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# Membrane Contactors-Assisted Liquid-Liquid Extraction of Biomolecules from Biorefinery Liquid Streams: A Case Study on Organic Acids

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## Abstract:

The use of membrane contactors (MC) for the recovery of biomolecules in biorefinery processes has become increasingly popular thanks to their desirable properties such as robustness, large surface area, modularity and flexibility, as well as their non-dispersive nature. This review article provides a recent comprehensive and critical look into the recent progress made in the application of MC for the recovery of biomolecules such as aroma compounds (acetophenone, 2-phenylethanol, etc.), butanol, antibiotics, and organic acids from aqueous media and fermentation broths. Although some previous reviews have discussed the design and operation of membrane contactors for applications such as dissolved gases management and CO<sub>2</sub> capture, this review focuses on the liquid-liquid extraction of biomolecules from biorefinery liquid streams. It includes a detailed discussion of the technical characteristics of MC and their applications for liquid-liquid extraction of organic molecules from bioconversion and liquid media. A focus is then put on the use of MC for the extraction of organic acids, looking at the effects of operating conditions, extracting phase, and feed phase on the extraction process, as well as proposing back-extraction of organic acids by MC. Some of the challenges and limitations currently associated with these applications are highlighted.

**Keywords:** Membrane contactor, biorefinery, liquid-liquid extraction, organic acids, purification, extraction; extraction; separation; recovery; aroma compounds; antibiotics

## Abbreviations

ABE	Acetone-butanol-ethanol
MC	Membrane contactor
ILs	Ionic liquids
ISPR	In-Situ Product Recovery
LLE	Liquid-liquid extraction
MIBK	<i>Methyl Isobutyl Ketone</i>
N-BDEA	<i>N</i> -Butyldiethanolamine
PE	Polyethylene
PP	Polypropylene
PTFE	Polytetrafluoroethylene
PVDF	Polyvinylidene difluoride
HFP	Hexafluoropropylene
TBP	Tributylphosphate
TEHA	Tris(2-ethylhexyl)amine
TOA	Trioctylamine
TOMAC	Methyl trioctyl ammonium chloride
TOPO	Trioctylphosphine oxide
TPA	Tripropylamine
v/v	Volume/volume
w/w	Weight/weight

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## 1. Introduction

Separation and purification processes are key pillars of biorefineries. They can be used for the extraction of phytochemicals from biomass, the separation or purification of different chemical species from a medium. Their costs represent 20 to 50% of the total costs of biorefineries, which can be explained by the low concentration of molecules to be recovered and the great diversity of biomass composition [1]. Thus, the separation and purification processes have a major influence on the success and commercialization of products from biorefineries. Many separation technologies, such as distillation, adsorption, membrane separation, ion exchange and liquid-liquid extraction, can be implemented according to the requirements of each biorefinery [2,3].

Liquid-liquid extraction (LLE) technology has been applied in many fields of biorefinery, such as biotechnology, pharmaceutical industry, food industry and wastewater biorefinery [4–6]. The LLE process is characterized by mild operational conditions and easy control compared to other separation technologies, which is especially suitable for biorefinery process based on bioconversion using microorganisms. Thus, the application of LLE technology in biorefinery encounters several challenges. First, many biorefinery processes involve microorganisms and enzymes, which may limit the application of some organic extractants. It is therefore necessary to find the suitable extractants that are biocompatible with regard to microorganisms while being efficient for the extraction, i.e. giving high yield and selectivity. Second, the formation of an irreversible gel/emulsion can make the separation impossible. Finally, biorefinery streams and biological systems are usually much more complex as they contain many more components and chemicals than conventional chemical reactions media.

The implementation of liquid-liquid extraction technology in membrane contactors (MC) has caught the attention of many researchers. In MC, the membrane functions as a barrier between two phases that prevents mixing but does not control the rate of transport of different components between phases. MC typically use porous capillary membranes in a shell and tube device. The hollow fiber is a solid, porous polymer matrix that can be hydrophobic or hydrophilic.

Applied to LLE, MC provides contact area between the two phases with interesting properties. Indeed, MC act as a barrier which prevents phase dispersion and emulsion formation near the contact areas. In addition, the available contact area remains constant whatever the flow rates. These properties facilitate the prediction of the LLE performance [7]. In addition, MC offers interesting opportunities for process intensification through its flexibility, compactness and modularity. Indeed, it is not necessary to have a difference in density between liquids, which limits the dispersion processes, as when using membranes [7]. Thus, MC is an interesting alternative for

Aqueous two-phase Systems (ATPS) showing a very low-density difference [8]. When used for the in-situ removal of microorganisms inhibiting substances in fermentation broths, the use of MC as an extraction interface represents a promising way to minimize solvent toxicity on microorganisms [9–11].

MC also have some drawbacks. MC may exhibit an additional resistance to mass transfer, due to static liquid filling the pores, not met in conventional operations, which is why very thin and very porous membranes are preferred. They are also subject to possible flow bypass in the shell side, resulting in a loss of efficiency, especially at large scale [12].

The aim of this paper is to provide an overview on recent applications of MC in biorefinery, especially for the liquid-liquid extraction of organic molecules either produced by microorganisms or contained from liquid media as wastes or effluents. A first part will discuss the application of MC for the extraction of volatile organic compounds such as aroma compounds and butanol from fermentation/bioconversion broths and liquid media. In a second part, a case study of application of MCs in the liquid-liquid extraction of organic acids present in liquid media or in fermentation/bioconversion media will be presented. In this part, the effects of operating conditions, organic phase composition and feed phase on the efficiency of the extraction process will be discussed. The back-extraction of organic acids by MC will be also proposed.

## **2. Membrane contactor-assisted liquid-liquid extraction**

The principle of LLE assisted by MC is the same as that of LLE, with the presence of a (meso, macro)-porous membrane which allows a stabilized interface between the two liquid phases [13]. Two immiscible liquids are put in contact in the membrane, the pores are filled by one of the two immiscible liquids (wetting liquid), depending on the hydrophilic or hydrophobic nature of the membrane material.

Membrane contactors can be manufactured from flat sheet membranes, and there are some commercial applications of this type of device. However, the most commonly available commercial membrane contactors are made from small diameter microporous hollow fibers (or capillaries), with fine pores extending across the entire wall of the hollow fiber, from the inner surface to the outer surface of the fiber. Figure 1 illustrates a single hollow fiber microporous membrane separating two phases circulating in the "shell side" and the "lumen side", i.e., the outside and inside of the hollow fiber, respectively.

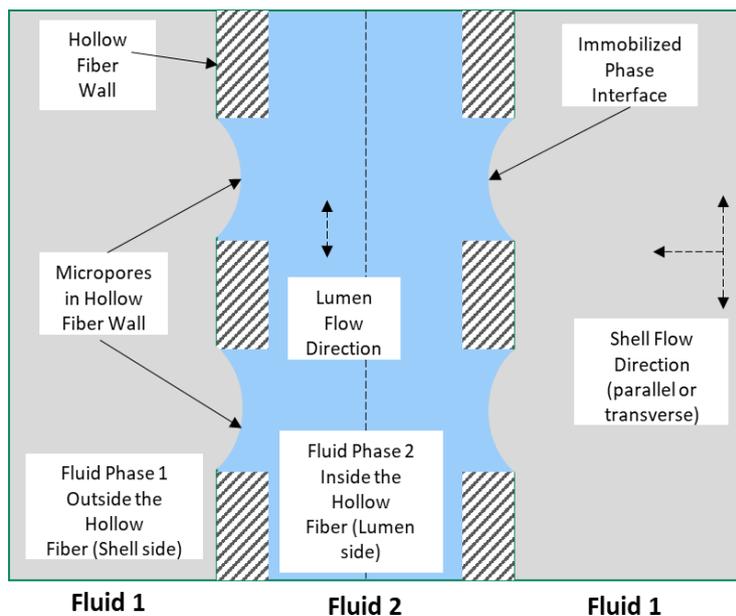


Figure 1. Single microporous hollow fiber with immobilized phase interface, adapted from Pabby et al. [14].

The feed phase which represents the aqueous phase goes through the membrane contactor in which the compounds circulates. Thus, molecules are transferred from the aqueous to the organic phase. Moreover, MC can be used to perform the back extraction, that is to say to recover the compounds contained in the organic phase which will be regenerated. The phase allowing the final recovery of compounds after the back extraction is called the stripping phase.

A membrane contactor would consist of thousands or hundreds of thousands of hollow fibers, like the one shown in Figure 1. Figure 2 shows the general schematic of a membrane contactor in a cylindrical shell (tube-in-shell) configuration, with identified inlet and outlet ports for the two fluids passing through the contactor.

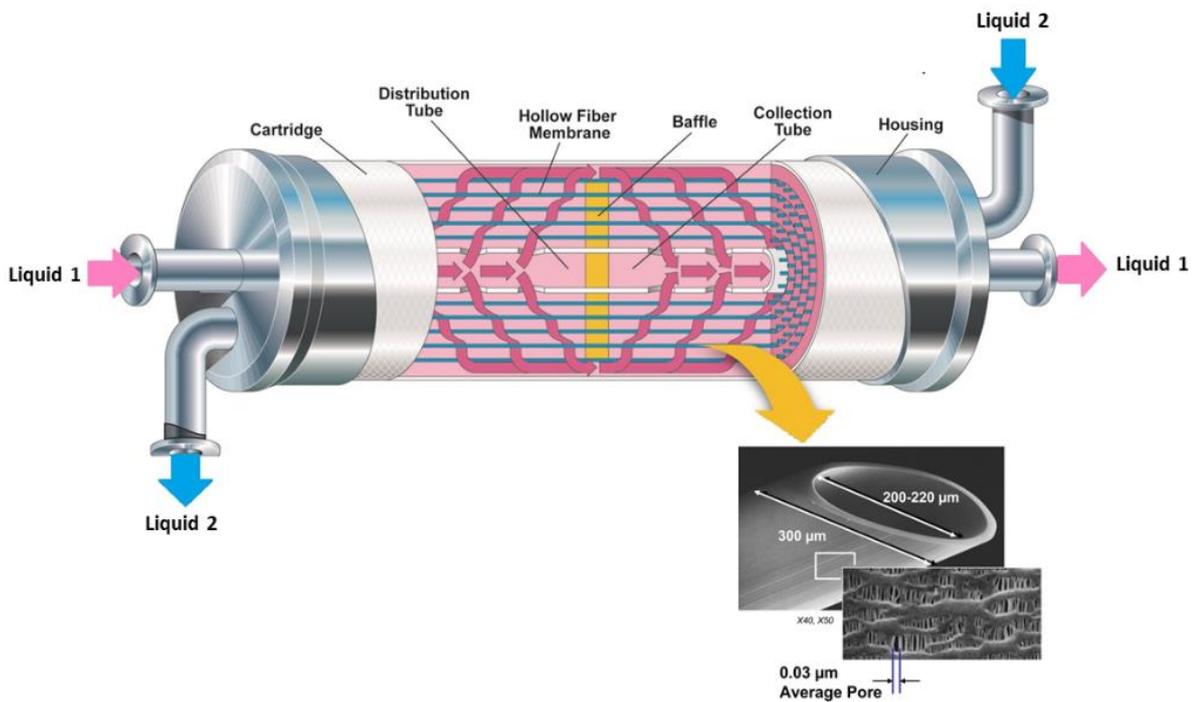


Figure 2: Module design and PP hollow fibers in Liqui-Cel® Membrane Contactors [15]

If the fiber material is hydrophobic, the pores will be filled with organic phase while if the fiber material is hydrophilic they will instead be filled with aqueous phase. A slight overpressure ( $\Delta P$ ) is applied on the non-wetting liquid side in order to stabilize the interface which avoids wetting phase passing through the membrane and, consequently, the appearance of an emulsion in the other phase (mixture of phases). If the  $\Delta P$  is too small, then the wetting fluid will pass through the membrane and disperse into the non-wetting phase. However,  $\Delta P$  must not exceed a limit beyond which the non-wetting phase would penetrate the pores of the membrane and mix with the wetting phase [16].

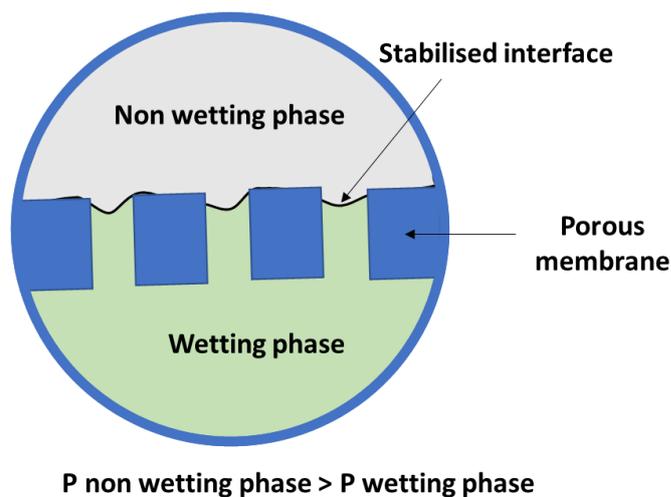


Figure 3: Interface between a wetting phase and a non-wetting phase in a porous membrane. P refers to the pressure of the liquid being considered

The  $\Delta P$  value from which the non-wetting fluid can pass through the pores of the membrane is named the critical pressure. Considering that the pore shape is cylindrical and that all the pores have the same diameter, this critical pressure can be estimated by the Young-Laplace equation [17] :

$$\Delta P_c = -\frac{2\gamma \times \cos \theta}{r} \quad \text{Eq. (1)}$$

Where  $\gamma$  is the interfacial tension between the two fluids,  $\theta$  is the contact angle at the triple point between the two fluids and the membrane material, and  $r$  the radius of the pore considered. It is preferred to use membrane with the narrowest pore size distribution. For a given membrane, it is better to consider the largest pore radius and not the average value, in order not to exceed the lowest critical pressure.

### **2.1. Diversity of membrane contactors (membrane materials and configurations)**

In membrane liquid-liquid extraction, the most common geometry of the contactor is a hollow fiber module. The configuration of the hollow fibers is generally ideal for the industrial scale given the greater compactness offered for the same membrane surface. In the case of Liqui-Cel® membrane contactors, the hollow fiber modules are made of fibers woven and wrapped around a central feed tube. One of the fluids circulates inside the fibers while the second circulates inside the shell (Figure 3).

There is a very wide variety of membrane contactors with different fill rates, fiber lengths and membrane materials (Table 1). According to the literature, the modules most commonly used for the extraction of organic acids come from the company 3M which sells PP hollow fiber membranes (Liqui-Cel®) whose exchange surface varies between 100 cm<sup>2</sup> and 220 m<sup>2</sup>. Membrane modules are systems offering great flexibility in terms of sizing of installations since it is possible to combine them in series and / or in parallel. In addition, different configurations are offered by circulating the fluids in co-current, in counter-current or even cross-current. Other types of contactors exist using either other fiber material such as Polyvinylidene difluoride (PVDF) or Polytetrafluoroethylene (PTFE) [18,19].

The choice of the membrane, as well as the geometry of the contactor, must be made in order to maximize material transfers, to stabilize the performance of the membrane contactor over the entire length of the module, but also to enhance the operational robustness of the process (wide range of applicable pressure). The modules can also be used continuously (a single pass through the contactor) or in batch mode (phase recirculation).

The membranes most used as contactors are polymeric membranes of low thickness (<100 microns), high porosity (>25%) and pore sizes between 30 and 100 nm. The most frequently used polymers are polypropylene (PP), PVDF and PTFE [20]. Regarding inorganic membranes, the most commonly used materials used are glass, stainless steel and different types of ceramics (alumina  $\text{Al}_2\text{O}_3$ , zirconium dioxide  $\text{ZrO}_2$ , titanium dioxide  $\text{TiO}_2$ ) [21]. However, the use of these materials as membrane contactors is reserved for liquid-liquid extraction under very acidic conditions [22] or in emulsification [23].

The stability, tendency to block, and cleanability of MC depend on several factors, including the membrane material, operating conditions, and fluid properties. It is important to carefully select and optimize these factors to maximize the performance and longevity of membrane contactors in LLE applications.

The stability of the membrane materials can vary significantly, with some materials being more stable than others under different operating conditions. PTFE is highly stable, while polysulfone (PSf) and cellulose acetate (CA) are less stable and more prone to degradation under high temperature and pressure. Although ceramic membranes, such as alumina and zirconia, are highly stable and resistant to fouling, they are more expensive than polymeric membranes [24]. Pre-treatment by filtration to remove suspended solids and colloidal material and pH adjustment are important to protect membrane contactors from fouling and clogging.

The tendency to block or foul can also vary depending on the membrane material and operating conditions. PSf and CA membranes are more prone to fouling than PTFE and ceramic membranes, while PVDF and PP membranes are less prone to fouling. The tendency to block can be reduced by optimizing the flow rate and operating pressure [24].

The cleanability of the membrane materials can also vary, with some materials being more easily cleaned than others. PTFE, PP and PVDF membranes are more easily cleaned than PSf and CA membranes, while ceramic membranes are highly resistant to fouling and can be easily cleaned with chemical agents or physical methods such as backwashing.

Table 1: characteristics of MC used for the separation of organic molecules from fermentation broths and liquid media according to the literature

Membrane module	Configuration	Material	Average number of fibers	Effective fiber length (mm)	Inner diameter of fibers ( $\mu\text{m}$ )	Outer diameter of fibers ( $\mu\text{m}$ )	Wall thickness ( $\mu\text{m}$ )	Porosity (%)	Pore size ( $\mu\text{m}$ )	Total contact area ( $\text{m}^2$ )	Reference
Teflon (PTFE) capillary membrane contactor (Memo3, Switzerland)	Counter-current	PTFE	--	--	$2.97 \times 10^3$	$3.49 \times 10^3$	260	54	0.47	0.059	[25]
Membrane contactor (Memo3 GmbH, Switzerland) with 3 PTFE hollow-fiber	Counter-current	PTFE	3	200	$3 \times 10^3$	$3.1 \times 10^3$	--	55	1	0.0056	[26]
Hollow fiber module Membrana GmbH (Wuppertal, Germany)	Counter-current	PP	120	--	600	800	200	--	--	0.0719	[27]
Accurel® PP S6/2 (MEMBRANA GmbH)	MC immersed in an airlift reactor	PP	169	1285	$1.8 \times 10^3$	$2.7 \times 10^3$	--	80	0.2	1.842	[28]
Microporous hollow-fiber membrane contactor, 5PCM 218, Celgrad X-30 (Hoechst Celanese NC, USA)	Counter-current	PP	10 000	150	240	300	--	--	--	1.4	[29]
Microporous hollow-fiber membrane contactor, Celgrad X-20 (Hoechst Celanese NC, USA)	Counter-current	PP	--	159	--	400	--	--	0.03	0.2	[30]
Commercial PP	Counter-current (cascade process)	PP	1000	300	350	450		0.75		0.424	[31]

Microporous PVDF hydrophobic hollow fiber membrane contactor	Counter-current	PVDF	30	200	812	886	--	82	--	--	[32]
VL-120PP-FOB Small Laboratory Hollow Fiber Membrane Contactor GE Osmonics (Trevose, USA)	Parallel flow	PP	4000	210	350	450	50	45	0.2	1.2	[33]
Hollow fiber membrane module (Microdyn, Wuppertal, Germany)	--	PP	38	--	--	--	--	--	0.2	0.1	[34]
Microporous hydrophobic isotactic (semicrystalline) MC (Memtec, Australia)	Counter-current	PP	80	330	250	540	--	70	--	0.04	[35]
			566	270	250	540	--	70	--	0.26	
Cellulose diacetate membrane module (Dicea 1701, Baxter Healthcare)	Counter-current	Cellulose diacetate	--	--	$200 \times 10^3$	--	15	non-porous	--	1.7	[36]
Microporous hollow-fiber module	Parallel flow	PP	300	210	--	470	75	45	0.1437	0.0633	[37]
Hollow fiber membrane module Elastomer Products Ltd (Auckland, New Zealand)	Counter-current	PP	40	470	1800	2600	--	--	0.2	0.1	[38]
Single fiber membrane contactor; Porocrit™ (Berkeley, CA)	Counter-current	PP	1	1067	$0.6 \times 10^3$	$1.02 \times 10^3$	--	75	0.2	--	[39]
Microporous hollow-fiber; Liqui-Cel® Extra-Flow module (Charlotte NC, USA)	Counter-current	PP	10 000	150	240	300	--	30	0.03	0.4	[40,41]
hollow fiber Liqui-Cel® Extra-flow 2.5 x 8 module (Hoechst Celanese, Bridgewater, NJ)	Counter-current	PP	35000	150	240	300	--	25	0.03	1.4	[42]

Hollow fiber membrane contactor (2.5x8 X50 Liqui-Cel® module, Membrana, USA)	Counter-current	PP	9800	146	220	300	46	40	0.03	1	[9,43]
PVDF-HFP hollow fiber membrane contactor	Counter-current	PVDF-HFP	60	200	400	600	--	84	0.038		[44]
Hollow fiber membrane contactor (Liqui-Cel® Extra Flow) module	Counter-current	PP	10200	160	240	300	--	40	0.03	1.4	[45]
Hollow fiber membrane contactor (Liqui-Cel® 2.5" × 8" Extra Flow; Membrana-Charlotte Celgard, USA)	Counter-current	PP	10200	250	220	300	--	40	0.03	1.4	[46]
Hollow fiber membrane contactor (Liqui-Cel® X50, 2.5 x 8, Membrana USA)	Counter-current	PP	10000	150	200-240	300	--	40	0.03	1.4	[47]
Hollow fiber membrane contactor (Liqui-Cel®-X50, 4 × 13; Membrana, USA)	Counter-current	PP	48000	270	200-240	300	--	40	0.03	8.1	[47]
Microporous hollow-fiber membrane contactor (5PCM-218, Celgard X-30; Separation Products Division, Hoechst Celanese Corporation, Charlotte, NC)	Parallel flow	PP	10 000	150	240	300	--	--	--	1.4	[48]
Hollow-fiber membrane contactor	Parallel flow	PP	900	358	--	470	75	45	0.1437	0.3237	[37,49]
Hollow-fiber membrane extractors (Celgard X-30, Liqui-Gel Extra-flow 2.5 in. × 8 in., Hoechst Celanese)	Counter-current	PP	800	160	240	--	30	0.4	0.03	1.4	[50]

Membrane contactor (Memo3 GmbH, Switzerland)	Counter-current	PTFE	-	-	$2.97 \times 10^3$	$3.49 \times 10^3$	80	40	0.47	-	[51]
	Counter-current	PTFE	-	-	$2.95 \times 10^3$	$3.11 \times 10^3$	260	54	0.50	-	

## 2.2. Mass transfer in membrane contactors

To illustrate the mass transfer in MC, the solute concentration profiles in solvent extraction from aqueous media with interfaces immobilized in a hollow fiber membrane contactor is shown in Figure 4. Most of the MC extraction modeling relies on the boundary layer model [7].

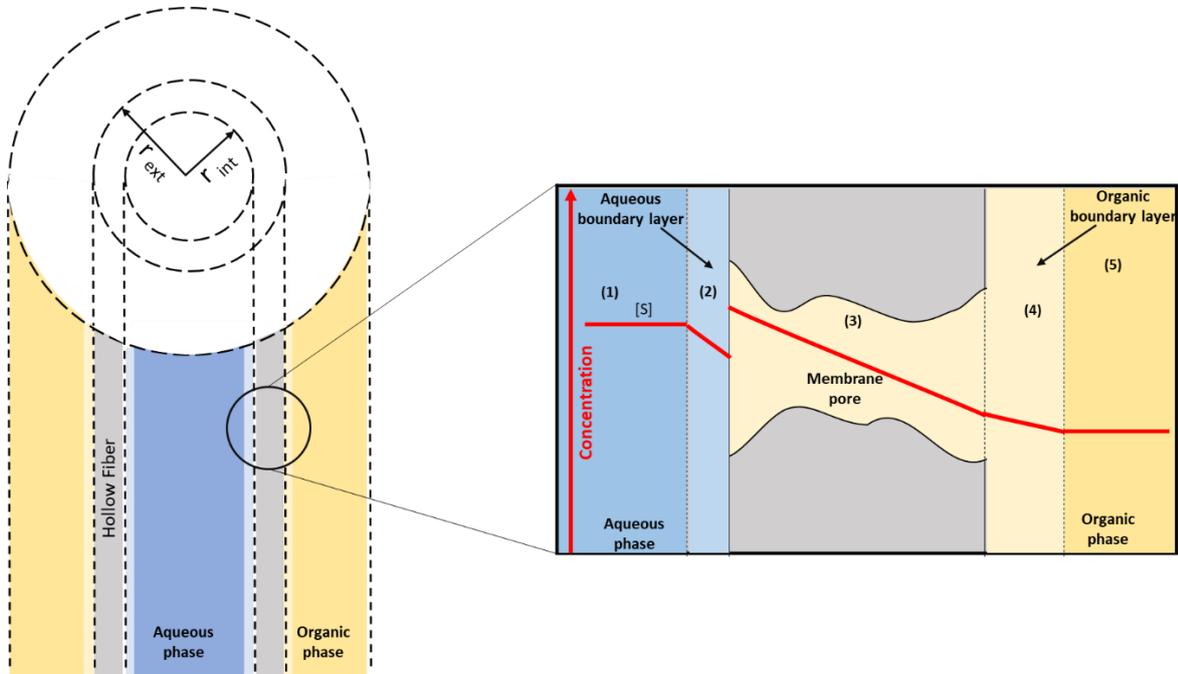


Figure 4: Conceptual view of the boundary layer model in a MC during solvent extraction adapted from [52] with modifications

In an extraction process in MC, the transport is separated into five zones: (1) the aqueous bulk phase, (2) the aqueous boundary layer, (3) the membrane pores, (4) the organic boundary layer and (5) the organic bulk phase.

The mass flux can also be described by an overall mass transfer coefficient. It is then defined as the coefficient of proportionality between the flow and the overall driving force. This latter represents the shift from the thermodynamic equilibrium obtained between the two phases, this equilibrium being determined by the partition (or distribution) coefficient [53,54]. A pseudo steady-state regime can be assumed if no significant accumulation of species occurs in the aqueous boundary layer and in the organic boundary layer due to their comparatively small volume. Thus, the flux can be expressed as follows:

$$J_x = K_x \times A_x \times ([X]_{int} - [X]) \quad Eq. (2)$$

Where,  $J_x$  (kg/s) is the flux of the species  $x$  across the layer of the organic phase,  $K_x$  (m/s) is the mass transfer coefficient of species  $x$ ,  $A_x$  (m<sup>2</sup>) is the surface open to the transfer of species  $x$ ,

$[X]_{int}$  (kg/m<sup>3</sup>) is the concentration of the species  $x$  at the interface,  $[X]$  is the concentration of the species  $x$  in the corresponding bulk and  $x$  is the transferred species.

In the aqueous phase, the flux can be expressed as follows:

$$J = K_{aq,T} \times A \times (C_{aq} - C_{aq}^*) \quad Eq. (3)$$

Where  $J$  is the mass flux,  $K_{aq,T}$  is the mass transfer coefficient in the aqueous phase,  $A$  is the surface open to transfer,  $C_{aq}$  is the bulk concentration and  $C_{aq}^*$  is the interfacial concentration. The equation (3) can also be expressed as follows:

$$J = K_{aq,T} \times A \times \left( C_{aq} - \frac{C_{org}}{D} \right) \quad Eq. (4)$$

Where  $D$  is the partition coefficient (or distribution coefficient in case of reactive extraction) which is defined as the total concentration of the solute in organic solutions divided by that in aqueous solutions (equation (5)):

$$D = \frac{C_{org}^{eq}}{C_{aq}^{eq}} \quad Eq. (5)$$

The configuration most used in the literature to recover organic acids is a hydrophobic hollow fiber with the aqueous phase circulating in the fibers. In this case and assuming the equality of fluxes in the three boundary layers (aqueous, membrane pores, organic) and equilibrium is reached at the interface, it has been shown that the overall material transfer coefficient is given by equation (6) for a constant  $D$ .

$$\frac{1}{K_{aq,T}} = \frac{1}{K_{aq}} + \frac{1}{D_{org}K_m} \times \frac{d_{int}}{d_{lm}} + \frac{1}{D_{org}K_{org}} \times \frac{d_{int}}{d_{out}} \quad Eq. (6)$$

Where  $K_{aq}$  is the local transfer coefficient on the aqueous side,  $K_m$  is the transfer coefficient in the pores of the membrane,  $K_{org}$  is the local transfer coefficient on the organic side,  $d_{int}$  is the internal diameter of the fibers,  $d_{out}$  is the external diameter of the fibers and  $d_{lm}$  is the logarithmic mean diameter of the fibers. The use of the logarithmic mean diameter can be explained by the fact that the fibers have a cylindrical geometry and the transfer area in the fiber wall changes with the radial distance from the axis of the cylinder [7,16]. This expression is widely used in the literature with analogous expression for other configurations and membrane materials [16].

The transport in the pores of the membrane is assumed to be diffusive and therefore the transfer coefficient (Eq (7)) is defined as the ratio between the diffusion coefficient of the solute in the solvent filling the pores and the distance traveled by the solute at inside the pore [16]. Most often, a

corrective term corresponding to the porosity of the membrane is included in the equation to take into account the fact that the transfer surface corresponds only to that opened by the pores.

$$K_m = \frac{\varepsilon D_{is}}{\tau_m e} \quad \text{Eq. (7)}$$

Where  $\varepsilon$  is the porosity of the membrane,  $D_{is}$  is the diffusion coefficient of the solute in the solvent filling the pores,  $\tau_m$  is the tortuosity of the membrane and  $e$  its thickness.

Local mass transfer coefficients in the phases on both sides of the membrane can be estimated using relationships between dimensionless numbers, mainly the Sherwood, Reynolds and Schmidt numbers. For the transfer coefficient in tube side, the subsequent expression (L  v  que's solution) has been shown by several researchers to predict tube side mass transfer coefficients ( $k_{tube}$ ) in MC [55–57] :

$$Sh = 1.62 (Re \times Sc \times \frac{d_{int}}{L})^{0.33} \quad \text{Eq. (8)}$$

$$Sh = \frac{k_{tube} d_{int}}{D_{is}} \quad \text{Eq. (9)}$$

$$Re = \frac{d_{int} v_f}{\nu} \quad \text{Eq. (10)}$$

$$Sc = \frac{\nu}{D_{is}} \quad \text{Eq. (11)}$$

$$k_{tube} = 1.62 \frac{D_{is}}{d_{int}} \left( \frac{d_{int}^2 v_f}{L D_{is}} \right)^{0.33} \quad \text{Eq. (13)}$$

Where  $L$  is the length of the tube,  $v_f$  is the flow rate in the tube side,  $D_{is}$  is the diffusion coefficient of the solute in the solvent filling the pores,  $d_{int}$  is the internal diameter of the fibers.

For the transfer coefficient in the fluid contained in shell side, a multitude of correlations have been developed based on the following expression:

$$Sh = \alpha \times Re^\alpha \times Sc^{\alpha\beta} \times f(\text{geometire}) \quad \text{Eq. (14)}$$

Where  $\alpha$  is a proportionality coefficient and  $f(\text{geometire})$  is a factor linked to the geometry of the module used [7,55–57]. Equations for predicting individual mass transfer coefficients in different modules and geometries of MC were reviewed in detail by [7].

Based on the above equations, it appears that hydrodynamic conditions with high  $Re$  increase the mass transfer coefficients. However, the implementation of such conditions comes with high fluids flowrates which induce high pressure levels in the streams feeding the MC, a fact that has to be taken

into account to ensure the interface stability. Accordingly, the design of the MC module is a key aspect [58].

The inverse of the global transfer coefficient is defined as the overall transfer resistance ( $R_T$ ) which depends only on three independent terms: resistance on the aqueous side ( $R_{aq}$ ), resistance in the membrane side ( $R_m$ ) and resistance on the organic side ( $R_{org}$ ).

$$R_T = \frac{1}{K_{aq,T}} \quad Eq. (15)$$

$$R_{aq} = \frac{1}{K_{aq}} \quad Eq. (16)$$

$$R_m = \frac{1}{D_{org} K_m} \times \frac{d_{int}}{d_{lm}} \quad Eq. (17)$$

$$R_{org} = \frac{1}{D_{org} K_{org}} \times \frac{d_{int}}{d_{out}} \quad Eq. (18)$$

It is then obvious that if the partition or distribution coefficient of the solute is very high, the resistances of the membrane and of the organic phase may be negligible, which has been observed experimentally by D'elia et al. [53].

### **3. Membrane assisted liquid-liquid extraction of aroma compounds from liquid effluents**

#### **3.1. Liquid-liquid extraction with MC from liquid food wastes**

Aroma compounds are small molecules with a molecular weight generally lower than 400 g/mol. They are characterized by their hydrophobicity and their volatility. In food industries, these compounds often generate odorous effluents, which may be a source to recover volatile valuable compounds of natural origin. The treatment of this kind of effluents must take into account the physicochemical properties of these molecules in order to propose a non-destructive process that could permit, the deodorization, and also the recovery of a valuable aromatic fraction in order to refund totally or partially the cost of the treatment.

The application of membrane contactors process in the recovery of aroma compounds from liquid effluent streams, especially from food industry, represents a promising solution for the valorization of these by-products. It allows the preservation of the molecular integrity of aroma compounds as no high temperatures are needed, furthermore, the process is easy to implement and operate.

Recently, Cao et al. (2021) [59] have compared the impact of solvent type, the aqueous solution pH, feed flow rate on the vanillin extraction in MC. In addition, membrane specifications, such as fibers length and number, as well as porosity-to- tortuosity ratio, were investigated. The lowest pH value of 7 and butyl acetate as solvent gave the best extraction efficiency. The feed flow rate played considerable role for vanillin extraction and it was significantly decreased with increasing it from 1 L/h to 4 L/h (Eq. 8-14). Also, the results showed that the vanillin extraction is higher when feed entered into the tube side of the MC. In terms of membrane specifications, increasing the fiber length enhanced vanillin extraction largely as it improved interphase mass transfer between two phases as well as increasing feed residence time in the contactor.

Pierre et al. (2001) [60] have studied the extraction of three sulfur aroma compounds (dimethyldisulfide, dimethyltrisulfide, S-methyl thiobutanoate) by *n*-hexane from a dilute aqueous solution representing a food industry wastewater. The extraction was carried out without dispersion of phases using a MC module and with a high extraction efficiency (90-99%). The authors have also suggested that the substitution of *n*-hexane by other extracting solvents, such as natural vegetable oils, avoided issues in terms of food security. In this context, Baudot et al. in (2001) [61] have tested sunflower oil as an extracting phase for eight aroma compounds through a MC from model aqueous solution. The authors have found that the extraction of the aroma compounds was more efficient when flowing the sunflower oil in the hydrophobic fibers than inside the shell side as the mass transfer of aroma compounds was more efficient in the shell side than in the lumen side. In fact, for aroma compounds presenting a partition coefficient (Eq.5) smaller than 100, the resistance in the membrane pores filled with the solvent or in the solvent was the greatest one. They explained this phenomenon with lower diffusivities of these species in the solvent than in the aqueous feed (10 times lower) [61]. The same tendency was confirmed by Bocquet and co-workers in 2006 [62] who have shown that, when the feed flows inside the shell, the extraction is enhanced for aroma compounds presenting a high partition coefficient. For compounds with a low partition coefficient, similar results are obtained whatever the configuration. Miglyol, which is considered as an edible oil composed of a mix of triglycerides of the fractionated vegetable fatty acids C<sub>8</sub> and C<sub>12</sub>, was tested as a extracting phase for ten aroma compounds [63]. This solvent has the advantage to be used in the food industry, and to be low soluble in water. In 2004, Souchon and co-workers have found that miglyol presents a higher partition coefficient for dimethyl disulfide (DMDS) than hexane. However, the best kinetic of extraction in MC was observed with hexane. This advantage of hexane was explained by its lower viscosity, leading to a higher diffusivity of DMDS in hexane than in miglyol. In fact, when using viscous solvents, the membrane mass transfer resistance becomes higher than for the extraction with low viscous solvent. This resistance is considered as the mass transfer limiting step [63]. To avoid membrane mass

transfer resistance, the choice of the extracting phase should take into account its good affinity for the solute to extract, its ability to wet the membrane, as well as the low viscosity of the extracting phase. Another process parameter that can be of importance is the wall thickness of the fibers. Using a MC with a lower wall thickness of the fibers could induce a lower mechanical resistance of fibers. This module leads to a decrease of the resistance in the membrane which is negligible for a solute with high partition coefficient, but quite important for a solute with low partition coefficient [62]. The porosity to tortuosity ratio of the fibers and solvent flow rate have no effect on the extraction of aroma compounds having larger partition coefficients [64]. The summary of the several works on the extraction of aromatic compounds by membrane contactors using different organic phases at various conditions are detailed in Table 2.

### **3.2. Liquid-liquid extraction with MC from bioconversion media**

Many natural compounds used as flavours and aromas, such as 2-phenylethanol (2-PE), can be produced, both synthetically and biotechnologically, or extracted from natural resources. 2-Phenylethanol is a high-value aroma compound with a rose-like odor and is used widely in flavor and fragrance compositions [65,66]. Although for most applications, natural flavors are preferred, due to limited natural resources for 2-PE, biotechnological production of this molecules is essential. The production of 2-PE, through the bioconversion of L-phenylalanine by yeasts has been studied in several works [27,28,67–73]. One of the main limitations of this bioconversion is the inhibition of yeast growth by 2-PE. To overcome this inhibition and to increase the production of 2-PE during bioconversion, an In-Situ Product Recovery (ISPR)-based strategy using MC was implemented by several authors [27,28,70]. Recently, Cordero-Sonto and co-workers in (2021) have succeeded in intensifying the bioproduction of 2-PE by coupling the bioconversion of L-phenylalanine by *Kluyveromyces marxianus* ITD0090 with LLE extraction assisted by MC of 2-PE using oleyl alcohol as solvent. This ISPR configuration (in loop set-up with counter-current LLE) allowed the continuous recovery of the 2-PE produced, reaching a final concentration of 3.02 g/L after 56 h. The whole process was then refined by 80-85% [70]. Mihal et al. (2013) [28] improved the production of 2-PE by *S. cerevisiae* by combining the membrane extraction with continual extractant regeneration by distillation reaching a high conversion rate of L-phenylalanine (up 100%) and high volumetric production of 2-phenylethanol (up to 18.6 g/L). Adler et al. (2011) evaluated the bioproduction of 2-PE by *Kluyveromyces marxianus* CBS600 in an ISPR configuration using miglyol as solvent. The obtained results have shown an improvement in the concentration of 2-PE, from 1.4 g/L in conventional fermentation to 4.0 g/L in the intensified process by LLE in MC [27].

Table 2: Application of MC for the recovery of aroma compounds from aqueous media

Aroma compound	Aqueous phase	Organic phase	Membrane contactor module	Extraction conditions	Yield	Reference
Dimethyldisulfide Dimethyltrisulfide S-methyl thiobutanoate	Model aqueous solutions representing real effluent	<i>n</i> -hexane	MC (2.5x8 X40 Liqui-Cel® module)	Tube side: aqueous phase Shell side: organic phase T (°C): ambient	90-99%	[60]
Butanal 2-butanone <b>trans</b> -2-Hexenal 2-Hexanone 2-Heptanone Ethyl pentanoate 2-Nonanone Ethyl heptanoate	Model aqueous solutions	Sunflower oil	MC (2.5x8 X30 Liqui-Cel® module)	Tube side: organic phase Shell side: aqueous phase T (°C): 30	--	[61]
Dimethyl disulfide					80% in 15 min 80% in 70 min	
Dimethyl Trisulfide S-methyl thiobutanoate AUyl Isothiocyanate Hexanal Heptanal Benzaldehyde Ethyl butyrate Hexyl acetate Hexanol	Model aqueous solution of ten aroma compounds	<i>n</i> -hexane Miglyol	MC (2.5x8 X40 Liqui-Cel® module)	Tube side: organic phase Shell side: aqueous phase T (°C): 25 Aqueous flow rate = 173 L/h Organic flow rate = 20 L/h	- - - - - - -	[63]
2-phenylethanol Benzaldehyde Ethyl butyrate Dimethyltrisulfide	Model aqueous solutions	<i>n</i> -hexane	MC (2.5x8 X40 Liqui-Cel® module) and	Tube side: organic phase Shell side: aqueous phase Temperature (°C): 25 Aqueous flow rate = 40.2 L/h Organic flow rate = 42.6 L/h	15% (simulated) 67% (simulated) 68% (simulated) 71% (simulated)	[62]
( <b>S</b> )-(+)-carvone Terpinen-4-ol	Model bioconversion solution	<i>n</i> -heptane	MC (Memo3 GmbH, Switzerland) with 3 PTFE hollow-fibers	Tube side: aqueous phase Shell side: organic phase	>90%	[26]

Vanilin	Model aqueous solution	Butyl-acetate Ethyl acetate Diethyl-ether <i>n</i> -Hexane	MC (2.5x8 X10 Liqui-Cel® module)	Tube side: aqueous phase Shell side: organic phase	--	[59]
2.5-Dimethylpyrazine 2-Heptanone Benzaldehyde <i>cis</i> -3-Hexenol Dimethyldisulfide Dimethyltrisulfide Ethyl butyrate Ethyl hexanoate $\gamma$ -Decalactone Hexanal Hexanol Isoamyl acetate Isoamyl alcohol Linalool Terpineol	Model aqueous solution	<i>n</i> -Hexane	MC (2.5x8 X40 Liqui-Cel® module) and	Tube side: organic phase Shell side: aqueous phase T (°C): 25 Aqueous flow rate = 120 L/h Organic flow rate = 60 L/h	--	[74]

Vanillin is another example of aroma compound produced biotechnologically and that exhibits an inhibition effect towards the production cells. In fact, vanillin has a toxic effect and can be further transformed to vanillyl alcohol or vanillic acid [75]. Thus, the productivity of vanillin in bioconversion can be potentially enhanced by its continuous removal. Sciubba et al (2009) have highlighted the potential of application MC for the in-situ extraction of vanillin obtained by bioconversion of ferulic acid from the bioconversion broth using butyl acetates as solvent. Additionally, MC can be applied to the re-extraction of vanillin from the solvent by water at high pH, leading to concentrated aqueous solutions, thus simplifying the downstream processing [76].

The choice of the extraction solvent is considered as a critical point for the implementation of the ISPR process of biomolecules from bioconversion media. The selected solvent should have a high partition coefficient for the targeted compounds, no destructive effect on the experimental equipment, and low toxicity to microorganisms. Many solvents have been used for the extraction of aromatic compounds from bioconversion broths (Table 3). Heptane and pentane were used as organic solvents due to their hydrophobicity to the membrane, immiscibility in water, relatively low boiling temperature, and very low corrosivity to the membrane module materials compared to other solvents [77]. According to the toxicity test of pentane and heptane for yeast, pentane was chosen as a suitable extractant. Moreover, it has a low boiling point (36 °C), which is an advantage for its regeneration [28]. Other authors used oleyl alcohol and miglyol because of their biocompatibility (Table 3). Choosing the best solvent for the ISPR process is often complicated, since it is very rare to find a solvent that meets all the criteria at the same time. Recently, a solvent selection strategy was adapted for the liquid-liquid extraction of *p*-coumaric acid produced by an engineered strain of *Saccharomyces cerevisiae* [78]. The strategy consists in scoring different solvents based on different criteria such extraction performance, solvent biocompatibility and compatibility with materials. In this case, oleyl alcohol obtained the highest score and was therefore considered as the most suitable solvent for an ISPR process aiming at continuously extracting *p*-coumaric acid from the fermentation medium [78]. The selection of solvents could be based on the octanol-water partition coefficient ( $\log_{10}P$ ), which can be considered as an indicator for solvent toxicity [79,80]. Solvents having a  $\log_{10}P > 5$  are generally biocompatible for cellular biocatalysis [81]. Recently, Gössi et al. (2020) [25] have selected nine solvents for the in-situ removal of carboxylic acids from fermentation broth based on their  $10\log(P_{\text{octanol}})$ . An organic phase of 20 w/w% TOA in *n*-decanol was then selected due to its low toxicity and the high extraction efficiency.

Quantum chemistry calculations with simulation tools, such as COSMO-RS can also be used to predict the partition coefficient of compounds in various solvent systems. In this context, Janoscsek et al, in 2018 [26] demonstrated that combining in silico prediction by COSMO-RS with hollow fiber

membrane-assisted extraction is a promising approach for the recovery of hydrophobic compounds from aqueous solutions. The authors selected the appropriate solvent to extract (S)-(+)-carvone and terpinen-4-ol by predicting and validating the partition coefficient of these compounds in different solvent-water systems using the COSMO-RS simulation tool. In addition, COSMO-RS can also be used for solubility prediction in liquid-liquid systems in the presence of salts and glycerol which are typical media components in biotechnological processes.

For further decrease of the solvent's toxicity towards microorganisms, and to facilitate the implementation of the ISPR process, the use of hollow fiber membrane contactor as an extraction interface represents a promising way. In fact, the contact between the aqueous phase and the organic phase takes place *via* a membrane, so the contact area is small compared to LLE [11,82,83]. In addition, the size of the pores of the membrane being smaller than that of bacterial cells, they cannot pass into the organic phase [84].

Aroma compounds produced biotechnologically are not dissolved in water but in more complex medium, containing salts, proteins and other components. Biotechnologically produced hydrophobic substances must often be extracted from such complex media. Therefore, it is important to take into account the effect of the medium on the solubility of the desired substances, and therefore their extraction.

Table 3: Application of MC for the recovery of aroma compounds from bioconversion media

Aroma compound	Substrate	Microorganism	Organic phase	Membrane contactor module	Extraction conditions	Yield	Reference	
1-phenylethanol	Acetophenone	<i>Saccharomyces cerevisiae</i>	Pentane	MC MICRODYN® MD 020CP2N	Tube side: aqueous phase Shell side: organic phase T (°C): 30 pH 5 Aqueous flow rate = 69 L/h Organic flow rate = 6 L/h	Yield of (96%) and mean reaction rate of 0.226 mg/h/g	[77]	
1-Phenylethanol	Acetophenone	--	Heptane Toluene Ethyl acetate	VL-120PP-FOB Small Laboratory MC GE Osmonics (Trevose, USA)	Tube side: organic phase Shell side: aqueous phase T (°C): 25	--	[33]	
Vanillin	Ferulic acid	<i>Escherichia coli</i>	Butyl Acetate	MC (2.5x8 X10 Liqui-Cel® module) Accurel PP Q3/2 (Cap06 module)	Tube side: aqueous phase Shell side: organic phase T (°C): 30 pH 7	Aqueous flow rate = 50 L/h Organic flow rate = 50 L/h Aqueous flow rate = 45 L/h Organic flow rate = 25 L/h	--	[76]
2-Phenylethanol (PE) 2-Phenylethylacetate (PEA)	L-phenylalanine	<i>Kluyveromyces marxianus CBS 600</i>	Miglyol	MC GmbH (Wuppertal, Germany)	Tube side: aqueous phase Shell side: organic Phase Aqueous flow rate = 18 L/h Organic flow rate = 6 L/h T (°C): 33 pH 4	4.0 g/L 2-PE + 2-PEA vs 1.4 g/L in conventional fermentation	[27]	

2-Phenylethanol	L-Phenylalanine	<i>Kluyveromyces marxianus</i> ITD0090	Oleyl alcohol	MC (2.5x8 X50 Liqui-Cel® module)	Tube side: aqueous phase Shell side: organic phase Aqueous flow rate = 0.58 L/h Organic flow rate = 0.76 L/h T (°C): 30 pH: 5		[70]
2-Phenylethanol	L-Phenylalanine	<i>Saccharomyces cerevisiae</i>	Pentane	Accurel® PP S6/2 (MEMBRANA GmbH)	MC immersed in an airlift reactor Organic phase flow through the membrane module: 9 L/h T (°C): 25	conversion rate of 100%	[28]

#### 4. ABE extractive fermentation using MC

Butanol is a precursor of many industrial chemicals, and a fuel that is more energetic, safer and easier to handle than ethanol. It can be sustainably produced from several renewable biomass resources, including lignocellulosic ones such as agriculture and forest wastes by anaerobic fermentation [85,86]. Industrial synthesis of butanol was first realized during 1912–1914 by acetone–butanol–ethanol (ABE) fermentation of molasses and cereal grains using *Clostridium acetobutylicum* [87].

The ABE fermentation process using *Clostridium bacteria* typically allows production of biobutanol with an A:B:E ratio of 3:6:1 [88]. Since bacterial strains rarely tolerate more than 2 w/w% butanol, its concentration in the final broth will be less than this, and is often around 1.2 w/w% for many strains in use [86]. The low concentration of butanol is one of the main obstacles to biobutanol production at commercial scale, and integrating cost-effective recovery with fermentation is one of the challenges faced by scientists nowadays in trying to commercialize the technology [35].

The separation and purification of butanol fermentation broth is more complex and expensive than classic ethanol recovery from a yeast fermentation broth, due to three main reasons [89]: (1) the butanol concentration in the broth is much lower (about 2 w/w% of butanol compared to 15 w/w% ethanol); (2) the boiling point of butanol/water azeotrope at atmospheric pressure (93 °C) and that of water (100 °C) are very close (compared with 78.2 °C for the ethanol/water azeotrope); and (3) the final distilled butanol concentration in the aqueous azeotrope is only 55.5 w/w% compared to 95.5 w/w% for the ethanol analog [90–92]. Therefore, efficient and inexpensive separation or recovery techniques are highly desirable for biobutanol production in order to enhance its economic efficiency.

The in situ or in stream (ISPR) extraction of butanol is a strategy to reduce the concentration of the toxic butanol in the fermentation broth and therefore maintaining the cells alive and active longer [92]. LLE in MC represents one among many ISPR strategies that have been attempted by many researchers and varied success has been achieved.

The main characteristics for solvent to be used in LLE assisted by MC includes: no or low inhibition to the cell culture growth, high selectivity, high partition coefficient, no emulsion formation, high stability and almost no solubility in aqueous solution. Further necessary characteristics of solvents include low/no harmfulness to the environment, density significantly different from the broth for easy phase separation, low viscosity for less energy consumption during extraction, autoclavability, suitable volatility and commercial availability at low cost [89,92].

Oleyl alcohol is the most studied solvent for in situ ABE extractive fermentations. It is nontoxic and has a relatively good  $K_{D-BuOH}$  (3–4) and good selectivity, although it is nonvolatile [93,94]. Alkanes are just slightly toxic and highly selective, but their  $K_{D-BuOH}$  is generally low. The more lipophilic the

solvent, the lower the solvent concentration in the aqueous phase. It results in a low interaction of the solvent with cell membrane, low dispersion in growth media, low toxicity, but also low butanol extraction capability [94]. Aromatic hydrocarbons demonstrate a better  $K_{D-BuOH}$ , especially at high temperatures, but most of them are toxic to cells [95]. More studies about butanol partition coefficient and selectivity of solvents during liquid–liquid extraction with ABE fermentation broth have been recently reviewed by Jiménez-Bonilla & Wang in 2018 [89].

The technical possibilities of the microbial production of ABE from potato waste using in stream solvent recovery with a LLE in MC configuration, were evaluated by Grobbrn et al. in 1993 [34] using a PP MC system and a oleyl alcohol/decane mixture as the extractant, the product yield (based on total solvents and) increased from 0.13 g/g<sub>potato dry weight</sub> to 0.23 g/g<sub>potato dry weight</sub>. The membrane performed adequately for 50h, after which it fouled with the fermentation broth. To overcome the membrane fouling, authors incorporated a microfiltration step and used hydrophilic fibers instead of PP fibers in the first configuration; fatty acid methyl esters from sunflower oil were used as extractant. The new process configuration resulted in a comparable increase of ABE production [34]. In 2005, Qureshi and Maddox [96] used whey permeate as a substrate to produce butanol in batch mode with initial lactose concentration of 227 g/L in the medium. As soon as the ABE level reached approximately 4 g/L, product removal was initiated using a LLE system assisted by MC with oleyl alcohol as an extractant. As a result of reducing product inhibition, the cells utilized all the sugar in the bioreactor, and produced 98.97 g/L ABE, resulting in a yield of 0.44 g of ABE produced per g of lactose used. The authors stated that the batch system could be used for the production of ABE on a large scale without making any cost-prohibitive modifications in the existing distillery's infrastructure [38,96].

Supercritical and compressed fluid technologies have recently been extended to bioprocessing as an alternative to organic solvents. Unlike traditional organic solvents, the solvent strength and selectivity of compressed fluids are easily adjusted with temperature and pressure. Depressurization leads to a solvent-free solute and aqueous phase, which is very important for biologically based separations where solvent toxicity and contamination are serious concerns. In addition, high mass transfer rates are inherent to these processes due to low kinematic viscosities associated with supercritical and compressed fluids [39,97,98].

There have been several studies on the extraction of various organic solutes from aqueous solutions with compressed or supercritical CO<sub>2</sub>. In particular, the extraction of alcohol has been investigated in an effort to reduce energy consumption associated with dehydration and to take advantage of enhanced mass transfer associated with supercritical CO<sub>2</sub> [39,99,100]. Although several studies have proved the ability of CO<sub>2</sub> to extract bioconversion products from aqueous solutions, compressed CO<sub>2</sub> is not biocompatible with most microorganisms, making it a poor solvent for the in

situ extraction of fermentation broths [101]. The combination of supercritical and compressed fluids technology with MC can overcome this issue.

Compressed fluid solvents may be employed in bioprocessing applications where expensive separation steps and residual solvents hinder product recovery. These solvents can be adjusted with temperature and pressure to enhance extraction and provide a basis for selective extraction. Combining the tunability of compressed solvents and the high surface area to volume ratios of MC could also lead to the economical replacement of some organic solvents (hexane) by compressed solvents for the extraction of a variety of natural products.

In 2014, Moreno et al. [35] have investigated the technical feasibility of using supercritical CO<sub>2</sub> in lab-scale as an extracting phase in MC to efficiently recover butanol and acetone from aqueous solutions containing ABE in concentrations typically found in ABE fermentation broths. Two different sizes of MC were tested. They have found that the flow rate of the aqueous phase as well as the CO<sub>2</sub> density, are the key parameters to improve separation efficiency, since the predominant resistance to mass transfer was found in the aqueous phase. In the small contactor (total contact area of 0.04 m<sup>2</sup>), butanol recoveries of 86% were achieved for pressures over 100 bar and long aqueous residence times. The large contactor having the same packing density but a contact area 5.8-fold that of the smaller contactor, achieved 89% recovery under these conditions [35]. Compressed CO<sub>2</sub> (69 bar) and propane (34.5 bar) at ambient temperature have been used within a MC to study the feasibility of extracting aqueous ethanol and acetone as a model fermentation products [39]. The authors have found that the aqueous flow rate (tube side) and molar solvent to feed ratio have an important effect on the performances of the extraction. At the optimal conditions, compressed propane gave a yield of 14.3% and 90.6% for ethanol and acetone, respectively. Comparatively, compressed CO<sub>2</sub> was more effective, the yield was about 31.9% and 96.1% for ethanol and acetone, respectively [39]. The details of the aforementioned studies are presented in the Table 4. The MC used with supercritical CO<sub>2</sub> as the extracting phase are designed to withstand high pressures. For the ISPR of butanol, the conventional HMFC and organic phase are used (Table 4).

Table 4: Application of MC for extraction of acetone, butanol and ethanol from ABE fermentation broth

Compound	Aqueous phase	Microorganism	Organic phase	Membrane contactor module	Extraction conditions	Yield	Reference
Butanol	Aqueous model solution with concentrations equivalent to an ABE fermentation broth	--	Supercritical CO <sub>2</sub>	Microporous hydrophobic isotactic (semicrystalline) PP with 70% porosity (Memtec, Australia)	Tube side: Supercritical CO <sub>2</sub> (100 bar and 40 °C) Shell side: Aqueous phase T (°C): 40 °C	-The small contactor, butanol recoveries of 86% -The large contactor having a contact area 5.8-fold that of the smaller contactor, achieved 89%	[35]
Butanol	Fermentation broth (potato waste)	<i>Clostridium acetobutylicum</i> DSM 1731	A mixture of 50% (v/v) oleyl alcohol and 50% decane	Hollow fiber membrane module (Microdyn, Wuppertal, Germany)	Tube side: organic phase Shell side: fermentation broth T (°C): 37 °C Organic phase flow rate: 15 L/h Aqueous phase flow rate: 10 L/h	The product yield increased from 13% to 23%	[34]
Butanol	Fermentation broth (whey permeate medium, supplemented with lactose)	<i>Clostridium acetobutylicum</i> P262	Oleyl alcohol	Hollow fiber membrane module Elastomer Products Ltd (Auckland, New Zealand)	Tube side: organic phase Shell side: fermentation broth T (°C): 35 °C Organic phase flow rate: 15 L/h Aqueous phase flow rate: 25.5 L/h	ABE (98.97 g/l) were produced from lactose (227 g/l) at a yield of 0.44 and productivity of 0.21 g/L/h	[96]
Ethanol Acetone	Model fermentation products (dilute aqueous ethanol and/or acetone (10 w/w%))	--	CO <sub>2</sub> (69 bar)	Single hollow fiber membrane contactor Porocrit™ (Berkeley, CA)	Tube side: aqueous phase Shell side: organic phase T (°C): ambient	Yield of extraction: 31.9 % ethanol 96.1 % acetone	[39]

## **5. Application of MC in Aqueous Two-Phase Systems**

Aqueous Two-Phase System (ATPS) is an attractive liquid-liquid extraction method that employs two immiscible aqueous phases for the separation and purification of biological materials, including proteins, enzymes, nucleic acids, virus, antibodies, and cell organelles in the biotechnology field. ATPS is widely used due to its ability to preserve biological activity and maintain the stability of the extracted components. However, conventional ATPS requires phase separation, which can be time-consuming and costly [102]. To overcome this challenge, MC can eliminate the need for phase separation by allowing direct contact between the two aqueous phases, which enhances the efficiency of the extraction process. In 2008, Riedl et al., [103] investigated the application of MC technology for the extraction of BSA and lysozyme using an ATPS system consisting of PEG/Phosphate, a surfactant (Tween-20), and a hydrophobic membrane (Liqui-Cel X40). This setup allowed for successful extraction cycles without any technical problems, and for the generation of kinetic data of the extraction process.

Combining ATPS with MC offers numerous advantages and makes it a promising alternative to downstream purification steps such as chromatography. The technique provides enhanced selectivity and specificity and can be easily adapted to various biological materials. Furthermore, MC-based ATPS technology can be scaled-up easily, making it suitable for large-scale and cost-effective purification of biological material [103].

## **6. Case study: Application of membrane contactors for the recovery of organic acids**

### **5.1. Recovery from fermentation broths**

Recently, many carboxylic acids have been produced from the fermentation of carbohydrates such as glucose [11,25], but also glycerol [9,10,84]. After the production step, the recovery of these acids is necessary.

#### **6.1.1. Limitation of the productivity due to acid accumulation**

The accumulation of organic acids leads to acidification of the medium which makes it toxic to microorganisms. Thus, this accumulation in the medium is the main cause limiting the maximum concentration of product that can be reached during fermentation [104,105]. Therefore, the extraction of these acids from the fermentation broth at the same time as their production is a relevant strategy to reduce the inhibitory effect and improve the production yields of these acids. Continuous removal of acids from the fermentation broth will then be preferred over batch processing. Indeed, continuous elimination allows (1) an increase in the productivity and yield of microorganisms due to a decrease in

the inhibitory effect of the products [104,106], and (2) a pH regulation of the bioreactor without equimolar addition of base [105,107].

### **6.1.2. Toxicity due to the solvents during LLE**

The use of liquid-liquid extraction for the removal of organic acids can lead to problems of toxicity of the organic phase towards microorganisms [108–110]. Indeed, the aqueous phase containing the target acid and the microorganisms is in direct contact with an organic phase containing the extractant and the diluent. To minimize this toxicity, and to maintain an acceptable extraction performance (extraction yield and viscosity), it is important to implement a solvent selection strategy to find the adequate organic phase for an ISPR process during fermentation [78,109,111].

In 2020, Sánchez-Castañeda et al. [109] have adapted an organic phase (a mixture of extractant and diluent) screening methodology in order to select an adequate composition of the organic phase for in-stream extraction of 3-HP produced by *L. reuteri*. The authors have found that an organic phase composed of a mixture of 20% TOA, 47% dodecanol and 33% dodecane gave the best compromise between extraction yield, viscosity and biocompatibility.

### **6.1.3. Studies on MC to reduce the toxicity issues**

One of the first studies to reduce phase toxicity and inhibition of organic acids using MC dates to 1998. Jin and Yang [112] implemented MC during bioconversion of lactose by *propionibacterium acidipropionici* in propionic acid. Thus, they suppressed the phase toxicity of trioctylamine (TOA) in oleyl alcohol and the inhibition of bioconversion by propionic acid. Under these conditions, the bioconversion process remained stable for 1.5 months.

The prevention of phase toxicity by MC has also been highlighted by Gössi et al. [25]. The authors used a MC during the bioconversion of glucose into lactic acid. They found that the use of this type of contactor reduced the toxicity of the solvent (20% w/w TOA in *n*-decanol) during the continuous recovery of lactic acid. The bioconversion was thus able to run for 5 days with a rate of 80%. In the absence of MC protection of the microorganisms against the solvent (phase toxicity), less than 0.1% of lactic acid is formed [25]. Similarly, no microbial contamination in the bioreactor, nor any cross contamination between the two phases, were observed during the 2-week of butyric acid production by fermentation of glucose with *C. tyrobutyricum* [113]. The use of HMFC during reactive fermentation of butyric acid not only reduced product inhibition, but also allowed cells to produce more butyric acid from glucose through a change in metabolic pathway to butyrate formation, instead of other by-products such as CO<sub>2</sub> and acetate [50].

In 2017, Nelson et al. [114] obtained a very high productivity of butyric acid and hexanoic acid (0.26 g/L/h) during the fermentation of glucose and a lignocellulosic hydrolysate with *Megasphaera elsdenii*. The toxicity of the acids produced (acidification of the medium) was avoided by reactive extraction of the acid using a MC over 230 h [107]. MCs have also been used to prevent inhibition of *Clostridium kluyveri* due to the accumulation of *n*-caproic acid during its production from yeast-fermentation beer. Bioconversion was carried out over a period of 55 days with two MCs modules (small and large) [114].

In 2017, Burgé et al. [84] studied the toxicities generated using a MC for the bioconversion of glycerol into 3-hydroxypropionic acid by *Lactobacillus reuteri* DSM 17938. They observed that the phase toxicity in MC is more important to cells than the molecular toxicity. In fact, the use of *n*-decanol with TOA (20 v/v%) as organic phase in the shell side of the MC induced a high loss of cell viability (27% of viable cells after 0.5 h, 20% after 1 h, 10% after 2 h and only 3% after 3 h). To overcome this problem, they suggested a better control of the interfacial stability in the membrane contactor by changing membrane material or by reducing the interfacial tension of the system. The authors achieved a higher productivity of 7.73 g/L.h which was attributed to the ability to overcome the solvent toxicity (10 v/v% Alamine 336 in oleyl alcohol) and to enhance extraction efficiency using immobilized cells and hollow-fiber membrane extractors. Table 5 recaps the studies dealing with the application of MC in the recovery of bio-based organic acids from biotransformation media.

ISPR is an approach very often used during the implementation of fermentation processes. ISPR can be performed using various techniques of recovery. According to the studies reported in this section, the implementation of a liquid-liquid extraction of organic acids assisted by MC in a relevant ISPR approach. Indeed, it has been shown that it is possible to increase the productivity of the bioreactors while avoiding any toxicity towards microorganisms.

As shown in Figure 5, the MC can be used for various purpose: the extraction of organic acids and the regeneration of the organic phase.

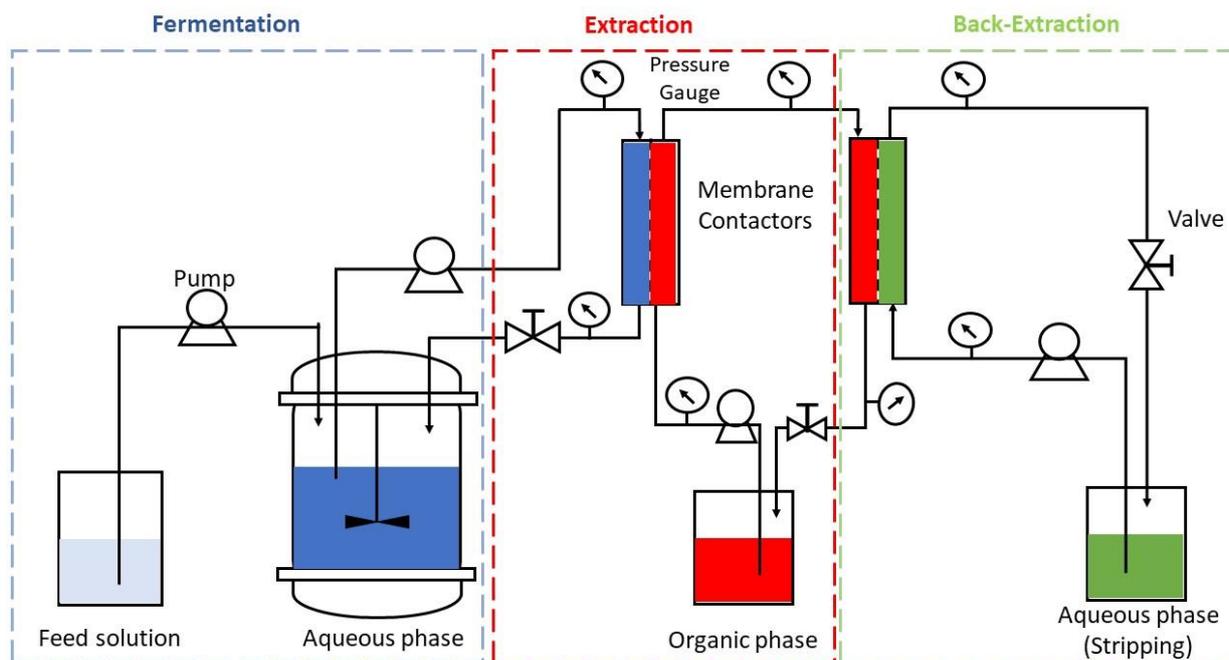


Figure 1: general scheme for liquid-liquid extraction by MC in an ISPR configuration

Table 5: Application of MC in the recovery of bio-based organic acids from biotransformation media

Organic acid	Source	Microorganism	Organic phase	Reference
<i>p</i> -Coumaric acid	Fermentation of glucose	<i>S. cerevisiae</i> (AGB010)	Oleyl alcohol	[115]
Lactic acid	Fermentation of glucose	<i>Lactobacillus plantarum</i> (DSMZ 2648)	20 w/w% TOA in <i>n</i> -decanol	[25]
3-Hydroxypropionic acid	Bioconversion of glycerol	<i>Lactobacillus reuteri</i> DSM 17938	20 v/v% TOA in <i>n</i> -decanol	[9]
3-Hydroxypropionic acid	Bioconversion of glycerol	<i>Lactobacillus reuteri</i> DSM 17938	20 v/v% TOA in <i>n</i> -decanol	[84]
Acetic acid Propionic acid Butyric acid Valeric acid Caproic acid	Fermentation of thin stillage from industrial wastewater	Yeast	Aliquat 336 in 1-octanol in molar ratio of 1:2	[116]
<i>n</i> -Caproic acid	Fermentation of yeast fermentation beer	<i>Clostridium kluyveri</i>	Light mineral oil and 3% tri- <i>n</i> -octylphosphineoxide	[114]
Acetic acid Propionic acid Butyric acid Valeric acid Caproic acid	Mock bioreactor solution	--	50% Cyanex 923 and 50% mineral oil	[105]
Butyric acid Hexanoic acid	Fermentation of glucose and lignocellulosic hydrolysate by <i>Megasphaera elsdenii</i>	<i>Megasphaera elsdenii</i>	10 v/v% TOA in oleyl alcohol	[107]
Lactic acid	Synthetic fermentation solution	--	Reactive extraction of lactic acid at the fermentation conditions	[48]

## 6.2. Recovery of organic acids from aqueous media

Organic acids present in aqueous media can be either products or by-products of a reaction, or a pollutant in industrial wastewater. Their recovery is essential whether to purify them, concentrate or prevent environmental pollution.

MCs have been used for the extraction of organic acids from aqueous media. Fumaric acid has been recovered from industrial wastewater by a MC using trialkylamine as extractant [37]. An integrated process combining MC and reverse osmosis for the back-extraction made it possible to recover fumaric acid [49]. Benzoic acid was extracted from a model solution replicating wastewater using hydrophobic MC with a removal efficiency of up to 95% [46]. In 2015, Moraes et al. [36] achieved the extraction of succinic acid by implementing a system containing two coupled hollow fiber modules allowing simultaneously the extraction of the acid from an aqueous phase to an organic phase and its back-extraction from this organic phase towards the stripping phase. The acid recovery rate was multiplied by 5 compared to a conventional MC approach. A total recovery close to 50% is then obtained.

The use of MC for the recovery of organic acids from fermentation broths is a relatively emerging application that faces specific challenges as compared to their recovery from aqueous solutions. Firstly, the toxicity towards the microorganisms must be taken into account when choosing the extraction phase, which may restrict the use of extractants with high distribution (or partition) coefficients. Secondly, pH conditions have to be a tradeoff between the optimum level for extraction and the optimum one for the microbial the activity. A further consideration deals with the broth complexity that rises potential competition phenomena, hindering the acids' extraction. Table 6 recaps the process of extraction of organic acids from different sources using various extracting phases.

Table 6: Application of membrane contactor for the recovery of organic acids from aqueous media

Organic acid	Source	Extracting phase	Process of extraction	Reference
Succinic acid	Aqueous solution	10 w/w% Primene JM-T1 in 1-octanol	Recovery process of succinic acid by two MC integrating both extraction and back-extraction steps	[36]
3-Hydroxypropionic acid	Aqueous solution	20 v/v% TOA in 80% <i>n</i> -decanol	Reactive LLE of aqueous of 3-hydroxypropionic acid	[10]
Fumaric acid	Industrial wastewater	Trialkylamine 0.7137mol/L in kerosene/ <i>n</i> -octanol at the volume ratio of 7/6	Transport (reactive extraction) of a carboxylic acid through a MC with strip dispersion	[37]
Succinic acid	Aqueous solution	30% (v/v) TOA–TPA 2:8 (TOA: TPA) in 1-octanol	Reactive LLE using MC	[45]
Benzoic acid	Model solution replicating wastewater	0.12M TOA diluted in 1-octanol 5% (v/v)	Reactive LLE using MC	[117]
Acetic acid Formic acid Phenylacetic acid	Aqueous solution	1 w/w% TOPO in dodecane	LLE of a carboxylic acid through MC with back-extraction	[47]
Fumaric Acid	Industrial wastewater	Trialkylamine 0.7137 mol/L in kerosene/ <i>n</i> -octanol at the volume ratio of 7/6	LLE of fumaric acid by an integrated process MC-strip dispersion with reverse osmosis	[49]
Succinic acid	Aqueous solution	10 w/w% Primene JM-T1 in 1-octanol	LLE of succinic using a MC with a re-extraction step	[36]
Formic acid Acetic acid Propionic acid	Aqueous solution	Ethyl acetate, and diisopropyl ether	Physical separation of carboxylic acids using three different MC made of polysulfone, polyethersulfone, and polyvinylidene fluoride	[118]

Aqueous solution: model solution of organic acid

In the biomedical field, organic molecules with acidic properties have raised specific challenges for their removal from aqueous streams. Indeed, since these molecules are broadly used for human, veterinary and agriculture purposes, they can be discharged into the environment through wastewaters [119]. Studies have shown that antibiotics cannot be totally removed during biological treatment processes and can be maintained in the receiving water systems [44,120,121]. The presence of antibiotics in the environment is of concern due to their potential to promote bacterial resistance, as well as trigger long term adverse human health effects [119]. They can cause unpleasant odor, skin disorder, and may cause microbial resistance among pathogen organisms or the death of microorganisms which are effective in wastewater treatment. For these reasons, antibiotic waste needs to be treated before being disposed of in the environment.

Generally, the concentration of antibiotics in hospital and urban wastewater is in the range of 0.3 to 200  $\mu\text{g/L}$  [122,123]. LLE assisted by MC is considered as the technology of interest for chemical and environmental engineers in the treatment of wastewater containing low concentrations of metal ions, pharmaceuticals and organic compounds [124–126].

Amoxicillin, 6-(*R*)-hydroxy- $\alpha$ -amino phenyl acetamido) penicillanic acid, is a  $\beta$ -lactam antibiotic that has a broad in vitro spectrum against gram-negative and gram-positive bacteria, as well as good absorption and penetration into tissues. It is a type of frequently used antibiotic to treat several infections [127]. The LLE assisted by MC of amoxicillin was investigated by Pirom et al. [40–42]. The transport mechanism and separation of amoxicillin during a LLE assisted by MC are illustrated in Figure 6.

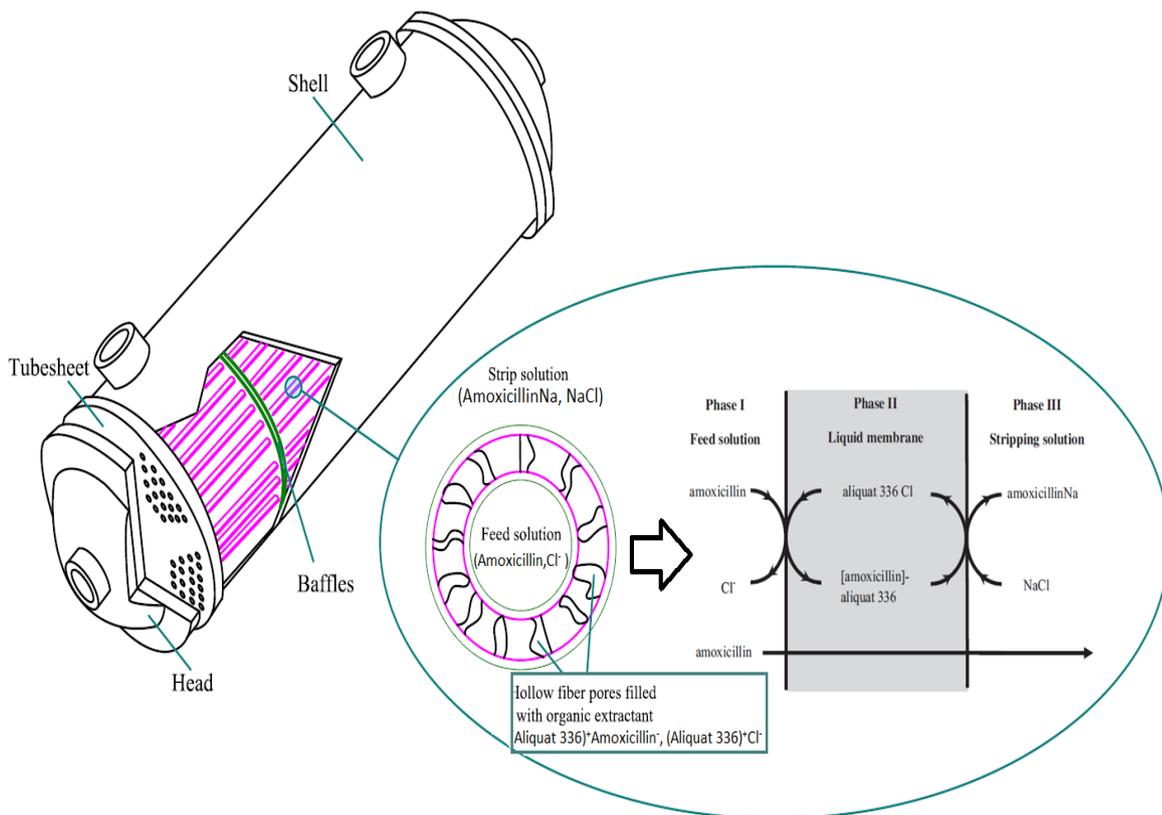


Figure 6: Transport mechanism of amoxicillin using Aliquat 336 as the extractant in a MC (membrane supported reactive extraction) [40,41]

The membrane pores are filled with an organic extractant. The membrane separates the feed and the stripping phases. At the feed–membrane interface, the amoxicillin reacts with the extractant (Aliquat 336) to form complex species. Subsequently, the complex species diffuse across the extractant filling the membrane pores and react with the stripping solution at the membrane–stripping interface. Then, they are stripped into the stripping phase.

In 2017, Primo et al. [42] have studied the effect of the type of extractant as well as diluent, length of hollow fibers and operating time on the permeation coefficient of amoxicillin. In order to determine the effective length of the hollow fibers, authors have compared the permeation coefficient of amoxicillin at three hollow fibers lengths (15, 30 and 45 cm) using single, double and triple MC modules. Data showed that increasing the hollow fiber length results in a lower amoxicillin pertraction. This implies having MC modules in series is effective in increasing surface area but results in decreasing the permeation coefficient of amoxicillin. Thus, the length of hollow fiber which provided the highest permeation coefficient of amoxicillin was 15 cm. Regarding the extractant and the diluent, the authors have found that Aliquat 336 is the best extractant, better than Alamine336 or di(2-ethylhexyl) phosphoric acid; 1-decanol as diluent loaded with Aliquat 336 showed the best permeation coefficient.

The permeation coefficient increased following the order of chloroform/ethylene dichloride/dichloromethane/benzene/1-decanol [42].

In 2015, Primo et al. [40] have studied the effects of parameters such as pH, feed concentration, carrier concentration, and flow rates of feed and stripping solution, which influence the effective separation of amoxicillin by using LLE assisted by MC technology based on Aliquat 336 as an extractant. At optimal conditions (pH 8; 6 mmol/L of amoxicillin; 6 mmol/L of Aliquat 336 in decanol and 6 L/h for feed and stripping solutions) the percentages of extraction and recovery of amoxicillin from the feed phase reached 85.21% and 80.34%, respectively. In another work, Primo et al. (2015) [41] have found that temperature is an influential tool for governing and adjusting the performance for the separation of amoxicillin from aqueous solution. It was found that by increasing the temperature of the system from 5 to 45 °C, extraction of amoxicillin increased from 81.81% to 89.65% and the stripping of amoxicillin increased from 76.63% to 84.70%, respectively. The effect of temperature was attributed to a fast diffusion rate at higher temperature, resulting in a decrease in viscosity of the target solution which improved the penetration of the aqueous matrix and the extraction. Furthermore, higher temperature can reduce the intermolecular force between the solute and distilled water in the feed phase which contributes to an easier interaction of solute with the extractant at the feed-membrane interface [41,128].

Penicillin G (Pen-G) is one of the most widely used antibiotics because of its bactericidal activity, broad spectrum, low toxicity, and excellent distribution throughout the body. Pen-G is also an important raw material for semisynthetic antibiotics. It has played an important role in medicine since it was commercialized in 1940s [129]. The LLE extraction of Pen-G from aqueous solutions using MC was studied by many authors. Smith and Hossain (2007) applied a pilot-scale PP hollow fiber membrane contactor for extraction and recycling of Pen-G. The effect of pH and temperature of the aqueous feed on the extraction efficiency of Pen-G was investigated. Using an organic phase of 5 w/w% Aliquat 336 in both the solvents Shellsol TK and oleyl alcohol achieved extraction at pH 7 in the range 40–45% within 1 h at a recirculating feed flow rate of 14.4 L/h. The percentage extraction was slightly increased by the operating temperature before reaching a plateau at 25–30 °C [29].

The feasibility of cascade process for Pen-G recovery using PP hollow fiber membrane modules was studied by He et al. (2016). Using aqueous phase flow rate of 2.7 L/h in the shell side and organic phase (7 v/v% di-*n*-octylamine + 30 v/v% *iso*-octanol + 63 v/v% kerosene) flow rate of 1.18 L/h in the lumen side of the modules in the cascade mode, the extraction and recovery efficiencies of 97% and 82% for Pen-G were achieved after 7 stages, respectively [31].

Extraction of Pen-G with *N*-lauryl-*N*-trialkylmethylamine (Amberlite LA-2) as the extractant through PP hollow fiber membrane contactors was investigated by Young and Cuessler in 2002 [130].

*N*-butylacetate was found to be much better than decanol as a diluent for such an extraction, although decanol can provide a distribution coefficient four times larger. The overall mass transfer coefficient was extensively related to the aqueous phase flow rate in the lumen side of the hollow fibers and it was less dependent on the flow rate in the shell side. Lazarova et al. (2002) [131] studied simultaneous extractive removal and stripping of Pen-G using two large-scale MC. The diffusional resistance in the aqueous phase was the dominant factor for extraction of Pen-G, which could be minimized by increasing the aqueous phase velocity. The overall mass transfer coefficient in the extraction module was significantly higher than the resultant value in the stripping module.

Table 7 summarizes the studies on antibiotic recovery using MC technology. Most of the extractions were performed from model solutions or waste streams. This choice of extraction media can be explained by the attention given to the risks related to the presence of antibiotics in the wastewater. Different models of contactor membranes with different fiber materials were investigated. The extraction rates varied from 40 to 98%. The composition of the extraction phases and the operating parameters are detailed in the table below.

Table 7: Application of MC for extraction of antibiotics

Antibiotic	Aqueous phase	Organic phase	Membrane contactor module	Extraction conditions	Efficiency	Reference
Amoxicillin	Aqueous solution	6 mmol/L of Aliquat 336 in 1-decanol	Microporous hollow-fiber; Liqui-Cel® Extra-Flow module	Tube side: organic phase Shell side: aqueous phase Aqueous flow rate = 6 L/h Stripping phase flow rate = 6 L/h	85.21% of extraction and 80.34% recovery of amoxicillin from the feed phase	[41]
Penicillin-G	wastewater	5 w/w% of Aliquat 336 in oleyl alcohol	PVDF-HFP hollow fiber membrane contactor	Tube side: aqueous phase Shell side: organic phase Aqueous flow rate = 3 L/h Organic flow rate = 8.6 L/h	--	[44]
Penicillin-G	Aqueous solution	5% Aliquat 336 in Shellsol TK 5% Aliquat 336 in oleyl alcohol	Microporous hollow-fiber membrane contactor, 5PCM 218, Celgrad X-30	Tube side: aqueous phase Shell side: organic phase pH 7 Aqueous flow rate = 14.4 L/h Organic flow rate = 8.6 L/h	Extraction of 40-45%	[29]
Penicillin-G	Aqueous solution	7 v/v% di- <i>n</i> -octylamine + 30 v/v% <i>iso</i> -octanol + kerosene	Commercial PP	Tube side: organic phase Shell side: aqueous phase pH 6 Aqueous flow rate = 2.7 L/h Organic flow rate = 1.18 L/h	Extraction of 97%	[31]
Penicillin-G	Potassium salt of penicillin G (M = 372.2), potassium phosphate buffer	Amberlite LA-2, 10% isodecanol as modifier and kerosene as diluent	Celgard X-10 microporous PP hollow fiber	Tube side: aqueous phase Shell side: organic phase pH 5.3-5.4 Aqueous flow rate = 219.6 L/h Organic flow rate = 43.2 L/h	--	[131]
Penicillin-G	Aqueous solution	Amberlite LA-2 in one of the solvents (Shellsol TK/butyl acetate/tributyl phosphate)	Microporous hollow-fiber membrane contactor, 5PCM 218, Celgrad X-30	Tube side: aqueous phase Shell side: organic phase pH 3-5.5 Aqueous flow rate = 12.96 L/h Organic flow rate = 15.8 L/h	Extraction of 90–98%	[132]

Penicillin-G	Aqueous solution	7 v/v% di-n-octylamine + 30 v/v% iso-octanol + kerosene	Microporous PVDF hydrophobic hollow fiber membrane contactor	Tube side: organic phase Shell side: aqueous phase Aqueous flow rate = 6 L/h Stripping phase flow rate = 6 L/h	--	[32]
Penicillin-G	Aqueous solution	5 v/v% Aliquat 336 in Shellsol TK	--	Tube side: aqueous phase Shell side: organic phase Temperature (°C): 30 pH 7 Aqueous flow rate = 10.8-26 L/h Organic flow rate = 10.8-26 L/h	Extraction of 54%	[133]
Shengjimycin	Aqueous solution	1.5 w/w% of amberlite LA-2 in sunflower oil	Microporous hollow-fiber membrane contactor, 5PCM 218, Celgrad X-30	Tube side: aqueous phase Shell side: organic phase Temperature (°C): 30 pH 7.2-7.8 Aqueous flow rate = 12-13 L/h Organic flow rate = 9-10 L/h	Extraction of 70%	[134]
Cephalosporin antibiotics	Fermentation broth	Aliquat 336 (0.05 mol/L) in <i>n</i> -heptane	Microporous hollow-fiber membrane contactor, 5PCM 218, Celgrad X-20	Tube side: aqueous phase Shell side: organic phase pH 8 Aqueous flow rate = 3.6 L/h Organic flow rate = 0.9 L/h	Extraction > 70%	[30]

### **6.3. Effect of operating conditions on the MC efficiency**

To assess the efficiency of a MC, several parameters can be measured: the extraction yield of the organic acids, the time necessary to reach the extraction equilibrium, membrane mass transfer coefficient and the selectivity of the process to the organic acid.

#### **6.3.1. Effect of temperature**

The extraction process kinetics and thermodynamics are significantly influenced by temperature. High temperature enhances the diffusivity of compounds, resulting in a shorter time required to attain equilibrium. However, it also results in low partition coefficients in the organic solvent, resulting in reduced extraction yields. Since the membrane resistance is considered as the limiting factor in the mass-transfer process of LLE assisted by MC, reducing it requires increasing the diffusion coefficient according to Eq. (7). This can be achieved by increasing the temperature or decreasing the viscosity of the organic phase that wets the membrane pores.

In their research on Membrane-based solvent extraction and stripping of lactate in MC, Coelho and colleagues [58] reported a significant increase of membrane mass transfer coefficient (1.5 fold) and diffusion coefficient of the extractant-lactate complex in the organic phase (1.6 fold) when reactive extraction was performed at 40 °C instead of 22.5 °C. The authors showed that increasing the temperature from 22.5 °C to 40 °C resulted in a significant decrease in the viscosity of the organic phase.

#### **6.3.2. Effect of the flow rate**

In liquid-liquid extraction processes, it is known that the mass transfer coefficient, as well as the interfacial area between the two phases, decrease as the flow rate decreases [135]. Concerning membrane contactors, the interfacial area remains unchanged and the mass transfer coefficient varies little with the flow rate. A slight decrease was observed at low flow rates [7,135].

The flow rate of the liquid through the hollow-fiber membrane contactor affects the thickness of the liquid film on the membrane surface and, thus, may affect the mass transfer rates during the extraction. Furthermore, as indicated in Equation 13, the mass transfer coefficient should increase with the liquid velocity.

Several authors have compared the efficiency of extraction and back-extraction of carboxylic acids at different flow rates. In a recent study, Gössi et al. (2022) [51] have studied the removal of lactic acid from aqueous streams with a PTFE capillary membrane. They found the concentration profiles were similar for different flow rates (6-50 kg/h) for both organic and aqueous phases, and the mass

transfer coefficient remained constant. This suggests the mass transfer resistance is governed by the membrane. In 2004, Huang et al. [136] investigated the extraction rate of lactic acid from an aqueous solution (10 g/L) at different flow rates (from 25 to 125 mL/min). They found that the extraction rate increases with the flow rate of the feeding phase. At low flow rates, the concentration of lactic acid in the hollow fiber and the extraction rate are both lower as the reactive extraction rate is relative to the lactic acid concentration at the interface. However, concerning the back-extraction, extraction rate was not significantly affected by a change in the flow rates of solvent and stripping phase [136].

The effect of organic phase flow rate was evaluated during the extraction of succinic acid from an aqueous solution by Agrahari et al. in 2014 [45]. They noticed a slight improvement in the extraction efficiency when the flow rate of the organic phase increases from 0.3 to 0.5 L/min. For the aqueous phase, the effect of the flow rate is greater for low initial concentrations of succinic acid (5000 ppm), than for high concentrations (30,000 ppm). In fact, at high concentrations, the removal at 0.1, 0.2, and 0.3 L/min was approximately 100% whereas, at low concentrations, the removal is 99, 97, and 95%, respectively [45]. In 2014, another study, Agrahari et al. [45] tested different flow rates of the organic phase during the removal of benzoic acid from water by reactive extraction. They noticed little improvement in extraction with an increase in the flow rate from 0.2 to 0.5 L/min. During the reactive extraction of succinic and benzoic acids, the improvement in the efficiency of the extraction as a function of the increase in the extraction flow rate was explained by an increase in the mass transfer coefficient of the acid-amine complex from the membrane to the organic phase [117]. The variation on benzoic acid extraction at different flow rates of the aqueous phase was also studied. The data show that the extraction at 0.3 L/min flow rate is always higher than that at a feed flow rate of 0.1 or 0.2 L/min [117].

The effect of the flow rate of the feed and stripping phases on the extraction efficiency of carboxylic acids in MC was studied by Patil et al. in 2017 [137]. The results obtained showed that the degree of carboxylic acid transfer increases with flow rate. The percent of transfer observed for flow rates between 50 and 100 mL/min (74-89%) is less than for flow rates between 200 and 500 mL/min (95-98%) [47]. However, only few studies have found that the effect of the flow rate of the aqueous and organic phases may be weaker and suggests that the overall extraction is not significantly affected by the mass transfer of lactic acid [25,48]. Examples of the flow rates of phases employed for the liquid-liquid extraction of organic acids in MC are summarized in Table 8.

Table 5: Flow rates of phases used during the liquid-liquid extraction of organic acids in MC

Aqueous phase	Aqueous phase flow rate (L/min)	Organic phase	Organic phase flow rate (L/min)	Stripping phase	Stripping phase flow rate (L/min)	Extraction performance	Reference
Phenylacetic acid solution at 0.05M	0.05	1 w/w% TOPO in dodecane	200	1M NaOH solution	0.05	Percent transfer: 74%	[47]
	0.1				0.1	Percent transfer: 89%	
	0.2				0.2	Percent transfer: 95%	
	0.3				0.3	Percent transfer: 97%	
	0.5				0.5	Percent transfer: 98%	
Succinic acid solution (5000 ppm)	0.2	30 v/v% TPA in 1-octanol	0.3	--	--	Removal efficiency at 30 min: 72%*	[45]
						Removal efficiency at 75 min: 98%*	
						Removal efficiency at 30 min: 88%*	
	Removal efficiency at 75 min: 98%*						
	Removal efficiency at 30 min: 78%*						
	Removal efficiency at 75 min: 98%*						
0.1	Succinic acid removal: 99%*						
0.2	Succinic acid removal: 97%*						
0.3	Succinic acid removal: 95%*						
Benzoic acid in water (200 ppm)	0.2	0.12 M-TOA diluted in 1-octanol (5 v/v%)	0.2	--	--	Removal efficiency after 2h: 88%*	[117]
			0.4			Removal efficiency after 2h: 91%*	
			0.5			Removal efficiency after 2h: 95%*	
Benzoic acid in water (900 ppm)	0.1		Removal efficiency at 15 min: 50%*				
	0.2		Removal efficiency at 60 min: 85%*				
	0.3		Removal efficiency at 15 min: 58%*				
Succinic acid solution (0.17 mol/L)	1.8	10 w/w% Primene JM-T1 in 1-octanol	0.6	Water solution	1.8	Removal efficiency at 60 min: 88%*	[36]
						Removal efficiency at 60 min: 88%*	
						Removal efficiency at 15 min: 67%*	
						Extraction efficiency: 77 %	

Lactic acid (0.2 M) at the fermentation conditions	0.25-0.75	10 v/v% TOA in tri-butyl phosphate	0.25-0.75	--	--	Extraction efficiency: 93 %	[48]
Carboxylic acids from fermentation broth:						D = 0.14 for lactic acid	
Lactic acid	0.1	20 w/w% TOA in <i>n</i> -decanol	0.2	--	--	D = 0.15 for mandelic acid	
Mandelic acid						D = 0.50 for itaconic acid	[25]
Itaconic acid						D = 0.56 for succinic acid	
Succinic acid							
Aqueous lactic acid solutions (2.8 w/w%)	<u>50 kg/h</u> <u>6 kg/h</u> 6 kg/h	20 w/w% TOA in 1-decanol	<u>6 kg/h</u> <u>6 kg/h</u> 50 kg/h	--	--	<u><math>K_{ov} = 2.2 \cdot 10^{-7}</math></u> <u><math>K_{ov} = 2.2 \cdot 10^{-7}</math></u> $K_{ov} = 2.2 \cdot 10^{-7}$	[51]

\* data from figures; D: distribution coefficient;  $K_{ov}$ : overall mass transfer coefficient

The magnitude of the effect of flow rate on the efficiency of the extraction process varies from study to study. This difference could be explained by the variation of several parameters, such as the physicochemical properties of organic acids and their distribution (or partition) coefficient in the two phases, the characteristics of MC, the nature and the composition of the aqueous and the organic phases, as well as the type of mechanism of the extraction of the acid.

### 6.3.3. Overpressure levels ensuring interface stability

The pressure difference (Equation 19) between the tube side and the shell side of the membrane contactor is one of the crucial parameters in the process of the extraction.

$$\Delta P = (P_{non-wetting\ phase} - P_{wetting\ phase}) \quad Eq. (19)$$

If the fiber material of the MC is hydrophobic, the pores will be filled with the organic phase while if the fiber material is hydrophilic they will instead be filled with the aqueous phase. To avoid the wetting fluid from entering into the non-wetting one, slightly higher pressure is applied on the side of the non-wetting fluid (Figure 3). Thus, the non-wetting fluid does not penetrate through the pores as long as the pressure on the non-wetting side is kept below the critical pressure ( $\Delta P_c$  given by equation 1) [7,138].

Generally, in MC, the pressure difference between fluids has no significant effect on the mass transfer coefficient [16]. However, some authors have found that the pressure difference influenced the extraction efficiency [37]. According to literature data,  $\Delta P$  is generally  $< 0.5$  bar, beyond this value, the risk of the breakthrough of the non-wetting phase is high.

Table 9 presents the different transmembrane pressures used in membrane contactors. These values vary from 0.02 to 0.69 bar, depending on the nature of the membrane fibers, the composition of the organic phase and the presence of small amounts of tensides in the aqueous phase, reducing the tension of the aqueous phase and thus the stability of the process [103]. As mentioned before, the transmembrane pressures do not exceed 0.5 bar regardless of the nature of the membrane and the organic phase.

Table 6: Overpressure ensuring interface stability in MC during the reactive liquid-liquid extraction of organic acids

Organic acid	Fiber side materiel	Fiber side phase	Shell side materiel	Shell side phase	Transmembrane pressure (bar)	Reference
Fumaric acid	PP	0.7137 mol/L N7301 in kerosene/n-octanol at the volume ratio of 7/6	Polymethylmethacrylate	Industrial waste water	0.14 0.34 0.48 (optimum) 0.69	[37]
Benzoic acid	PP	Benzoic acid-laden water	PE	0.12M TOA diluted in 1-octanol 5% (v/v)	0.42 (0.62 bar in the lumen-side and 0.2 bar in shell-side liquid)	[117]
3-Hydroxypropionic acid	PP	Bioconversion broth	PP	30% (v/v) TOA in n-decanol	0.4	[10]
3-Hydroxypropionic acid	PP	3-HP aqueous solution	PP	10% (v/v) TOA mixed with 10% (v/v) Aliquat 336 in n-decanol.	0.25-0.4	[9]
Succinic acid	PP	Succinic acid aqueous solution	PE	- 30% tripropylamine (TPA) in 1-octanol - 30% TOA-TPA mixture in a 2:8 weight ratio and in 1-octano	0.42 (0.62 bar in the lumen-side and 0.2 bar in shell-side liquid)	[45]
Succinic acid Lactic acid Itaconic acid Mandelic acid	PTFE	20 w/w% TOA in n-decanol	--	Succinic acid, lactic acid, itaconic acid and mandelic acid solutions at 0.3 to 3% (w/w)	0.02 (100 mbar in the shell side (aqueous phase) and 80 mbar in the fiber/lumen side)	[25]
Lactic acid	PP	Model solution of fermentation broth with lactic acid at 0.2 M	PE	10 w/w% TOA in tri-butyl phosphate	0.3	[48]
Butyric acid	PP	10 v/v% Alamine 336 in oleyl alcohol	PE	Butyric acid solution and fermentation broth	0.27	[50]

#### 6.3.4. Effect of the organic phase composition on the MC efficiency

The main role of the organic phase is to improve the selectivity of the extraction process that is to say to increase the distribution (or partition) coefficient ( $D$ ) of the organic acid in the organic phase (org) compared to the aqueous phase (aq).

Most applications of MC use reactive liquid-liquid extraction for the recovery of organic acids. Figure 7 illustrates the principle of this type of extraction.

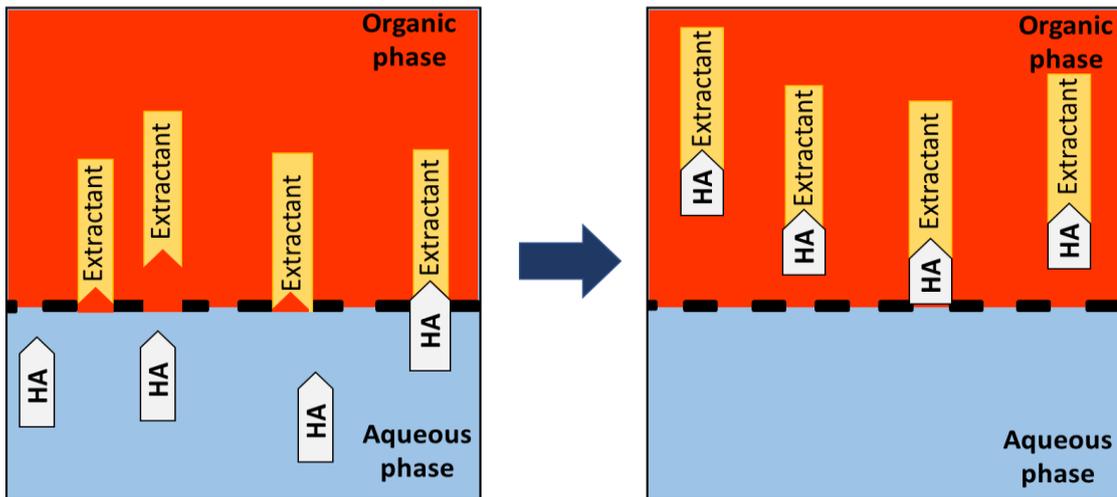


Figure 7: Liquid-liquid extraction mechanism in MC pores in the case of reactive extraction

The organic phase, in the case of reactive extraction, consists in composite solvents, including an extractant which forms complexes with the organic acids, and a diluent. Depending on the operating conditions of the extraction (e.g., nature and the concentration of the extractant, temperature, pH) different types of complexes can be formed, the reactions having variable stoichiometry. The proportion of complex formation in the medium is governed by the solubility of the extractant in the diluent and the strength of the interaction between the extractant and the organic acid. Two types of bonds are mainly observed, hydrogen bonding and proton transfer bonding [139,140]. A combination of these two mechanisms is also possible [141].

The choice of the composition of the organic phase for the liquid-liquid extraction in MC has a major influence on the efficiency of the extraction process. The physicochemical properties of the extractant such as low solubility in water, low viscosity, high distribution (or partition) coefficient of organic acids, physicochemical stability, low toxicity and low price should be taken into account [83]. Among all these parameters, two are of great importance: solubility in water and viscosity.

In MC, the low solubility of water in the organic phase is a key parameter for the membrane stability because it prevents the breakthrough of the organic phase in the feed phase, and vice versa. In addition, solvents and/or diluents with high solubility in water could induce molecular toxicity

towards microorganisms in the case of ISPR configuration. The low viscosity of the organic phase is also important to facilitate the transport of organic acids. Indeed, pure extractants cannot be used alone for the liquid-liquid extraction in MC due to their high viscosity [142,143]. The presence of a diluent is essential to improve the physical properties of the organic phase and the solvation of the acid-extractant complex [144]. Thus, studies must be carried out to determine the most suitable diluent(s) with the extractant as well as its concentration in the organic phase. For example, the concentration of extractant suitable for recovering fumaric acid from industrial wastewater is 0.7137 mol/L  $N_{7301}$  in kerosene/*n*-octanol at the volume ratio of 7/6 according to [37]. In this study, *n*-octanol (polar diluent) was the appropriate co-solvent compared to MIBK (electron donor diluent) and chloroform (electron acceptor diluent). The effect of the extractant in the recovery of lactic acid by a microporous hollow fiber membrane contactor was studied by [48]. The authors found that the presence of extractant in the diluent had a significant effect on the efficiency of the extraction. The test with sunflower oil only (diluent) did not give good results with an extraction efficiency of only 9%.

Several extractants or several diluents can be used. It has been shown that a synergistic effect between the extractants can occur. Experimental tests with 30% extractant composed of Aliquat 336 and TOA reached an extraction efficiency of 33% [48]. The two extractants (Aliquat 336 and TOA), combined at a 1:1 ratio, gave higher distribution coefficients than when individual extractants were used [48,145–147]. In addition, the synergistic effect of the mixture TOA (10 v/v%) and Aliquat (10 v/v%) in *n*-decanol on the extraction performance of 3-hydroxypropionic acid was also recently proven by Moussa et al. [148]. The authors found that using a mixture of these extractants exhibited high distribution coefficients over a wide range of pH values and acid concentration in the aqueous phase [148]. Table 10 shows a synthesis of all the studies in which the organic phase was optimized for extraction with MC. For each organic acid, the authors tested several extractants in several diluents at different concentrations. The extraction efficiencies are also presented for each condition.

Three main categories of extractants are generally used in liquid-liquid extraction by MC: (1) those based on phosphorous such as tributylphosphate (TBP) or trioctylphosphine oxide (TOPO), and (2) those based on nitrogen-based extractants such as Alamine, trioctylamine, tridecylamine, and quaternary ammonium salts (Aliquat 336). Diluents are usually classified into two categories: (1) active diluents having one or more functional groups, which play a role in the transfer of the acid between phases by modifying the capacity of the extractant [149]. They prevent the formation of a second organic phase by solubilizing the acid-extractant complex. Active diluents are generally alcohols, halogenated hydrocarbons or even ketones [150]. (2) inactive diluents which are mainly used to dilute the extractant without chemically influencing the liquid-liquid equilibrium, such as benzenes or alkanes [149,151].

The extraction mechanisms of each category of extractants and diluents, as well as the effects of operating conditions in liquid-liquid extraction, have recently been reviewed by [152]. These mechanisms are influenced by several parameters including the characteristics of the acid, extractants and diluent. The influence of the diluent on extraction is not only determined by its polarity, solvation capacity, and acid dimerization constant, but also by specific interactions and complex stabilization when using active diluents. The use of active, polar and proton donor diluents results in higher distribution ratio values compared to inactive diluents. The hydrophobicity of acids, and the presence of additional functional groups, are also important factors in the liquid-liquid extraction mechanism. Regarding the effect of acids, in general, the more hydrophobic and stronger monocarboxylic acids have a higher distribution ratio in the extractant phase. The authors of the review also highlighted the interest of ionic liquids (ILs) for the extraction of carboxylic acids [152]. To the best of our knowledge, ILs have not yet been used in liquid-liquid extraction with MC for the extraction of organic acids.

### **6.3.5. Effect of the feed phase composition and pH on the extraction of organic acids**

#### **A. Composition of the feed phase**

The composition of the feed phase can affect the performance of liquid-liquid extraction of organic acids into MC. The presence of certain compounds such as salts and mineral acids would influence the extraction of organic acids and their purity in the organic phase [153]. Studies have reported that the presence of salts reduces the extraction of carboxylic acids. For example, the presence of sodium chloride results in the formation of hydrochloric acid from the Cl<sup>-</sup> anion and the proton from the carboxylic acid moiety. Hydrochloric acid then competes with propionic acid for extraction [154]. Hence, their presence in fermentation broths or in aqueous media should be avoided or minimized.

Table 7: Effect of the organic phase composition on the extraction of organic acids in liquid-liquid extraction assisted by MC

Organic acid	Concentration	pH	Extractant	Diluent	Concentration in diluent	Temperature (C°)	Extraction efficiency	Reference
Fumaric acid	6.47 g/L	1.67	0.7137 mol/L N <sub>7301</sub> in kerosene	MIBK	30 w/w%	--	Extraction efficiency: 88% *	[37]
				Chloroform	30 w/w%		Extraction efficiency: 82% *	
				n-Octanol	10 w/w%		Extraction efficiency: 82% *	
					20 w/w%		Extraction efficiency: 83% *	
					30 w/w%		Extraction efficiency: 90% *	
					40 w/w%		Extraction efficiency: 85% *	
Succinic acid	0.17 mol/L	--	1-Octanol	1-Octanol	100 w/w%	25	Extraction efficiency: 15.9%	[36]
			Primene JM-T1	1-Octanol	10 w/w%		Extraction efficiency: 86%	
			Primene TOA1	1-Octanol	10 w/w%		Extraction efficiency: 4.8%	
			n-BDEA	1-Octanol	10 w/w%		Extraction efficiency: 3.7%	
			TEHA	1-Octanol	10 w/w%		Extraction efficiency: 32%	
Benzoic acid	200 ppm	--	0.12 M-TOA	1-octanol	5 v/v%	Ambient (~25)	Removal > 95%	[117]
Lactic acid	3 %	5	TOA	n-Decanol	20 w/w%	Ambient (~25)	--	[25]
Acetic acid Butyric acid Hexanoic acid	10.4 g/L (total acids)	5.5	TOA	oleyl alcohol	10 w/w%	37	Extraction efficiency: 70%	[107]
Phenylacetic acid	0.05 M	--	TOPO	Dodecane	1 w/w%	--	Removal ~ 99%	[47]
Butyric acid	100 g/L	4.5	Alamine 336	Olyel alcohol	10 w/w%	25	Extraction rate (g/h): 12.5 ± 0.45	[50]
			Adogen 283	Olyel alcohol	10 w/w%	25	Extraction rate (g/h): 11.62 ± 0.36	
			Corn oil	Corn oil	100 w/w%	25	Extraction rate (g/h): 8.36 ± 0.28	
Lactic acid	0.2 M	2.4	Sunflower oil	Sunflower oil	100 w/w%	Ambient (~25)	Extraction efficiency: 9% *	[48]
			Aliquat 336 and TOA (ratio 3:1)		10 w/w%		Extraction efficiency: 25%*	
			Aliquat 336 and TOA (1:1)		33 w/w%		Extraction efficiency: 33%*	

\* data from figure

In their work on reactive extraction of 3-hydroxypropionic acid, Moussa et al, (2016) [148] compared the acid extraction efficiency from a model aqueous solution and a real bioconversion broth. They hypothesized that some cell-originating compounds could adsorb at the aqueous–organic interface. This effect, added to the possible competition between 3-hydroxypropionic acid and compounds capable of reacting with extractants, leads to limitations in the yield and selectivity of the extraction. This result was confirmed in a MC by Burgé et al. in 2016 [9]. They observed a lower extraction on a real bioconversion broth (63.2% and  $K_D = 1.67$ ) than on a binary solution containing 3-hydroxypropionic acid and water (85.0% and  $K_D = 5.67$ ). This decrease in yield is due to the presence of residual salts which compete with 3-hydroxypropionic acid for its extraction by a mixture of TOA and Aliquat 336 [9]. To understand this trend, Chemarin et al. [52,155] investigated the influence of the composition of the bioconversion broth on the extraction of 3-hydroxypropionic acid using TOA in *n*-decanol. They found that the increase of salt concentration in the medium induces a decrease in the extraction yield. Limiting the accumulation of salts in the fermentation broth has been recommended for good process efficiency. On the contrary, no influence of proteins on the efficiency of the process has been reported.

It is worth mentioning that other studies have shown that the presence of salts does not significantly affect the extraction efficiency of lactic acid from fermentation broth [48,145]. Thus, the effect of salts could depend on the type of organic acid to be extracted.

The initial concentration of organic acid in the feed phase is one of the parameters that can affect the efficiency of extraction. It is a key factor involving the driving force of the acid for its transfer from the feed phase to the organic phase and/or for the formation of an acid-extractant complex in the case of reactive extraction.

The extraction kinetics of 3-hydroxypropionic acid in a MC were investigated as a function of the initial acid concentration [10]. The authors found that an increase in the initial acid concentration leads to a decrease in the constant rate of the extraction kinetics and an increase in the yield of extraction (66% at 0.5 g/L and 77% at 10 g/L). At low acid concentrations, the kinetics of extraction are rapid due to an excess of extractant (TOA) which leads to a higher complexation yield. The same trend was observed when the initial acid concentration was increased from 0.5 to 2 g/L with a mixture of 10 v/v% TOA and 10 v/v% Aliquat 336 in *n*-decanol as extractant. The yield of extraction slightly decreased when increasing the initial concentration of 3-hydroxypropionic acid: 95%, 93% and 90% for 0.5, 1 and 2 g/L, respectively. The distribution coefficient varies according to the same trend, and goes from 22.25 to 8.94. According to the authors, the differences obtained for the distribution coefficients can be explained by the decrease in the ratio between the concentration of extractant and that of the acid [10].

Agrahari et al. [45] studied the effect of the initial concentration of succinic acid at different ranges during the extraction by a microporous MC. They showed that the physical and thermodynamic properties, such as the diffusion coefficient and solubility of succinic acid, do not change for low concentrations of succinic acid. Nevertheless, for higher concentrations, important differences were observed. Similar results have already been reported by Z. Jin and Yang [156] who have established that the extractive fermentation of propionate by MC is not sensitive to small variations in pH and to the initial propionate concentration.

## **B. pH of the feed phase**

In the literature, it has been shown that the use of reactive liquid-liquid extraction assisted by MC as an ISPR method increases the productivity and the yield of the organic acid recovery. However, the coupling of the bioconversion with the extraction faces certain limits of compatibility between the optimal conditions for the development of microorganisms and the liquid-liquid extraction, in particular the pH of the broth.

Since most extractants and solvents can only extract acids in their protonated form (AH), the efficiency of the extraction mainly depends on the initial pH of the aqueous phase which determines the percentage of formation of non-dissociated and dissociated acids.

In 2003, Wu and Yang [50] studied the effect of pH for the extraction of butyric acid obtained by *C. tyrobutyricum*. Fermentation is optimal at pH 6 while the mechanism of reactive extraction with 10% Alamine 336 in oleyl alcohol is effective at lower pH ( $\text{pH} < 4.76$ ) as it only extracts the form protonated of butyric acid ( $\text{pK}_a = 4.76$ ).

In a recent study, Chemarin et al. [10] studied the influence of the initial pH of the aqueous phase on the extraction efficiency of 3-hydroxypropionic acid by an organic phase composed of 20 v/v% TOA in *n*-decanol. They found that the pH effect is mainly due to the variation in concentration of the non-dissociated fraction of 3-hydroxypropionic acid in the aqueous phase. Indeed, at pH 5, 4 and 3.2, the percentages of non-dissociated (AH) acid are 24, 76 and 97% and the extraction yields are 8, 43 and 74%, respectively. Thus, the efficiency of extraction increases with the proportion of the non-dissociated acid present in the aqueous phase.

In 2016, Burgé et al. [9] studied the association of two extractants (TOA and Aliquat 336) with different mechanisms of action regarding the pH. Indeed, TOA extracts molecules under their protonated form, whereas Aliquat 336 acts through an anion exchange mechanism. The combination of these two extractants has been shown to be effective in extracting both dissociated and non-dissociated forms of acids [11,157]. In the range of pH tested (3.2 to 7), they found that the reactive

extraction of 3-hydroxypropionic acid was possible and efficient ( $K_d > 1$  see Table 11) [9]. The results obtained are promising for performing an in-situ extraction of 3-hydroxypropionic acid from fermentation broths.

On the other hand, extractive fermentation using MC can also be used to control the pH of the fermentation broth. Indeed, the carboxylic acid produced during fermentation should decrease the pH of the broth, but the latter is extracted during fermentation which makes it possible to avoid this reduction. Thus, the fermentation products do not inhibit microorganisms and allow to have similar fermentation yields [158,159].

The extraction and fermentation performances therefore vary inversely with the pH and this limits the efficiency of the integrated processes. Optimized bioconversion rates usually require higher pH values, but extraction performance is better at low pH values. Thus, the extractive bioconversion would be carried out at a pseudo-stationary pH if the rate of acid production is equivalent to the rate of removal of acid from the medium by extraction. As can be seen in Table 11, the pH used for the integrated process is often a compromise corresponding to a value not too acidic for the microorganisms and not too neutral for the extraction. The pH range between 4.5 and 5.5 is often used in the literature as a compromise for the recovery of lactic acid by reactive extraction [25,48,50].

Table 8: pH values of the aqueous phase during the liquid-liquid extraction assisted by MC of organic acids

Organic acid	pKa	Aqueous phase	pH	Organic phase	Extraction performance	K <sub>D</sub>	Reference
3-hydroxypropionic acid	4.51	Aqueous solution of 3-HP (1 g/L)	3.2	10 v/v% TOA 10 v/v% Aliquat 336 in <i>n</i> -decanol	Extraction yield (%): 92.9 ± 0.1	13.0 ± 0.24	[9]
			4		Extraction yield (%): 85.0 ± 1.0	5.67 ± 0.68	
			5		Extraction yield (%): 75.8 ± 1.0	3.13 ± 0.24	
			6		Extraction yield (%): 67.2 ± 0.7	2.05 ± 0.06	
			7		Extraction yield (%): 53.3 ± 0.6	1.14 ± 0.08	
		Extractive fermentation	4.5	18 v/v% TOA and 2 v/v% Aliquat 336 in <i>n</i> -decanol	Extraction yield (%): 62.5 ± 0.6	1.67 ± 0.08	
Butyric acid	4.82	Aqueous solution of butyric acid (100 g/L)	4.5	10 w/w% Alamine 336 in oleyl alcohol	Extraction rate (g/h): 12.50 ± 0.45	[50]	
			5		Extraction rate (g/h): 7.17 ± 0.24		
			5.5		Extraction rate (g/h): 2.78 ± 0.23		
			6		Extraction rate (g/h): 1.67 ± 0.06		
Extractive fermentation	5.5	--	--				
Lactic acid	3.86	Extractive fermentation	5	20 w/w% TOA in <i>n</i> -decanol	Conversion rate of 81% mol of the fed glucose	[25]	
3-hydroxypropionic acid	4.51	Aqueous solution of 3-hydroxypropionic acid (1 g/L)	5	20 v/v% TOA in <i>n</i> -decanol	Extraction yield: 8%	[10]	
			4		Extraction yield: 43%		
			3.2		Extraction yield: 74%		
Lactic acid	3.86	Aqueous solution of lactic acid (0.2 M)	4	15 w/w% Aliquat 336 and 15% TOA in sunflower oil	--	2.2*	
			5		--	0.7*	
			6		--	0.2*	
		Synthetic fermentation broths	4.5	10 w/w% TOA and 90 w/w% TBP.	Extraction efficiency: 90%	--	
Fumaric acid	pK <sub>a1</sub> : 3.02 pK <sub>a2</sub> : 4.38	Industrial wastewater	0.19 <sup>a</sup>	0.7137 mol/L N7301 in kerosene/ <i>n</i> -octanol 7/6 (v/v)	Extraction efficiency: 73 %*	[37]	
			0.5 <sup>a</sup>		Extraction efficiency: 76 %*		
			0.75 <sup>a</sup>		Extraction efficiency: 79 %*		
			1 <sup>a</sup>		Extraction efficiency: 84 %*		
			1.65 <sup>a</sup>		Extraction efficiency: 81 %*		

\* data from figures

<sup>a</sup> pH were calculated from the [H<sup>+</sup>]

#### 6.4. Back-extraction of organic acids in a MC

The back extraction of organic acids corresponds to their recovery from the organic phase. This can be performed in different ways depending on the physicochemical properties of the acids, the organic phase and the chemical mechanism involved in the extraction (physical extraction, reactive extraction involving ionic or hydrogen bonds). When the acids and/or the organic phase are volatile, the simplest method is either evaporation of the organic phase or distillation of the organic acid from the organic phase [105,160,161]. Recently a liquid-liquid extraction assisted by MC has been integrated with downstream distillation in an ISPR approach to selectively extract and purify organic acids (caproic acid, acetic acid propionic acid, butyric acid, valeric acid). In this process, the organic acids were extracted by Cyanex 923 in MC, then recovered as free acid as a distillate from the organic phase in a distillation column (Figure 8) [105].

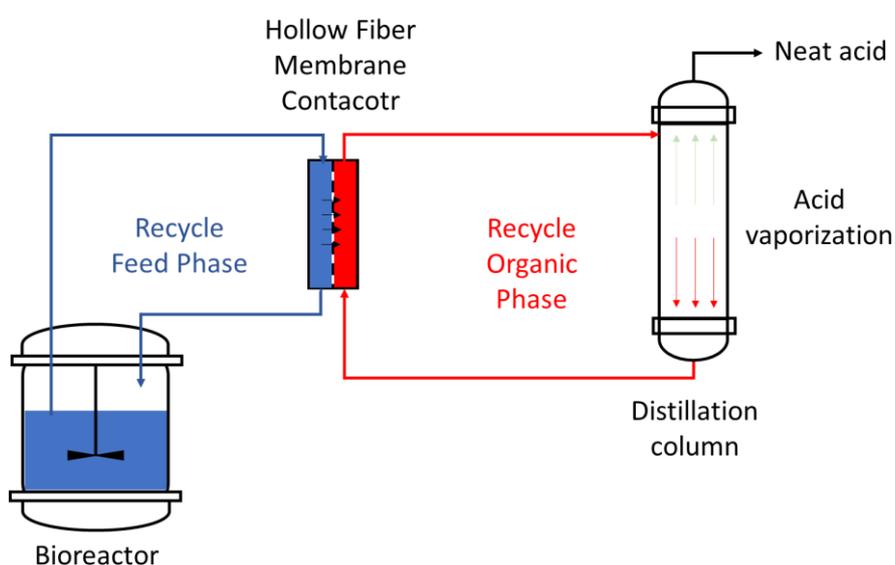


Figure 8: Fermentation reactor coupled a MC and a distillation system for back-extraction of the acids from the organic phase. Adapted from [105].

In the event that neither the acids nor the organic phase are volatile, other regeneration techniques can be used:

- (1) reactive back-extraction with HCl or NaOH solutions,
- (2) physical back-extraction by temperature-swing. The temperature in the back-extraction column is increased to lower the complexation constants and thus recover the organic acids.
- (3) back-extraction by diluent-swing. The composition of the organic phase is changed by removing an active diluent or adding an inactive diluent as an anti-solvent.

These regeneration techniques have been reviewed in detail by Sprakel and Schuur [152].

MC allows the continuous in-stream back-extraction. This involves the use of a stripping phase composed of reagents such as water, neutral or basic salts. The extraction and back-extraction steps

could be coupled into a single process as shown in the figure. 5. The advantage of this coupling is to be able to shift the equilibrium obtained during the extraction. Hence, the total amount of acids recovered from the feed phase is increased by regenerating the organic phase, thus reducing the associated operating costs of the process.

The composition of the stripping phase (nature of the stripping reagent and its concentration in the solution) may significantly impact the performance of the back-extraction step (Table 12). An excess of stripping reagent should be used to avoid the formation of a boundary layer depleted in the reagent [153]. In the case of reactive extraction, the amino-acid complex is stable in the organic phase, thus the back-extraction of the acid into an aqueous phase can be relatively challenging. Li et al. [37] have tested sodium hydroxide (10%), sodium carbonate (10%) and water as stripping reagent to extract fumaric acid. The results obtained revealed that the highest extraction yield is obtained when sodium hydroxide is used (Table 12). To optimize the stripping solution of sodium hydroxide, they have tested different concentrations from 2 to 20%. They found that the extraction increases with NaOH concentration and reaches a maximum at 10%. Morales and co-workers [36] studied the back-extraction of succinic acid from Primene JM-T1 diluted in 1-octanol as a function of the pH of the stripping phase. They identified that for pH of the aqueous phase included between 2 and 12, the recovery was extremely low (< 15%). At a strongly basic initial pH (pH > 13) they observed a significant increase in recovery of the acid, with a rate of about 60%. Lee et al. in 2008 [163] described that in basic medium, when the pH is greater than  $pK_{a1}$  and  $pK_{a2}$  of succinic acid, back-extraction of the acid is possible by dissociating the complex and forming a more soluble succinate salt in the aqueous phase. When the extraction and back-extraction of succinic acid were coupled in a single step, the total acid removed from the feed is almost 5 times higher than for a single extraction [36].

Table 12: Examples of back-extraction of organic acids using MC

Acid	Concentration in organic phase	Organic phase	Stripping phase	pH	Back-extraction efficiency	Reference
Fumaric acid	6.47 g/L	0.7137 mol/L N7301 in kerosene/n-octanol at the volume ratio of 7/6	Water solution	--	78.5%*	[37]
			10% Na <sub>2</sub> CO <sub>3</sub> solution		82.5%*	
			10% NaOH solution		89%*	
Succinic acid	0.17 mol/L	10w/w% Primene JMT1 in 1-octanol.	Water solution	13 (adjusted by 0.1 mol/L sodium hydroxide solutions))	60%	[36]
Phenylacetic acid	~ 0.05 M	1 w/w% TOPO in dodecane	1M NaOH solution	--	--	[47]
Lactic acid	54 g/L	20 w/w% TOA in n-decanol	Water (the receiving phase) and heptane (antisolvent)	--	S/F 1:1, 36.7% recovery S/F 1:2, 31.4% recovery S/F 1:4, 23.1% recovery S/F 1:8, 14.3% recovery	[25]
Butyric acid	100 g/L	10 w/w% Alamine 336 in oleyl alcohol	6N NaOH solution	pH > 10	--	[50]
3-hydroxypropionic acid	8 g/L	20 v/v% TOA in decanol	NaOH in stoichiometric proportion	--	80%	[43]

\* data from figure  
S/F (n-decanol phase to water)

A non-dispersive back-extraction of lactic acid from TOMAC in oleyl alcohol was achieved in a microporous MC by an aqueous solution of NaCl [164]. Satisfactory recovery was reached, suggesting the great potential for integrating membrane back-extraction with extractive fermentation process for lactic acid production [164].

When coupling fermentation with integrated extraction and back-extraction steps, temperature appears as a key parameter. Indeed, solubility and diffusivity are temperature dependent: the higher the temperature, the better the mass transfer. However, the temperature increase should not hinder the chemical reactivity of the acid with the extractant. For the extraction out of fermentation broth, it could be beneficial to operate at a moderate temperature level, when allowed by the microorganism physiological ability. This level has to be the same in both phases (feed broth and extraction solvent), since the MC facilitates heat transfer. For back-extraction, working at reduced temperature promotes the purity of the organic acids in the stripping phase by reducing the solubility of undesired components.

Back-extraction can be performed using temperature swing. This technique states that, after extraction, the acid is recovered in the aqueous phase upon heating. For reactive extraction of organic acids, this technique relies on the thermal reversibility of the acid-amine complexation reaction. The dissociation of the acid-amine complex into its two components, namely the acid in the aqueous phase and the amine in the organic phase, can be achieved by increasing the temperature of the organic phase in the presence of an aqueous phase. As a result, heating a loaded organic phase in contact with an aqueous phase can result in some back-extraction. This technique is particularly interesting since it does not require any additional chemicals and facilitates the recovery of the protonated acid [141].

Chemerin et al, [165] investigated the temperature swing back-extraction of 3-HP from an organic phase consisting of 20%v/v TOA in decanol across a wide temperature range (4 – 140 °C) and observed that higher temperatures led to greater 3-HP recovery. Specifically, at 140 °C, approximately 78% of the 3-HP was present in the aqueous phase with no observed degradation products, surpassing previously reported recovery rates for propionic acid (25-35%) [166] and lactic acid (32%) [167] using TOA in decanol as the organic phase.

## 7. Conclusion

Membrane contactors appear as an innovative and robust separation technology, particularly for the recovery of biomolecules from liquid effluent streams and bioconversion media, the decontamination of industrial effluents, and the optimization of the biorefining process. They are non-harmful to microorganisms and allow for the preservation of the molecular integrity of biomolecules without the need for high temperatures, and are easy to implement and operate.

The complexity of scaling up a liquid-liquid extraction technology in the biorefinery process is greater than that of a chemical process due to the interactions of components in biosystems. The emergence of MC and the development of new extraction solvents, such as ionic liquids, supercritical and compressed fluid, deep eutectic solvents, and new approaches such as aqueous two-phase systems (ATPS), are expected to significantly boost the potential of liquid-liquid extraction as a valuable tool in biorefinery production processes. It is essential to select an extraction solvent wisely for the success of purification processes, as the ideal solvent should possess a high partition coefficient for the desired compounds, must not cause any damage to the process equipment and should be non-toxic to microorganisms.

The applications of MC for liquid-liquid extraction of organic acids from fermentation broths and liquid media have been reviewed since 2005. In the case of the extraction from fermentation broths, the advantage of using MCs has been confirmed for the reduction of solvent toxicity towards cells by avoiding direct contact, and thus improving the productivity of the bioreactors. Moreover, MCs have proven their effectiveness in the back-extraction and the regeneration of the organic phase. The reported results thus reveal the high potential of MCs in an ISPR approach applied to the bio-production of organic acids. The recovery of organic acids from liquid media has shown to be efficient and less complicated as the conditions of extraction are easily adjustable, this feature extends the potential of application of MCs to other fields such as the treatment of industrial wastewater and the valorization of biorefinery effluents.

The efficiency of the whole process of extraction is influenced by multiple parameters as well as the property of the MC material. For the liquid-liquid extraction of organic acids, the most frequently used material is PP with 40% porosity and pore size of 3 nm. The flow rate of phases has been found to affect the transfer rates during extraction and back-extraction, thus this parameter should be optimized in order to provide the suitable thickness of the liquid film and concentration of the acid on the membrane surface. The transmembrane pressure is one of the key parameters for the stability of the interfaces in the MC. The membrane fouling, particularly biological fouling, can affect the performance of the process, but this tends to be more a problem with pressure-driven devices than

with concentration-driven ones such as membrane contactors. Nonetheless, highly packed MC can face potential fouling or biological material deposition after long term exposure to real media. Furthermore, blocking effect can be observed for MC with small diameter fibers [168]. However, such phenomena can be overcome with conventional chemical cleaning. The complexity of the composition of the feed phase, particularly fermentation media, can affect the transfer of biomolecules from one phase to another in a positive or negative way, and even affect the stability of the interface when tensioactive compounds are present. The efficiency of the extraction depends also on the properties of the organic and the feed phases. The choice of the composition of the organic phase must take into account the mechanism of extraction of the acid (physical or reactive extraction), as well as certain physicochemical considerations such as the high distribution coefficient with organic acid, low viscosity, physicochemical stability, low toxicity and low solubility in water. For the feed phase, the most important parameter to take in consideration is the pH as it affects the dissociation equilibrium of the acid, and thus its extraction. Concerning the composition of the feed phase and its initial acid concentration, some authors have confirmed their impact on the extraction, while this impact was insignificant for others. These two parameters could affect the driving force and the complexation reaction during the transfer of the acid at aqueous boundary layer.

The recovery of the pure acid from the organic phase and its regeneration is an important challenge for the efficiency of the whole process of extraction. MCs have shown their convenience for this purpose. The use of a simple stripping solution of water at basic pH was shown to be effective in the recovery of the acid. MC could also be integrated with other downstream techniques of separation to recover pure acid such as distillation and reverse osmosis which show the flexibility of this technology.

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