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Review

Chiral Separation in Preparative Scale: A Brief Overview of Membranes as Tools for Enantiomeric Separation

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Abstract: Given the importance of chirality in the biological response, regulators, industries and researchers require chiral compounds in their enantiomeric pure form. Therefore, the approach to separate enantiomers in preparative scale needs to be fast, easy to operate, low cost and allow obtaining the enantiomers at high level of optical purity. A variety of methodologies to separate enantiomers in preparative scale is described, but most of them are expensive or with restricted applicability. However, the use of membranes have been pointed out as a promising methodology for scale-up enantiomeric separation due to the low energy consumption, continuous operability, variety of materials and supports, simplicity, eco-friendly and the possibility to be integrated into other separation processes. Different types of membranes (solid and liquid) have been developed and may provide applicability in multi-milligram and industrial scales. In this brief overview, the different types and chemical nature of membranes are described, showing their advantages and drawbacks. Recent applications of enantiomeric separations of pharmaceuticals, amines and amino acids were reported.

Keywords: enantioresolution; preparative scale; membranes

1. Introduction

Chiral separation is an essential undertaking throughout discovery and development of biological active substances, with enantiomeric forms often possessing different biological effects [1,2]. Given the importance of chirality in the biological response, regulators, industries and researchers require chiral compounds in their enantiomeric pure form [3,4]. There are two approaches to obtain an enantiomerically pure substance: the "chiral approach", based on the development of an asymmetric synthesis for the production of only one enantiomer, and the "racemic approach", that focus on the synthesis of both enantiomers and subsequent separation of the racemic mixture [5,6]. Particularly, at an early stage of development of new chiral molecular entities, it is essential to evaluate the differences in biological activity and toxicity of both enantiomers to maximize the effectiveness of the product and minimize the possible negative side effects. At this stage, a large library of molecules, in small quantities, is required, and most compounds are only made once for initial biological activity

screening. Considering that, all stereoisomers are required for biological screening, in both racemic mixture and enantiomerically pure form. In this sense, the "racemic approach" achieves products by a reaction sequence that, generally, presents a much lower degree of difficulty and cost than the reaction involved in "chiral approach". Furthermore, in the "racemic approach", the pure enantiomers can be obtained by different techniques available for separation of the racemic mixture. Therefore, methodologies to separate enantiomers in preparative scale need to be fast, easy to operate, low cost and allow obtaining the enantiomers at high level of optical purity. There are a wide variety of methods to achieve enantiomerically pure compounds through the "racemic approach" including preparative liquid chromatography (LC) [7,8] and supercritical fluid chromatography (SFC) [9–11] with chiral stationary phases (CSPs), asymmetric catalysis [12], diastereomeric crystallization [13,14], dynamic kinetic resolution [15], simulated moving bed [16–18], enzyme-mediated kinetic resolution [19,20], molecular imprinting technology [21], optical force [22], methods based on liquid−liquid partitioning such as liquid−liquid extraction (LLE), and membranes [23]. Diastereomeric crystallization is commonly applied, but this technique is very limited because often requires the use of reagents that may be effective only for a specific system [24,25]. LC and SFC have been the first alternative to crystallization but the high cost of the CSPs and the low capacity of many commercially available CSPs are the main drawbacks. Methods based on liquid−liquid partitioning such as enantioselective LLE (ELLE) including the use of ionic liquids or membranes can be an attractive alternative to crystallization and LC concerning the possibility to operate on all scales from laboratory separations to bulk-chemical-scale processes in the chemical industry. Therefore, the use of membranes have been pointed out as a promising methodology for scale-up enantiomeric separation, with different types of membranes (solid and liquid) providing a complementary choice to the ELLE, LC and SFC techniques [23,26]. The advantages of using membranes are the low energy consumption, high processing capacity, continuous operability, variety of polymeric materials, simplicity, eco-friendly, economic, and the possibility to be integrated into other separation processes as well as to scale up [26–28]. Many examples with membrane techniques are described proving the feasibility for enantiomeric separation in preparative scale [29–38], however, so far, only few applications have been found for industrial scale use [26]. Thus, more research in membranes development and applications are required.

2. Membranes for Chiral Separation

The first work describing the application of membrane technology for enantiomeric resolution was reported by Cram et al. in 1980 [39]. They also described a successful enantioseparation of amino acid salts on catalytic resolution machine, which gave a research momentum in this area [40]. Moreover, although the work of Pirkle et al. has been more devoted to the development of successive generations of CSPs for LC [41–43], they also left a milestone in this area describing an enantioselective extraction of amino acids derivatives on prototype membrane unit using a transport agent [44]. Since then, different types of membranes have been developed for chiral resolution, which were compiled in several fundamental reviews [23,26,27,45–53].

Enantioselective or non-enantioselective membranes can be used to achieve chiral resolution [26,28]. Beyond good transport rate with high selectivity, the ideal enantioselective membrane should provide high stability in high range of pH and different types of solvents as well as good reproducibility and robustness. Enantioselective membranes are able to achieve selectivity through the binding of the enantiomers to chiral recognition sites with different affinities [26,51] as consequence of diverse types of interactions, including hydrogen bonding, hydrophobic interactions, van der Waals interactions, as well as steric effects [54]. The chiral sites of the membrane, responsible for preferentially allowing a specific enantiomer to be adsorbed or diffused into the membrane, can be either bulk structures of membrane materials [27,51,55–58] or chiral selectors added to the membranes [54,59,60].

The enantioselective membranes can be categorized as liquid or solid according to the status of the membrane phase [26,51].

A representative liquid membrane consists of an organic liquid between aqueous donating and receiving phases. The liquid membrane phase should not be miscible in either the two aqueous phases, and to allow the dissolution of the chiral selector. A complex is formed between the chiral selector and one enantiomer at the interface of donating and organic solutions, which is then transported through the liquid membrane to another aqueous solution (receiving phase), frequently in the presence of a pH or concentration gradients [26,51]. Several liquid membranes containing different types of chiral selectors, including biomacromolecules such as human serum albumin [61,62] or enzymes [63], chiral crown ethers [64,65], cyclodextrins [66–68], chiral small molecules [69–71], and calixarenes [72,73], have been reported.

Chiral liquid membrane is known as the combination of membrane separation and chiral extraction technology, which can carry out an effective real-time process to extract and recover compounds by a single unit operation. Chiral liquid membrane technology has been extensively investigated for the separation of enantiomers due to its high separation factor and mass transfer flux. The main advantage of this kind of membrane is the higher solubility and diffusivity coefficients of compounds in a liquid medium than in a solid membrane. Liquid membranes can be generally divided into three categories, i.e., emulsion liquid membrane, bulk liquid membrane and supported liquid membrane (Figure 1).

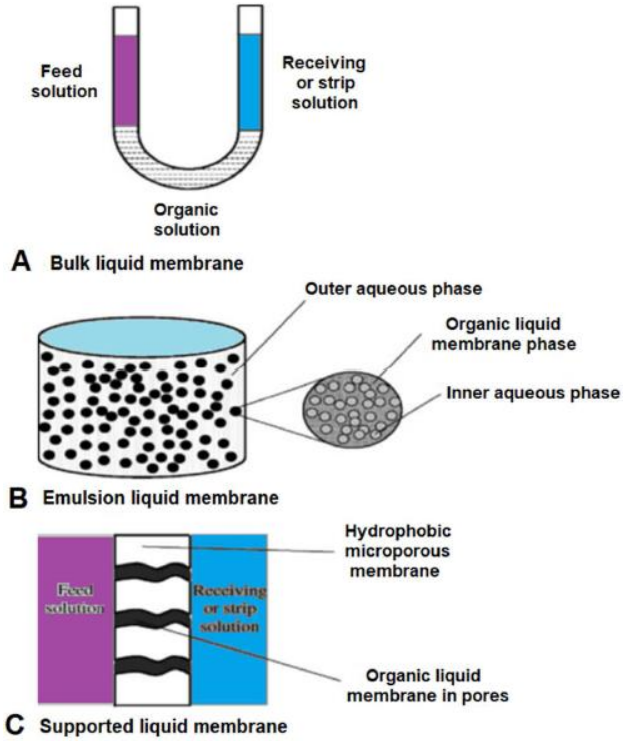

Figure 1. Representative device of chiral liquid membranes membranes: (**A**) bulk liquid membrane, (**B**) emulsion liquid membrane, and (**C**) supported liquid membrane (figure adapted and reproduced with permission from Ref. [74]).

Among these three systems, emulsion liquid membrane has a good separation performance, however a complicated operation procedure is required and cannot effectively avoid membrane leakage. Emulsion liquid membranes consist of double emulsions and are usually prepared by first forming an emulsion between the aqueous receiving phase and the organic phase containing the chiral carrier. This emulsion is then dispersed in the aqueous phase containing the racemic mixture to be resolved. The advantage of this configuration is the high interfacial area between the phases. However, the drawback is the need to use other compounds to stabilize and break the emulsions. Bulk liquid

membrane is relatively stable, but its mass transfer rate is very low. It is most common simple apparatus for a liquid membrane study. Therefore, this configuration is almost exclusively used for preliminary tests, for example, in the evaluation of possible carriers for a given separation, since they provide low interfacial area and low reproducibility of results. Compared with emulsion liquid membrane and bulk liquid membrane, supported liquid membrane recently has attracted a considerable attention because of its easy scaling-up, and low operating costs (extraction and re-extraction in one step). Here, liquid is held inside the support pores by capillary forces and transport takes place between the source and receiving phases, which pass over either side of the membrane surface. In general, the organic solvent contains the selective carrier in the feed solution. The supported liquid membrane is more attractive for possible industrial application than bulk liquid membrane and emulsion liquid membranes. Recently, support liquid membrane systems with hollow fiber membrane have been applied for separation of pharmaceutical compounds [75,76].

In general, the use of liquid membranes for chiral separations has the advantage that only a small amount of chiral extractant is required for a process of high productivity. In this technique, the chiral selector, which may be either a carrier or a solvent species, is used to introduce enantioselectivity into the separation process. However, the drawback of the liquid membrane is lack of long-term stability; the solvent consisting of membrane solution may evaporate, or the transporter and/or transporter/target molecule complex may be washed out during operation [65].

Regarding enantioselective solid membranes, two types were found, namely inherent chiral membranes (Figure 2) and membranes functionalized with immobilized chiral selectors (Figure 3). Different approaches are employed to prepare solid membranes from various polymers. Frequently, inherent chiral membranes are prepared by casting membrane-forming solutions of chiral polymers. The chiral polymers include those with chiral backbones and/or chiral side chains. Several membranes were prepared from chiral polymers where enantioselectivity was generated from chiral carbons in the main chain. Poly(γ-methyl-*L*-glutamate) [77,78], alginate [79,80], chitosan [79,81], cellulose [81–83] and their derivatives are frequently used as chiral polymers for the preparation of chiral membranes.

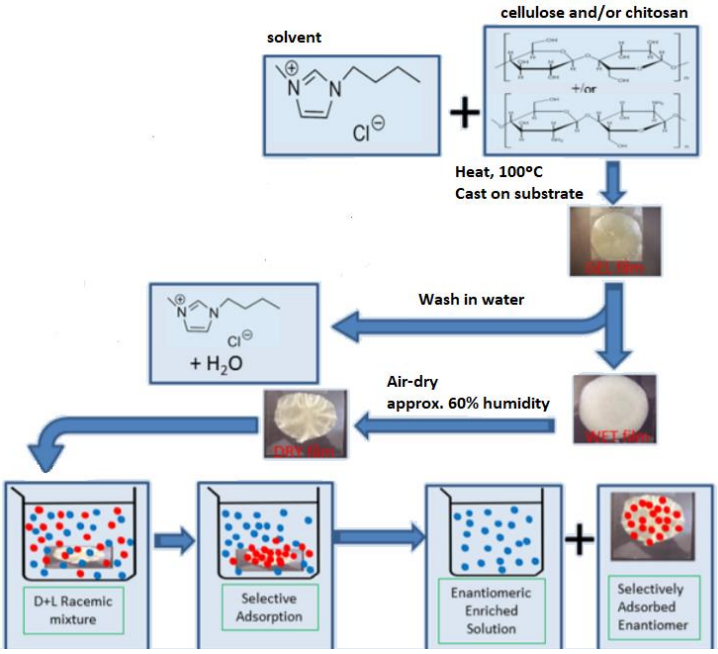

Figure 2. Representative example of inherent chiral membranes containing cellulose and/or chitosan (adapted from Ref. [81]).

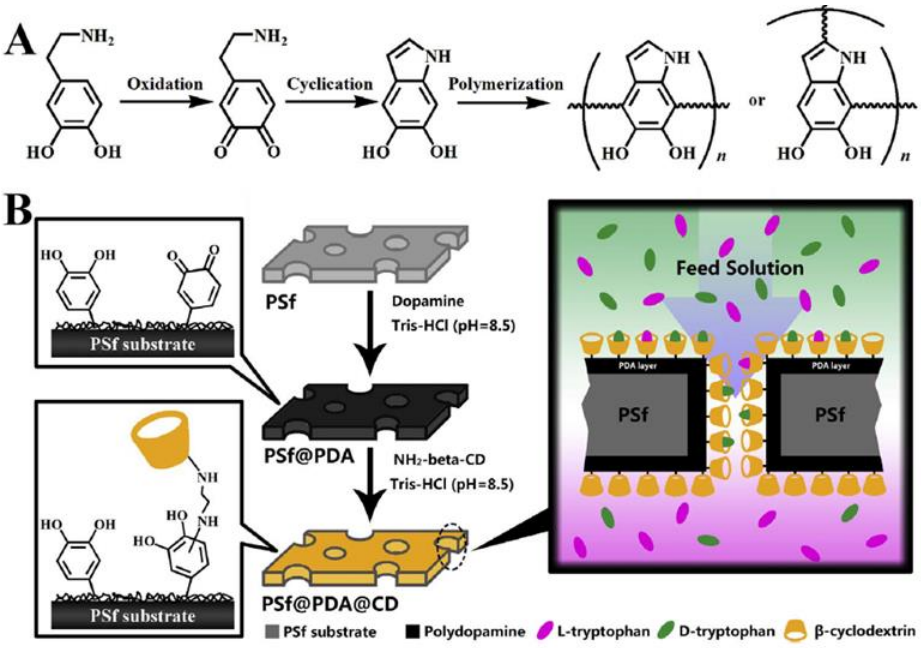

Figure 3. Representative example of membranes functionalized with immobilized chiral selectors: (**A**) the formation mechanism of PDA; and (**B**) procedure for preparation of a PSf-based enantioselective membrane (Reprint permission from Ref. [67]).

However, sometimes it is rather difficult to make high efficient chiral separation with membranes from chiral polymers alone, when the enantiomers interact with the flexible side chains of the membrane polymers not comprising chiral sites important for the effectiveness of the molecular interactions and, consequently, enantiorecognition. Therefore, membranes were prepared using modified polymers with a chiral branch including the polymer membrane containing chiral metal-Schiff base complexes [58], polymer membranes with saccharide side chains [84], polymer membrane obtained from acetylation of beta-cyclodextrin surface-functionalized cellulose [85] or from polysulfone grafted with *N*-dodecyl-4(*R*)-hydroxy-*L*-proline [86].

Polymers containing incorporated chiral selectors, such as beta-cyclodextrin [87–90], crown ether derivatives [91], bovine serum albumin [92], apoenzymes [93], antibodies [94], DNA [36,94–96], and terpenes [97] were used to obtain membranes functionalized with immobilized chiral selectors. Different methods can be used for chiral selector immobilization on surface, in pores, or in bulk configuration on base membranes, including impregnation, covalent grafting, or esterification [26]. Additionally, molecular imprinting can be used to create molecular recognition sites [98,99].

Molecular imprinting demonstrated to be a versatile and simple technique by introduction of molecular recognition sites for a desired template. In fact, it was found that molecularly imprinted polymers (MIPs) exhibit well-defined structures, high selectivity and binding affinity for the target molecules, considering that the caves created within MIPs are complementary to them in shape, size, configuration and functional moieties. Moreover, they have excellent chemical properties and comparing with other methods to introduce chiral recognition sites in polymeric membranes, the preparation of molecularly imprinted membranes (MIMs) are simple, low-cost, and effective [45,52]. Various review articles are found in literature regarding MIPs [45,48,49,100–107] and among them focusing on MIMs [52,98,99]. Figure 4 shows a representative example of a MIM.

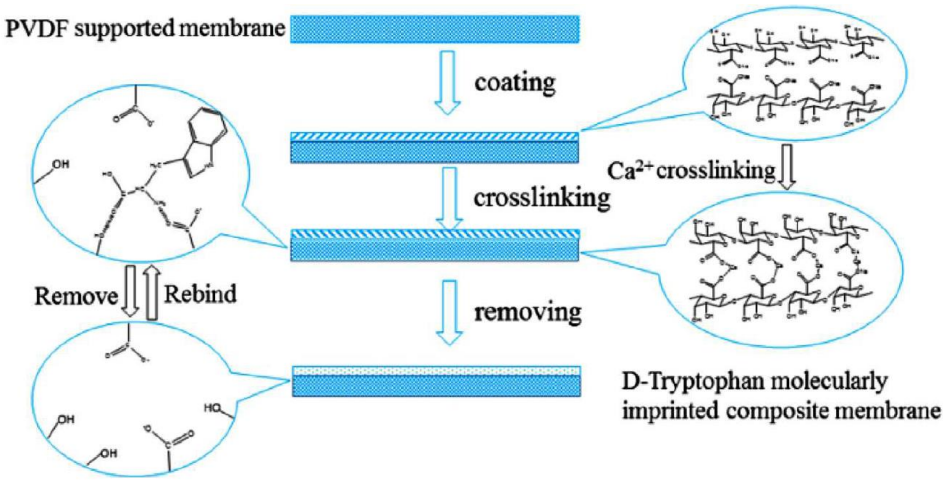

Figure 4. Representative example of MIM with preparation of *D*-tryptophan molecularly imprinted composite membrane (Reprint permission from Ref. [110]).

Generally speaking, all types of chiral membranes described have advantages and drawbacks, depending on the purpose of the application (Table 1).

Table 1. Advantages and drawbacks of the different types of chiral membranes.

Chiral Membrane	Advantages	Drawbacks
Bulk liquid membrane	Easy to design and operate. Good for preliminary studies in the evaluation of possible carriers for a given separation.	Low of long-term stability. The transporter and/or transporter/target molecule complex may be washed out during operation. Low reproducibility of results. Mass transfer rate is very low.
Emulsion liquid membrane	The fastest mass transfer rates of all liquid membrane systems. Highs separation factor and mass transfer flux can be achieved.	Complicated operation procedure. Leakage in the procedures. Low of long-term stability.
Supported liquid membrane	Easy to scaling-up and cascade design. Different type of supported can be used. Compared with emulsion and bulk liquid membranes, it could save the consumption and processing costs.	Leakage in the procedures. Low long-term stability.
Solid membrane with inherent chiral polymers	Several types of material are available: natural and synthetic polymers. High range of applicability.	Low efficiency in chiral separation.
Solid membrane functionalized with immobilized chiral selectors	Different type of support and material are available: natural and synthetic polymers. High range of applicability.	The synthetic strategies for development of chiral selectors to be immobilized on solid membranes could involve multi-step pathways with time-consuming and laborious work.
Imprinted membrane	High stability and reproducibility. High efficiency in chiral separation.	High specificity with consequent low range of applicability.

Finally, the non-enantioselective membranes generally are associated with other chiral recognition approaches such as enzymatic kinetic resolution [108,109], solution systems with micelles [110], and systems using chiral selectors [111–114]. They work as barriers or filtration mediums to selectively separate single enantiomers from a solution containing a racemate and enantioselective binding agents. Consequently, the resolution mechanism for this type of membranes is different from that for enantioselective membranes, being the differences in size the key to enantioseparation rather than the chiral recognition of one enantiomer by the membrane. For example, the formation of a complex of one enantiomer with a large chiral recognition molecule or the use of enzymes to selectively hydrolyze one of the enantiomers, followed by ultrafiltration of porous non-enantioselective membrane can be used to achieve enantioseparation [26].

Recently, non-enantioselective membranes have attracted much attention; however, the main objective of this work is on enantioselective membranes focusing in recent progresses and applications.

3. Recent Applications

Several enantioselective membranes have been developed allowing the enantioresolution of diverse classes of chiral compounds including pharmaceuticals, amines, amino acids, etc. (Figure 5).

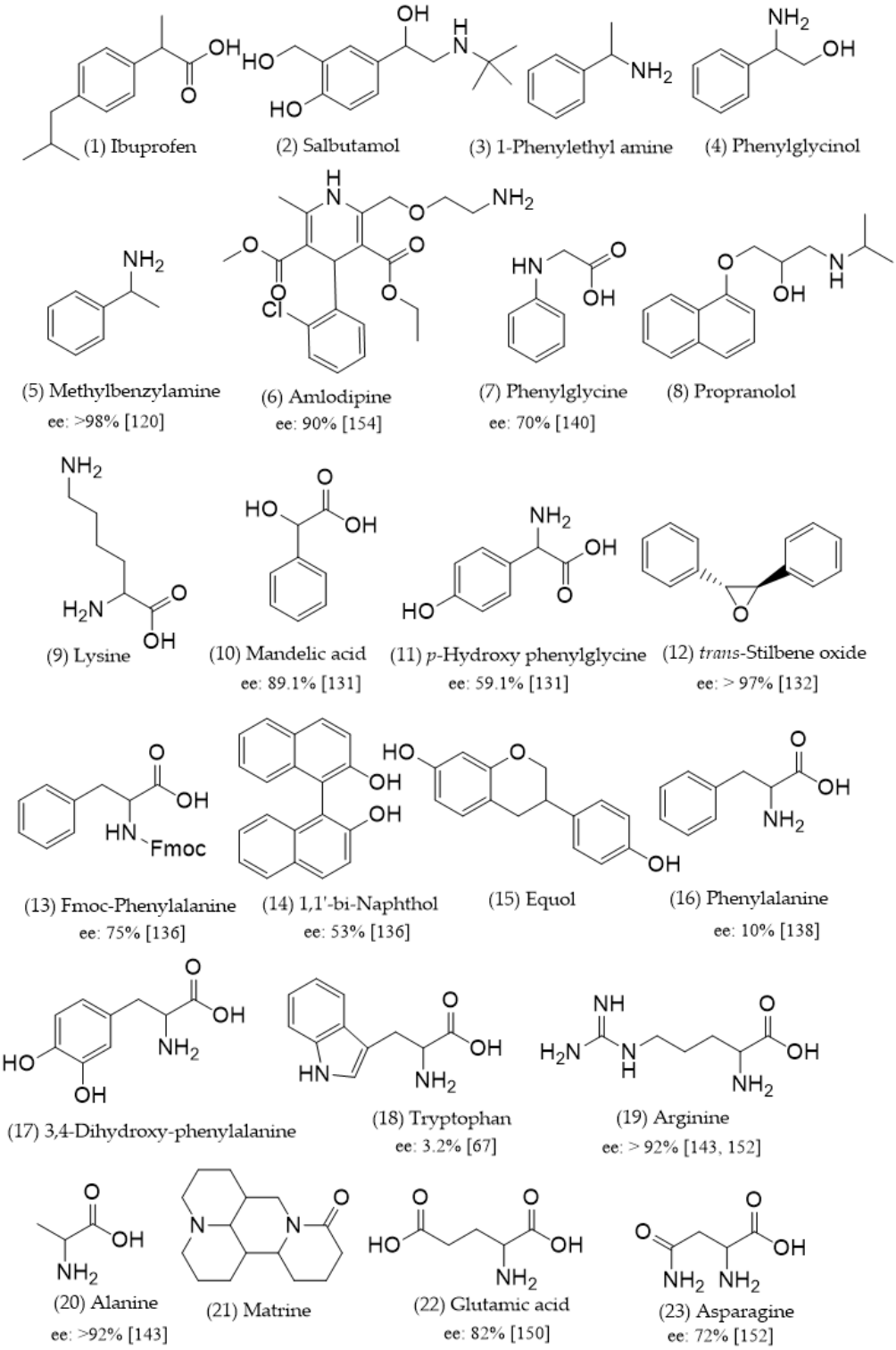

Figure 5. Chemical structures of compounds recently enantioseparated by membranes.

3.1. Liquid Membranes

The most recent applications of chiral bulk liquid membranes and supported liquid membranes for enantiomeric separation were described for pharmaceuticals, amines, amino acids, etc. For example, use of *L*-tartaric ester dissolved in n-octane as liquid membrane phase and polyvinylidene fluoride hollow fibers as membrane support was investigated to separate racemic ibuprofen (1). The cascade experiment allow the separation factor of 1.18 [75].

Salbutamol (2), a beta2-adrenergic agonist, was enantioselective separated with the simultaneous synergistic extraction and stripping method with *O*,*O*-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) and di(2-ethylhexyl) phosphoric acid (D2EHPA) as chiral and non-chiral extractants, respectively. Density Functional Theory (DFT) was also performed to better understands the chiral recognition mechanism of salbutamol enantiomers with (+)-DBTA. The synergistic extraction experiment was preliminarily performed and the maximum separation factor was up to 1.65. Hollow fiber supported liquid membrane was applied for the enantioseparation of salbutamol and the ratio of chiral to achiral extractant was 1.0:0.6, the separation factor was up to 2.0 in the stripping phase [76]. In another study, protonated phenylethyl amine (3) and phenylglycinol (4) were enantioselective transported with four enantiopure lipophilic crown ethers containing a diarylphosphinic acid unit in an aqueous source phase/lipophilic organic bulk liquid membrane/aqueous receiving phase system controlled by the pH of the media [115]. In previous study, crown ethers also showed appreciable enantiomeric recognition [116].

Bulk liquid membrane was also investigated with the chiral functionalized beta-cyclodextrin (heptakis (2,3,6-tri-o-acetyl)-β-cyclodextrin) as an extraction receptor in liquid-liquid extraction and carrier. The receptor exhibited carrier ability for aromatic amino acids transport through chloroform liquid membrane, especially for *L*-amino acids form [117].

Chiral amines, are important building blocks in the pharmaceutical industry, and biocatalytic synthesis of these compounds using ω-transaminases has been gradually more studied in recent years. A supported liquid membrane consisting of a hollow fibre membrane contactor in which the pores contain undecane was used for a supported liquid membrane, together with a packed bed reactor, to increase the yield of chiral amines produced through asymmetric synthesis using ω-transaminase. The reactor contained *Escherichia coli* cells with ω-transaminase from *Arthrobacter citreus*, immobilized by flocculation with chitosan. The system enabled continuous extraction of the amine product and was used to successfully shift the equilibrium in asymmetric synthesis of (*S*)-α-methylbenzylamine (5). A conversion of 98% was reached, compared to 50% without product extraction [118]. This system was further improved by implementing continuous control of the reactor pH using the amine donor substrate, and regeneration of the supported liquid membrane unit at regular intervals to maintain the extraction performance [119]. In another study with the amine transaminase catalyzed synthesis of chiral amines, alanine was investigated as amine donor for the reductive amination of a poorly water-soluble ketone (4-phenyl-2-butanone) in a combined in situ product removal approach using liquid membrane extraction together with an enzyme cascade. This strategy afforded very high product purity (>98%) with an integrated enrichment step and eliminated product as well as co-product inhibition [120].

Synergistic enantioseparation of amlodipine (6) from pharmaceutical wastewater by using hollow fiber supported liquid membrane was also examined. A chiral reaction flux mathematical model was applied. Relevant parameters affecting the enantioseparation efficiency of amlodipine were determined. It was found that the mathematical model proved to be in good agreement with the experimental data [121].

A polymeric pseudo-liquid membrane was constructed from poly(*N*-oleylacrylamide), and dibenzo-18-crown-6 (DB18C6) and dibenzo-21-crown-7 (DB21C7) were adopted as transporters for alkali metal ions. KCl was adopted as a model substrate for DB18C6 and CsCl the latter. *O*-Allyl-*N*-(9-anthracenylmethyl) cinchonidinium bromide was used as a transporter for chiral

separation of a racemic mixture of phenylglycine (7). The *L*-isomer was transported in preference to the antipode [65].

Extraction, separation, and quantification of propranolol (8) enantiomers from biological samples using electromembrane extraction combined with modified cyclodextrin capillary electrophoresis was also performed. Propranolol enantiomers were extracted from aqueous donor solutions, through a supported liquid membrane consisting of 2-nitrophenyl octyl ether impregnated on the wall of the hollow fiber, and into a 20-μL acidic aqueous acceptor solution into the lumen of hollow fiber. Numerous types of cyclodextrin were evaluated [122].

3.2. Solid Membranes with Inherent Chiral Polymers

Over the last few years, Ingole et al. have described several types of enantioselective polymer membranes for the resolution of chiral compounds [38,123–129]. More recently, they prepared and characterized chiral composite membranes using *L*-arginine, as a diamine monomer, through interfacial co-polymerization with trimesoyl chloride in-situ [130]. These composite membranes exhibited 64–78% separation of the tested α-amino acids. Excellent enantioselectivity for lysine (9) was achieved, with an enantiomeric excess and separation factor higher than approximately 92% and 21, respectively.

Membranes of cellulose, sodium alginate, and hydroxypropyl-beta-cyclodextrin were prepared for the chiral separation of mandelic acid (10) and *p*-hydroxy phenylglycine (11) [131]. The membrane material concentrations, the preparation conditions and feed concentrations were optimized to obtain good enantioseparations. Higher enantiomeric excess for mandelic acid (89.1%) was obtained on the cellulose membrane. For *p*-hydroxy phenylglycine, enantiomeric excesses of 42.6%, and 59.1% were obtained on the sodium alginate membrane, and on the hydroxypropyl-β-cyclodextrin membrane, respectively. It was the first report in which solid membranes of sodium alginate and hydroxypropyl-β-cyclodextrin were applied for the chiral separation of *p*-hydroxy phenylglycine [131].

New chiral polymeric membranes, based on a cellulose acetate propionate polymer were prepared and characterized for the chiral separation of *trans*-stilbene oxide (12), an important intermediate for the synthesis of chiral compounds [132]. The enantioseparation was possible through the membranes using a pressurized system. An enantiomeric excess over 97% was achieved when the membrane was prepared with 18 wt % cellulose acetate (CA) and 8 wt % cellulose acetate propionate (CAP) in the casting solution of dimethyl formamide/*N*-methyl-2-pyrrolidone/acetone. It was found that the effect of CAP content on the enantiomeric excess values was higher compared to the effect of CA content [132].

Polymers of intrinsic microporosity (PIMs) are other promising class of materials for preparation of membranes [133–135]. The first examples of chiral polymers of intrinsic microporosity were reported, in 2015, by Weng et al. [136]. They prepared and characterized the fluorescent ladder polymers (+)-PIM-CN and (+)-PIM-COOH derived from 5,5′,6,6′-tetrahydroxy-3,3,3′,3′-tetramethyl-1,1′-spirobisindane. Both polymers were solvent cast directly into semipermeable membranes and evaluated for their ability to enable the selective permeation of several racemates including, Fmoc-phenylalanine (13), and 1,1′-bi-2-naphthol (14). High enantiomeric excess values were observed revealing both high and enantioselective permeability for a range of racemates [136].

In another study, a monodisperse and surface-functionalized methyl methacrylate–*N*-isopropyl acrylamide (MMA–NIPAm) polymer was synthetized via atom transfer radical precipitation polymerization (ATRPP) in one-pot method. Then, MMA–NIPAm chiral selective cation-exchange membranes were prepared for efficiently separated racemic equol (15) [137].

A thermo-sensitive polymer comprising a poly(vinylidene fluoride) (PVDF) backbone and poly(*N*-isopropylacrylamide) (PNIPA) side chains was synthesized (PVDF-*g*-PNIPA), via radical copolymerization [138]. A chiral monomer, obtained by an acrylation reaction with *L*-phenylalanine and acrylyl chloride, and chiral micro-gels with *N*-isopropylacrylamide (NIPA), were also synthesized. By a phase inversion method, blending chiral micro-gels and PVDF-*g*-PNIPA, a new chiral thermo-sensitive membrane for chiral separation of phenylalanine (16) was prepared. Better

permeability was achieved for *D*-phenylalanine. The results showed that the temperature influenced the water flux of the membrane and consequently the enantiomeric excesses [138].

Nafion® and cellophane membranes in a two-compartment horizontal diffusion cell were used to measure the permeability and diffusion coefficients for the test system and for chiral separation of the racemic mixture of methyl lactates [139]. However, the chiral resolution was not reached. Additionally, a substantial difference between the transport and sorption of methyl lactates in Nafion® and cellophane was observed.

3.3. Solid Membranes Functionalized with Immobilized Chiral Selectors

Considering the wide choice of materials suitable for solid surface-modified membranes silica, polymeric surface are most common; however, a recent example with graphene oxide (GO) has also been described [140]. Robust mesoporous membranes comprising silica spheres were surface-modified with chiral selectors, including small molecules, macrocycles, and polymers were described [141]. Diffusion rates of enantiomers of a chiral dye through the resulting membranes were measured and corresponding permselectivities were calculated. The membranes showed enantioselectivities ranging 1.2–1.8, being not considerably affected by the structure of the surface-immobilized chiral selectors. It can be inferred that the enantiomeric selectivity resulted from the surface-facilitated mechanism of transport of enantiomers through the mesopores being on par with most reported polymer-based solid membranes and bulk liquid membranes [141].

GO based membranes derived from incorporating a chiral selector (*L*-glutamic acid) into GO flakes was prepared via simple vacuum filtration method. *L*-glutamic acid was used not only to provide the stacked GO nanosheets with the required stability to overcome their inherent dispensability in water environment but also finely tuned spacing of the GO nanosheets. 3,4-Dihydroxy-*D*,*L*-phenylalanine (17) was enantioseparated. Results showed that such membranes exhibited high chiral resolution ability, which were 1–2 orders of magnitude superior in the flux and greater in selectivity, compared to common chiral separation membranes [140].

Miao et al. reported a chiral resolution polysulfone membrane prepared via mussel-inspired chemistry. Modification of polysulfone membranes with dopamine, which underwent in situ polymerization on the membrane substrate, and using beta-cyclodextrin as chiral selector, provided a high resolution efficiency, in the optimal pH value, for the resolution of tryptophan (18) racemic mixture feed solution. The enantiomeric excess value of the membrane for racemic mixture achieved to approximately 3.2% when the feed solution of tryptophan racemic mixture was 5×10^{-5} mol/L and the operating pressure was 0.1 MPa. From these results an interesting application for large-scale production of efficient chiral membranes can be envisaged, inspired in natural products with the advantage of not requiring pre-treatment [67].

Composite enantioselective membrane was prepared by interfacial polymerization on a polysulfone support using vancomycin and 1,6-diisocyanatohexane as the monomers. The composite membrane was used for enantioseparation of phenylglycine (7)—which is an indispensable reagent in the syntheses of penicillins and cephalosporins. By optimizing the molar ratio of vancomycin and 1,6-diisocyanatohexane, the time of polymerization and the feed concentration of the racemate, an enantiomeric excess of over 70% of *D*-phenylglycine was obtained. Comparing the membrane adsorption, solid extraction, membrane chromatography, dialysis and ultrafiltration of vancomycin optical resolution membrane, the *L*-phenylglycine was prior adsorbed, while, the *D*-phenylglycine was first permeated the membrane suggesting that the enantioseparation mechanism of membrane was "adsorption-association-diffusion" [142].

Chiral resolution of arginine (19) and alanine (20) was reported by a chiral selective nanofiltration membrane containing *S*-(-)-2-acetoxypropionyl chloride [143]. The chiral selective layer of the membrane was prepared by interfacial polymerization of metaphenylenediamine, trimesoyl chloride, and *S*-(-)-2-acetoxypropionyl chloride in situ on the top of polysulfone membrane. The resolution capacity of the membrane improved by increasing *S*-(-)-2-acetoxypropionyl chloride in polymerizing

solution up to 0.03%. However, any increase exceeding 0.03% decreases the resolution capacity. Enantiomeric excess higher than 92% were observed for *D* enantiomers of both amino acids [143].

3.4. Imprinted Membranes

Among the different types of enantioselective membranes, only some MIMs have been developed after the last review (2016) specifically focusing this type of membranes [52].

Shah et al. prepared two types of phenylalanine imprinted adsorptive composite membranes by incorporating *D*-phenylalanine and *L*-phenylalanine imprinted submicron/nanoscale beads, into the *D*-phenylalanine and *L*-phenylalanine imprinted membranes matrix, respectively, by phase inversion technique after a uniform dispersion of beads within the polymeric solutions using simple physico-mechanical process [144]. The obtained phenylalanine imprinted composite membranes were employed in an ultrafiltration system for chiral separation of phenylalanine (16) racemate to achieve improved adsorption capacity and selectivity at a faster rate. Both types of membranes presented a higher adsorption capacity and selectivity comparing to control membranes and beads [144].

Zhou et al. described a totally green and clean preparation method for *D*-tryptophan imprinted composite membranes using the natural polymer sodium alginate as functional polymer, $CaCl_2$ as crosslinking agent and water as solvent [145]. As supported membrane, the polyvinylidene fluoride membrane was chosen. No additional organic solvent or compounds were used. By comparing to other previous described works aiming at the separation of *D*-tryptophan [80,129,146,147], besides being environment friendly and low cost, this method was found to increasing the enantioseparation [145].

To improve the performance of the MIMs, other innovative and creative strategies were developed allowing the preparation of grafting type MIMs. This type of MIMs showed high recognition and separation ability as well as good mechanical strength [148,149]. Recently, to specifically separate the alkaloid matrine (21), Gao et al. designed and prepared a novel polysulfone-based MIM with graft type (GMIM) by a film-forming method of immersion-precipitation phase transformation combined with molecular surface-imprinting technique [150]. By a phase inversion method a porous asymmetry membrane of chloromethylated polysulfone (CMPSF) was first prepared, and then was modified by amination with ethanediamine, resulting in an aminated polysulfone membrane (AMPSF). Then, methacrylic acid (MAA) was graft-polymerized onto the surface of the membrane. The matrine surface-imprinting was carried out using ethylene glycol diglycidyl ether (EGDE) as crosslinker. As expected, the obtained imprinted membrane GMIM showed specific recognition selectivity and excellent binding affinity for matrine (21) [150].

The same group successfully prepared a novel grafting-type MIM of a single enantiomer of amino acids by an innovative and advanced surface-imprinting technique of "synchronously graft-polymerizing and molecule imprinting" [151]. Firstly, the aminated microfiltration membrane of polysulfone, AMPSF membrane, was prepared creating a surface-initiating system of $-NH_2/S_2O_8$. Dimethylaminoethyl methacrylate (DMAEMA), used as functional monomer, was combined around the single enantiomer amino acid *L*-glutamic acid used as template. DMAEMA and the crosslinking agent *N*,*N*′-methylenebisacrylamide (MBA) produced graft/crosslinking-polymerization on the surface of AMPSF membrane, whereas *L*-glutamic acid molecules were wrapped within the grafted polymer layer, obtaining grafting type *L*-glutamic acid molecule-imprinted membrane (*L*-Glu-MIM). This membrane was found to present specific recognition selectivity and high enantioresolution for glutamic acid (22), since only the *L*-glutamic acid molecules in the racemate can efficiently pass across the membrane, being the *D*-glutamic acid molecules blocked. Hence, the penetrating fluid achieved an enantiomeric excess higher than 82%. Moreover, comparing with the previous method that they used to prepare imprinted membranes, i.e., "pre-graft polymerization and post-imprinting" [150], it was concluded that the present method was more effective and simple, and the obtained membranes revealed a better performance [151].

Ingole et al. prepared a *D*-arginine imprinted terpolymer P(AN-*co*-AA-*co*-AAm) membrane by the wet phase inversion method, using acrylamide and acrylic acid as the functional monomers,

and acrylonitrile as a cross linker [152]. The evaluation of the enantiomeric resolution ability of the α-amino acids arginine (19) and asparagine (23) was carried out in pressure driven ultrafiltration technique. Higher enantiomeric excess (93%) was obtained for arginine comparing to asparagine (72%).

Akgönüllü et al. reported the preparation of imprinted cryogel cartridge for the chiral separation of phenylanine (16) [153]. *N*-Methacryloyl *L*-phenylalanine (MAPA) was used as a functional monomer for complexing with *L*-phenylanine, being more selective for this enantiomer than *D*-phenylanineor both enantiomers of tryptophan (18). These membranes demonstrated to be reusable many times without significant loss of the adsorption capacity [153].

Lai et al. developed a triple recognition chiral extraction process to separate amlodipine (6) based on the combination of molecularly imprinted hollow fiber membrane and cross-flow biphasic recognition extraction [154]. A dismountable hollow fiber module coated with molecularly imprinted polymer was used for the enantiomer separation, and the cross-flow extraction was applied with *D*-tartaric acid in feed phase and sulfobutyl ether-beta-cyclodextrin in stripping phase. The synergistic effect of molecularly imprinted polymer and dual chiral additives was investigated. Excellent enantioseparation was obtained achieving optical purity up to 90% [154].

4. Conclusions and Future Perspectives

According to recent publications, the use of chiral membranes demonstrates to be a promising approach for scaling up enantiomeric separations, and a variety of new materials is under investigation, including chiral inorganic structures. Liquid membranes have been applied for pharmaceuticals, amine and amino acid separations, as well as in conjugation to biotransformation. Regarding solid membranes, the imprinted membranes are associated with the most auspicious methodology, as it can be designed for specific applications; it shows high stability; and the enantiomers are obtained with high enantiomeric purity. Despite different types of chiral membranes and variety of applications already described, the use of chiral membranes is still restricted to enantioseparation in small scale. Nevertheless, this technique did not find broad applicability as preparative enantiomer separation by LC, and most reports are related only to applications for amino acids. However, as can be inferred from many works, the imprinted chiral membranes have the potential for specific application, and polymers such as cellulose derivatives can be developed for broad application and high selectivity. However, future research is needed for industrial applications, as it is undoubtedly a very interesting area to explore.

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