher than those obtained with the coated PTFE-50 membrane (MBA = 1.73 g/m^2h, MPPA = 2.65 g/m^2h). The dense PDMS membrane was also by far the most selective. The impact of pore size on extraction efficiency was difficult to discern. Indeed, the fluxes first decreased for PTFE-100, increased slightly for PTFE-200 and then decreased again for PTFE-450. However, a decrease in selectivity can be discerned as the pore size increased. The PES-90 membrane showed similar extraction results

to PTFE-450 but was not selective.

The most effective and selective membrane for MBA and MPPA extraction was the dense PDMS membrane, but, it was unstable. A volume exchange occurred between the feed and strip solution, and a loss of solution was observed under the Teflon cell after 24 hours of ME. The coated PTFE-50 membrane showed the second best extraction and selectivity results, while retaining more than 90 % of the PDMS during ME. An increase in pore size seemed to indicate a decrease in selectivity but had very little impact on MBA and MPPA fluxes. PES-90 was non-selective when coated with PDMS. The PDMS coating enabled the stable and selective extraction of amines for PTFE membranes with different pore sizes. Reducing the coating time in the PDMS solution could, as with silica NPs, allow an increase in solute flux while maintaining stability. The dense PDMS membrane could become a promising alternative for amine ME, however, its stability needs to be improved and the causes of its instability investigated. Monitoring the ME experiment to determine the exact moment when the experiment fails, and studying the resistance of the membrane in various acidic and basic media, would be options for further study of this membrane for SLM applications.

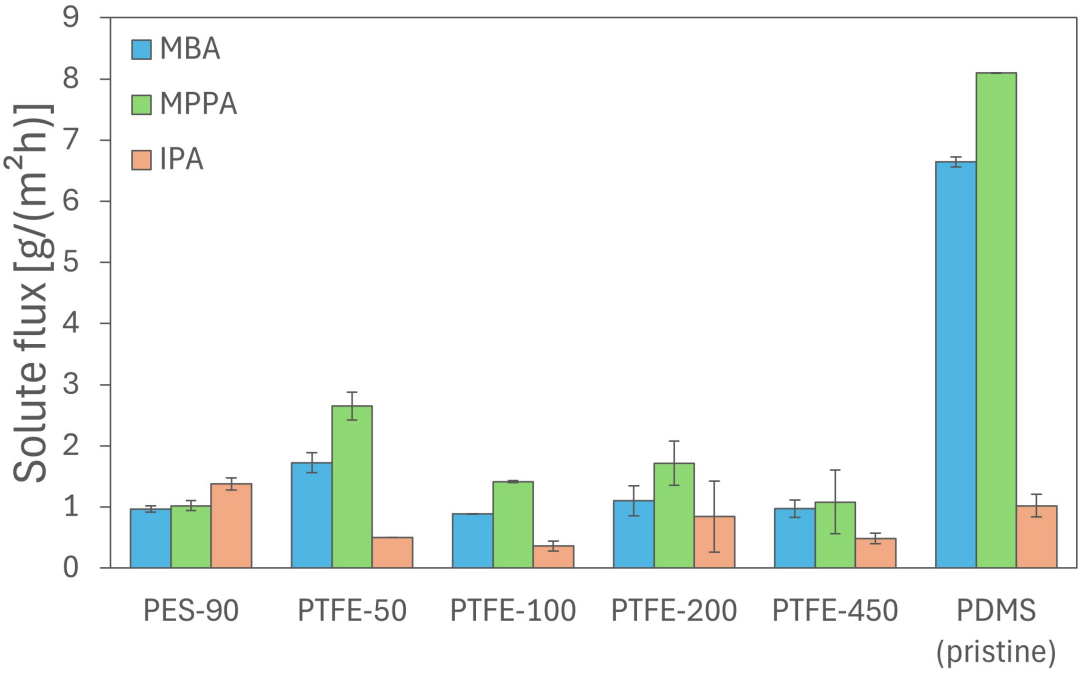

Figure 39: Solute flux during membrane extraction for PDMS coated membranes and the dense PDMS membrane.

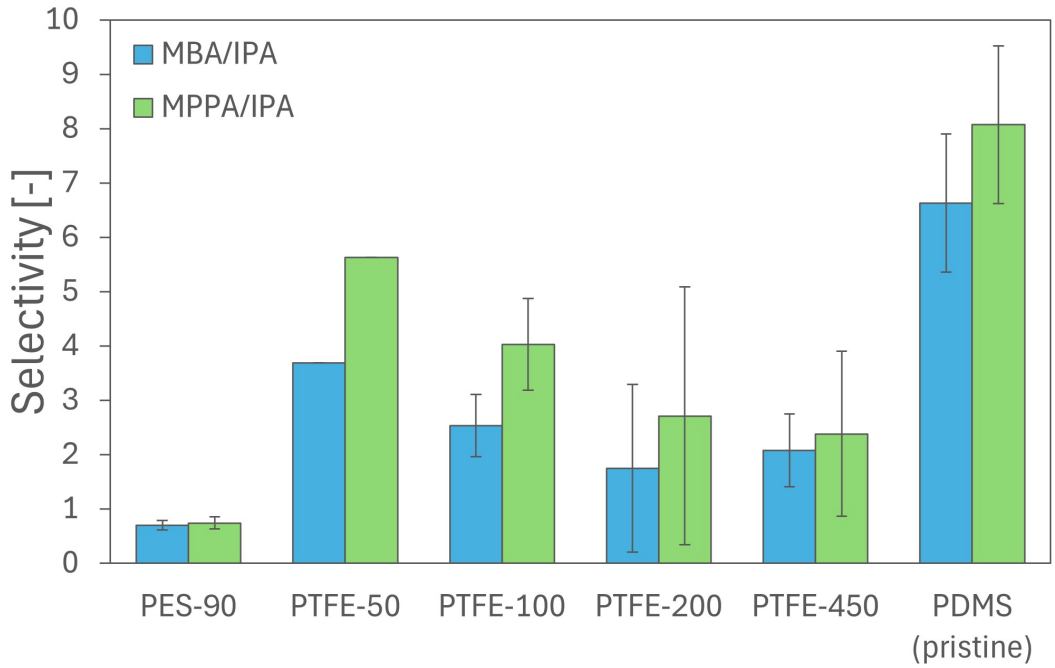

Figure 40: Selectivity towards MBA and MPPA during membrane extraction for PDMS coated membranes and the dense PDMS membrane.

4.3.6 Long-term stability tests

The 24-hour and 48-hour ME experiments were compared in terms of residual mass in Fig.41, and in terms of solute flux in Fig.42. The first conclusion that can be drawn is that the 48-hour experiments were successful, as the system remained stable and no volume exchange occurred between the feed and strip solution. The long-term stability tests were carried out using PTFE-50 membranes, results from ME experiments using PTFE-100 membranes were used for comparison.

The residual mass in the membrane pores decreased when the experiments last longer. A 20 % decrease in residual mass was observed for PDMS after 48 hours. This decrease can be explained simply by the longer duration of the experiment, which gave more time for the solvent or coating to be removed.

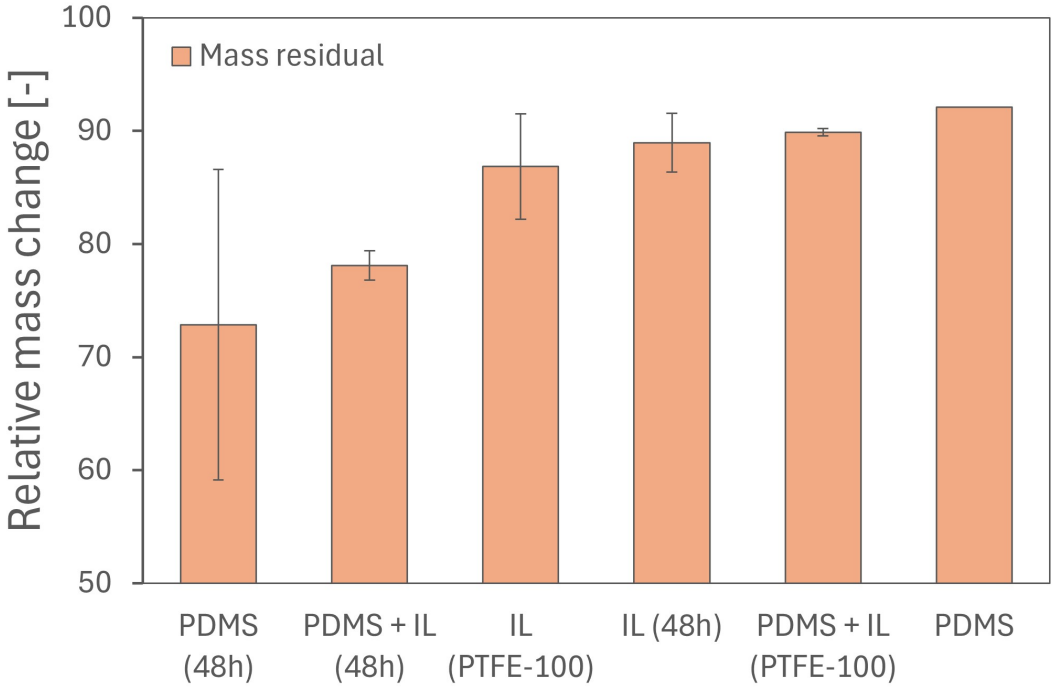

Figure 41: Relative mass change due to 24-hour and 48-hour membrane extraction for PTFE-50 and PTFE-100 membranes.

In terms of solute flux, the IL extracted MBA and MPPA less efficiently than the PDMS coating. A small decrease in flux was observed between the 24-hour PDMS experiment (MBA = 1.73 g/m^{2}h, MPPA = 2.65 g/m^{2}h) and the 48-hour experiment (MBA = 1.43 g/m^{2}h, MPPA = 2.04 g/m^{2}h). The IPA flux results must absolutely be interpreted with caution, as many IPA flux data were not usable or available to discuss. For this reason, no selectivity calculations were performed, due to the large variations on the IPA data.

The PTFE-50 membrane with a PDMS coating is the most effective for the MBA and MPPA extraction. The impact of adding [P6,6,6,14][N(Tf)2] to the PDMS coating seemed only to cause a loss of PDMS mass and a slight decrease in MBA and MPPA fluxes. It was also not possible to comment clearly on the selectivity results. When used alone, [P6,6,6,14][N(Tf)2] and PDMS enabled the stable and selective extraction of amines for a 48-hour period. In addition, the high residual mass values obtained indicate that these systems could remain stable for longer periods. Tests lasting 72 or 96 hours could confirm this long-term stability.

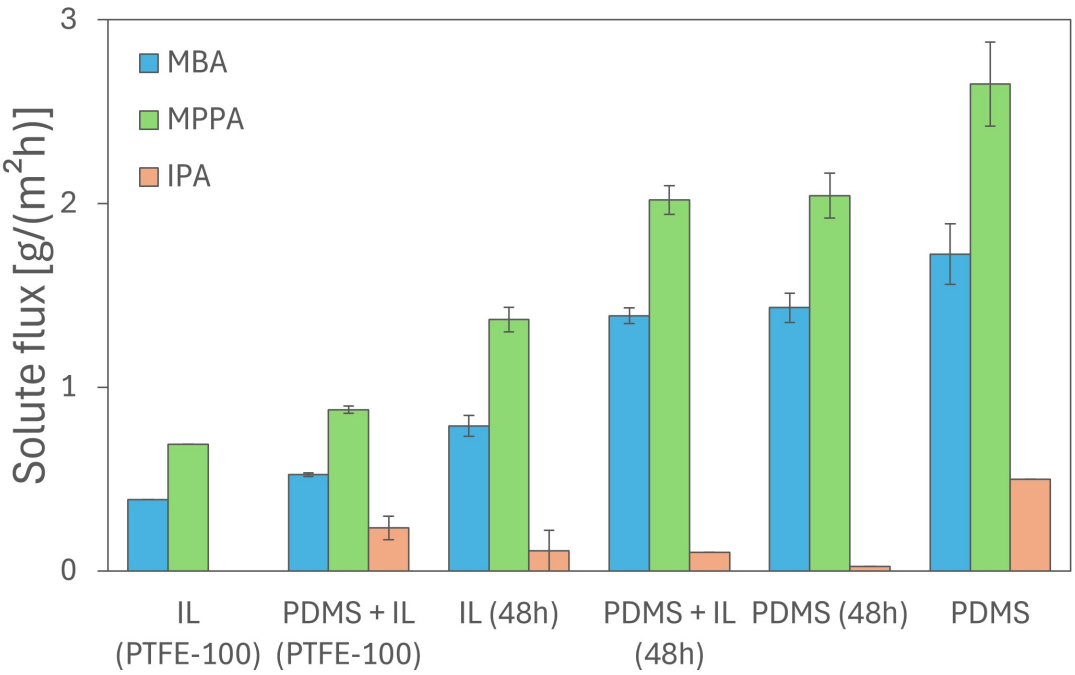

Figure 42: Solute flux during 24-hour and 48-hour membrane extraction for PTFE-50 and PTFE-100 membranes.

4.3.7 Summary

DESs were effective solvents for extracting amines, and the solute fluxes obtained were of the same order of magnitude as undecane, the reference organic solvent. However, DESs suffer from a consequent lack of stability that prevents the repetition of experiments, with the exception of TOPO:thymol. This stability could be improved, which would also reduce the loss of solvent due to ME. The oils, although promising in view of the LLE results, also lacked stability. Palm oil provided stable extractions, but these were not very efficient or selective, so other oils should be stabilised. The best advantage of oils as solvents remains their natural origin and their non-toxicity.

PDMS coating enabled less efficient extractions than DESs or [P6,6,6,14][N(Tf)2], but was extremely stable over long periods, which is what is required for SLM applications. Applying a PDMS coating to DES- or oil-impregnated membranes would be an option for optimising their stability. It should also be noted that combining [P6,6,6,14][N(Tf)2] with PDMS coating reduced extraction performance. The dense PDMS membrane stood out for its relatively high extraction capacity but lacked stability. Silica NPs coating with impregnated [P6,6,6,14][N(Tf)2] greatly reduced solute flux and made amine extraction non-selective. Silica NPs alone also induced very low solute fluxes and were non-selective. Reducing the quantity of NPs deposited on the membrane could be a solution for increasing flux. However, it should be noted that silica NPs used alone were strongly removed from the membrane during the experiment. The chitosan NPs had no visible effect on the extraction properties of the amines. New experiments using

higher concentrations of these NPs are needed to gain a better understanding of their possible effect. It is also possible that the non-perfect synthesis of these NPs was at the origin of this zero impact on the extraction efficiency.

It was again found that the dense PDMS membrane could be a potential candidate for amine extraction applications given the extraction performance recorded. However, the stability of the membrane needs to be improved before it can be used. Although [P6,6,6,14][N(Tf)2] and PDMS were not the most efficient for amine extraction, their stability for a period of 48 hours was proven during this work, making them promising candidates for stable long-term SLM extractions. TOPO:thymol was the solvent tested in this work whose extraction capabilities were closest to undecane. Other DESs were likely to be even more efficient but lacked the stability to compete with TOPO:thymol.

5 Conclusion

In this thesis, membrane extraction (ME) experiments were carried out, with the aim of separating α-methylbenzylamine (MBA) and 1- methyl-3-phenylpropylamine (MPPA) from isopropyl amine (IPA), the reaction precursor required for their production. The extraction was carried out using a supported liquid membrane (SLM) process, which consists of a solvent immobilised in the pores of a polymeric membrane extracting the amines from a feed solution into a strip solution. Overall, 78 ME experiments were carried out, and 34 different SLM combinations were tested. Fifty experiments resulted in stable extraction for 24 hours and 21 systems remained stable at least once. Three systems provided stable extraction for 48 hours.

Various solvents were immobilised in the membrane pores: deep eutectic solvents (DESs), natural oils, and an ionic liquid (IL). Silica and chitosan nanoparticles (NPs) and a solution of (PDMS) were prepared and deposited on the membrane before extraction. Porous membranes made of polytetrafluoroethylene (PTFE), polyvinylidene fluoride (PVDF) and polyethersulfone (PES) were used to impregnate the various solvents, and a dense PDMS membrane was also tested. The influence of pore size was studied for the PTFE membrane.

Different hydrophobic DESs were prepared and impregnated into a PTFE-50 membrane. It was determined that DESs are very efficient for amine extraction but severely lack stability to allow them to be used on a larger scale. This does not apply to trioctylphosphine oxide:thymol (TOPO:thymol), which combines efficient, selective and stable extraction. Increasing the stability of DESs is therefore crucial for their future applications in SLM. Natural oils have demonstrated desirable extraction properties for the liquid-liquid extraction of amines. However, they also lacked stability in ME experiments with PTFE-50. Palm oil alone provided more than a stable extraction, but it was not very efficient or selective. Nonetheless, oils remain an unavoidable opportunity to reduce the toxicity of the extraction process, given their natural origin, and increasing their stability is also a point that needs to be developed. The ionic liquid, which has already been recognised for its stability and extraction properties, has confirmed that it is an effective extractant. However, the IL impregnation leads to a non-negligible reduction in the hydrophobicity of the PTFE-100 membrane and therefore in the stability of the SLM.

The synthesised chitosan NPs had a different morphology to that expected and were aggregated into larger particles. They had no impact on the ME, either in terms of extraction efficiency or selectivity. Further characterisation of the particle size obtained and increasing the concentration of chitosan NPs impregnated into the membrane would seem to be logical steps to determine their potential impact on ME. The application of silica NPs improved the hydrophobicity of the membranes and therefore their stability. However, the amine fluxes obtained were too low to be considered effective, and the NPs made the extraction non-selective. Using these

NPs for SLM applications does not seem to be an attractive option. The PDMS coating led to an increase of the stability of the membranes, with the exception of the PVDF membrane, while maintaining relatively good amine fluxes. PDMS, described as a membrane-stabilising coating, is also a selective solvent for amines. The properties of this coating, which is easily applicable, should be studied for other amine systems.

PTFE membranes are the most suitable for ME applications due to their natural hydrophobicity. They were generally more stable, more selective and allowed higher solute fluxes than PVDF and PES membranes. The PTFE membrane with the smallest pores (PTFE-50) was the most efficient and stable, however, performance differences were relatively limited with PTFE-100 and PTFE-200. The dense PDMS membrane provided highly efficient and selective but unstable amine extraction. Further experiments with this membrane need to be carried out to confirm this efficiency, and stabilising this dense membrane for longer periods seems to be a priority. During this work, stable MEs with PDMS or IL for 48 hours were achieved with a high solvent residual mass, which bodes well for attempting extraction experiments over longer periods. Extraction results comparable to undecane, the reference in the literature for amine extraction, were also observed for four membrane systems. PTFE-50 with TOPO:thymol, IL, and PDMS, and the dense PDMS membrane. Further investigations on this subject should focus on these systems in particular, as they are particularly promising for competing with undecane.

Further studies should focus on DESs for SLM extraction, as stabilising these efficient solvents is essential for their development in amine production. The PDMS coating should also be investigated further for its properties as a membrane stabiliser but also for the extraction of various amines. Studying novel solvents, stabilisers and membranes for SLM extraction of chiral amines seems likely interesting for the pharmaceutical industry.

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Appendices

A DESs preparation

Hydrogen bond donor (HBD)	10g		20g	
	m_{HBD}	m_{TOPO}	m_{HBD}	m_{TOPO}
	[g]	[g]	[g]	[g]
Thymol	4.38	5.63	8.75	11.26
p-toluenesulfonic acid	4.72	5.29	9.43	10.58
Menthol	4.47	5.53	8.94	11.06
Octanoic acid	4.27	5.73	8.54	11.46
Nonanoic acid	4.50	5.50	9.00	11.00
Decanoic acid	4.71	5.29	9.42	10.58
Dodecanoic acid	5.09	4.91	10.18	9.82
Oleic acid	5.95	4.06	11.89	8.12
Hexylene glycol	3.80	6.21	7.59	12.42

Table 7: HBD and TOPO mass for the preparation of 10 and 20 g DESs with a 2:1 molar ratio.

B Feed buffer preparation

Date	MBA	MPPA	IPA
	[mg]	[mg]	[mg]
08-09-23	252.1	258.1	251.3
11-09-23	499.5	504.0	499.6
19-09-23	503.0	504.1	501.3
21-09-23	508.4	506.9	505.0
02-10-23	509.4	504.2	502.7
11-10-23	506.9	502.4	500.4
24-10-23	501.1	501.4	503.1
09-11-23	506.5	503.5	500.6
29-11-23	501.1	504.6	501.0
06-12-23	502.7	509.8	503.8
13-12-23	509.0	500.6	501.0
06-02-24	500.3	502.9	506.2
13-02-24	502.9	507.1	501.7
21-02-24	504.4	513.8	499.9
29-02-24	501.3	501.8	500.5
11-03-24	501.6	504.8	503.0
19-03-24	505.8	499.5	499.0
04-04-24	506.7	501.2	508.2
15-04-24	502.1	502.5	501.1
23-04-24	500.8	501.9	501.5

Table 8: Mass of MBA, MPPA and IPA added to the feed buffer.

C ME results

Solvent: DES	ME			Solvent: oil	ME		
TOPO:thymol	✓	✓	✓	olive oil	✓	✗	✗
TOPO:p-toluenesulfonic acid	✓			peanut oil	✗	✗	
TOPO:menthol	✗	✗		sunflower oil	✓	✗	✗
TOPO:octanoic acid	✗	✗		corn oil	✗	✗	
TOPO:nonanoic acid	✗	✗		coconut oil	✗	✓	✗
TOPO:decanoic acid	✗			palm oil	✓	✓	
TOPO:dodecanoic acid	✗	✗		castor oil			
TOPO:oleic acid	✗						
TOPO:hexylene glycol	✗	✗					

Table 9: ME results for DESs and oils, green corresponding to a successful experiment and red to a failure.

Membrane	Coating	Solvent	Time	ME		
PTFE-50	Si	IL	24h	✗	✓	✓
	PDMS	N/A	24h	✓	✓	
	N/A	IL	48h	✓	✓	
	PDMS	N/A	48h	✓	✓	
	PDMS	IL	48h	✓	✓	
PTFE-100	N/A	IL	24h	✓		
	Si	N/A	24h	✓	✓	✓
	Si	IL	24h	✓	✓	✓
	PDMS	N/A	24h	✓	✓	
	PDMS	IL	24h	✓	✓	
	N/A	Chitosan + IL	24h	✓	✓	

Table 10: ME results for coated PTFE-50 and PTFE-100 membranes and long-term stability tests, green corresponding to a successful experiment and red to a failure.

Si + IL				PDMS			
Membrane	**ME**			**Membrane**	**ME**		
PTFE 50	✗	✓	✓	PTFE 50	✓	✓	
PTFE 100	✓	✓	✓	PTFE 100	✓	✓	
PTFE 200	✓	✓	✓	PTFE 200	✓	✓	✓
PTFE 450	✓	✓	✓	PTFE 450	✓	✓	
PVDF 100	✗	✓	✓	PVDF 100	✗	✗	
PES 90	✓	✓	✓	PES 90	✓	✓	
				PDMS (pristine)	✗	✗	

Table 11: ME results for PDMS coated and silica coated membranes impregnated with IL, green corresponding to a successful experiment and red to a failure.

D Relative mass changes results

Solvent/coating	Coating efficiency		Wetting efficiency		Mass residual	
	av.	st. dev.	av.	st .dev.	av.	st. dev.
	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	%	%
TOPO:p-toluenesulfonic acid	N/A	N/A	29.24	N/A	27.98	N/A
TOPO:oleic acid	N/A	N/A	15.34	N/A	38.43	N/A
TOPO:dodecanoic acid	N/A	N/A	15.82	1.79	41.24	6.54
TOPO:decanoic acid	N/A	N/A	13.48	N/A	46.43	N/A
TOPO:menthol	N/A	N/A	12.64	1.02	51.72	4.58
TOPO:hexylene glycol	N/A	N/A	15.61	0.13	56.45	1.99
TOPO:nonanoic acid	N/A	N/A	14.62	2.81	57.49	0.86
TOPO:octanoic acid	N/A	N/A	11.64	6.08	57.62	1.97
TOPO:thymol	N/A	N/A	12.56	4.73	81.70	29.15
peanut oil	N/A	N/A	20.28	8.25	58.94	14.99
palm oil	N/A	N/A	40.52	2.34	73.96	3.33
olive oil	N/A	N/A	17.41	3.37	79.56	2.82
coconut oil	N/A	N/A	19.06	2.22	80.90	13.83
corn oil	N/A	N/A	17.33	0.43	82.82	0.31
sunflower oil	N/A	N/A	17.09	3.19	83.82	1.06
Si + IL	5.11	5.21	8.06	3.34	82.49	13.33
PDMS	18.65	0.68	N/A	N/A	92.10	0.06
IL (48h)	N/A	N/A	24.70	3.45	88.98	2.60
PDMS (48h)	31.47	1.02	N/A	N/A	72.88	13.72
PDMS + IL(48h)	35.17	1.91	-9.33	2.30	78.10	1.31

Table 12: Coating efficiency, wetting efficiency and mass residual for PTFE-50 membranes.

Solvent/coating	Coating efficiency		Wetting efficiency		Mass residual	
	av.	st. dev.	av.	st .dev.	av.	st. dev.
	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	%	%
IL	N/A	N/A	44.04	5.25	86.86	4.66
Si	31.96	12.07	N/A	N/A	51.33	6.13
Si + IL	16.80	15.22	12.53	7.66	81.70	20.39
PDMS	30.57	1.37	N/A	N/A	92.96	1.59
PDMS + IL	25.69	1.20	6.59	1.75	89.88	0.33
Chitosan + IL	N/A	N/A	41.18	1.66	85.79	0.24

Table 13: Coating efficiency, wetting efficiency and mass residual for PTFE-100 membranes.

Membrane	Coating efficiency		Wetting efficiency		Mass residual	
	av.	st. dev.	av.	st .dev.	av.	st. dev.
	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	%	%
PTFE 50	5.11	5.21	8.06	3.34	82.49	13.33
PTFE 100	16.80	15.22	12.53	7.66	81.70	20.39
PTFE 200	36.66	18.84	3.88	16.27	87.77	1.59
PTFE 450	167.23	119.85	-50.22	50.79	82.24	5.61
PVDF 100	3.26	7.05	50.12	1.41	80.86	11.92
PES 90	-9.11	0.15	90.45	14.92	75.72	8.59

Table 14: Coating efficiency, wetting efficiency and mass residual for silica coated membranes impregnated with IL.

Membrane	Coating efficiency		Mass residual	
	av.	st. dev.	av.	st. dev.
	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	%	%
PTFE 50	18.65	0.68	92.10	0.06
PTFE 100	30.57	1.37	92.96	1.59
PTFE 200	44.26	37.32	79.49	15.03
PTFE 450	27.71	3.96	89.79	1.61
PVDF 100	21.99	2.08	42.55	17.38
PES 90	10.95	0.26	14.14	12.88

Table 15: Coating efficiency and mass residual for PDMS coated membranes.

E Solute flux and selectivity results

Membrane	Solute flux						Selectivity			
	MBA		MPPA		IPA		MBA/IPA		MPPA/IPA	
	av.	st. dev.	av.	st. dev.	av.	st. dev.	av.	st. dev.	av.	st. dev.
	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	-	-	-	-
TOPO:thymol	8.31	2.60	13.96	5.96	2.02	0.94	5.75	5.32	10.04	10.18
TOPO:p-toluenesulfonic acid	7.98	N/A	16.66	N/A	1.91	N/A	4.17	N/A	8.70	N/A
TOPO:menthol	7.42	N/A	18.52	N/A	1.79	N/A	4.15	N/A	10.37	N/A
TOPO:octanoic acid	10.06	N/A	21.13	N/A	2.29	N/A	4.39	N/A	9.22	N/A
olive oil	2.11	N/A	3.17	N/A	0.45	N/A	4.74	N/A	7.12	N/A
sunflower oil	2.05	N/A	3.35	N/A	0.28	N/A	7.39	N/A	12.10	N/A
coconut oil	1.30	N/A	2.36	N/A	0.11	N/A	11.50	N/A	20.87	N/A
palm oil	0.73	0.55	1.13	0.72	1.29	0.41	0.67	0.64	1.01	0.88
Si + IL	0.20	0.07	0.31	0.08	0.26	0.16	0.83	0.23	1.34	0.49
PDMS	1.73	0.16	2.65	0.23	0.50	N/A	3.69	N/A	5.63	N/A
IL (48h)	0.79	0.06	1.37	0.07	0.11	0.11	15.58	15.83	27.33	28.04
PDMS (48h)	1.43	0.08	2.04	0.12	0.02	N/A	57.74	N/A	82.09	N/A
PDMS + IL (48h)	1.39	0.04	2.02	0.08	0.10	N/A	13.29	N/A	19.23	N/A

Table 16: Solute flux and selectivity towards MBA and MPPA during ME for PTFE-50 membranes.

Membrane	Solute flux						Selectivity			
	MBA		MPPA		IPA		MBA/IPA		MPPA/IPA	
	av.	st. dev.	av.	st. dev.	av.	st. dev.	av.	st. dev.	av.	st. dev.
	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	-	-	-	-
IL	0.39	N/A	0.69	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Si	0.32	0.06	0.49	0.04	0.68	0.74	1.01	0.74	1.47	1.02
Si + IL	0.19	0.18	0.28	0.23	0.30	0.16	0.56	0.40	0.77	0.53
PDMS	0.89	N/A	1.41	0.02	0.36	0.08	2.53	0.57	4.03	0.85
PDMS + IL	0.52	0.01	0.88	0.02	0.23	0.06	2.33	0.67	3.90	1.13
Chitosan + IL	0.39	0.02	0.71	0.02	0.59	0.67	1.96	2.27	3.58	4.12

Table 17: Solute flux and selectivity towards MBA and MPPA during ME for PTFE-100 membranes.

Membrane	Solute flux						Selectivity			
	MBA		MPPA		IPA		MBA/IPA		MPPA/IPA	
	av.	st. dev.	av.	st. dev.	av.	st. dev.	av.	st. dev.	av.	st. dev.
	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	-	-	-	-
PTFE-50	0.20	0.07	0.31	0.08	0.26	0.16	0.83	0.23	1.34	0.49
PTFE-100	0.19	0.18	0.28	0.23	0.30	0.16	0.56	0.40	0.77	0.53
PTFE-200	0.30	0.26	0.53	0.47	1.06	1.01	0.59	0.50	1.04	0.88
PTFE-450	0.12	0.10	0.21	0.19	0.48	0.48	0.34	0.44	0.64	0.85
PVDF-100	0.74	0.03	0.79	0.03	0.89	0.18	0.85	0.20	0.91	0.22
PES-90	0.17	0.03	0.29	0.05	0.49	0.51	0.62	0.39	1.02	0.64

Table 18: Solute flux and selectivity towards MBA and MPPA during ME for silica coated membranes impregnated with IL.

Membrane	Solute flux						Selectivity			
	MBA		MPPA		IPA		MBA/IPA		MPPA/IPA	
	av.	st. dev.	av.	st. dev.	av.	st. dev.	av.	st. dev.	av.	st. dev.
	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	$\left[\frac{g}{m^2}\right]$	-	-	-	-
PTFE-50	1.73	0.16	2.65	0.23	0.50	N/A	3.69	N/A	5.63	N/A
PTFE-100	0.89	N/A	1.41	0.02	0.36	0.08	2.53	0.57	4.03	0.85
PTFE-200	1.10	0.24	1.71	0.36	0.84	0.58	1.75	1.55	2.71	2.37
PTFE-450	0.97	0.14	1.08	0.52	0.48	0.09	2.08	0.67	2.38	1.52
PES-90	0.96	0.05	1.02	0.08	1.38	0.10	0.70	0.09	0.74	0.11
PDMS (pristine)	6.64	0.08	8.10	N/A	1.02	0.18	6.63	1.27	8.07	1.45

Table 19: Solute flux and selectivity towards MBA and MPPA during ME for PDMS coated membranes and the dense PDMS membrane.

F Morphology chitosan NPs

The synthesised chitosan NPs were observed by TEM and compared to the chitosan NPs prepared by Jothimani et al. [95]. A comparison with a 1 µm resolution can be seen in Fig.43, and a 200 nm resolution in Fig.44.

It was observed that the NPs prepared during this thesis were larger than the NPs in the literature. They also aggregated together rather than being dispersed. This difference between the reference NPs and those prepared in this thesis could be due to difficulties during the preparation, *i.e.*, during the step where the pH of the solution had to be maintained between 7.3 and 7.5. By maintaining gentle reaction conditions, analytically pure products can be obtained [95], this was not the case during the preparation. The particle size distribution of the chitosan NPs could be determined in order to confirm the TEM observations.

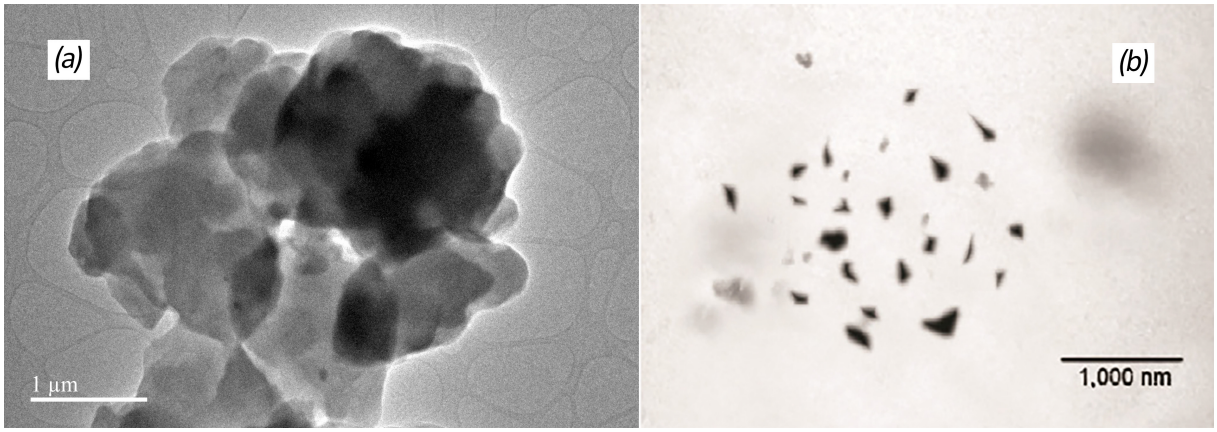

Figure 43: Morphology (1 µm) of the chitosan NPs synthesised during this thesis (a), and the NPs synthesised by Jothimani et al. [95] (b).

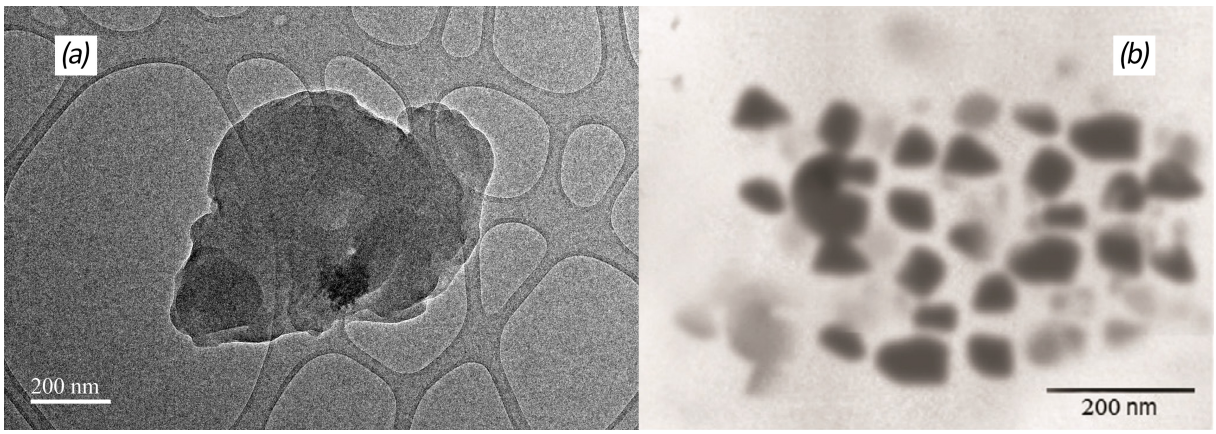

Figure 44: Morphology (200 nm) of the chitosan NPs synthesised during this thesis (a), and the NPs synthesised by Jothimani et al. [95] (b).

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