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Review

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Recent advances in chiral drug separation membranes: design, mechanisms, challenges, and prospects

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Abstract: The presence of chirality, a fundamental attribute found in nature, is of great significance in the field of pharmaceutical science. Chiral drugs are unique in that their molecular structure is non-superimposable on its mirror image. This stereoisomerism significantly impacts the functionality, metabolic pathway, effectiveness, and safety of chiral medications. The enantiomers of chiral drugs can exhibit diverse pharmacological effects in the human body. As a result, it is essential to separate and purify chiral drugs effectively. Despite the abundance of reports on chiral drug separation membranes, there is a dearth of comprehensive reviews. This paper aims to fill this gap by providing a thorough review from a materials perspective, with a focus on the design and construction of chiral drug separation membranes. Furthermore, it systematically analyzes the separation mechanisms employed by these membranes. The paper also delves into the challenges and prospects related to chiral drug separation membranes, with the intention of imparting valuable insights for further research and development in this field.

Key words: Chiral drugs; Chiral separation; Separation mechanisms; Membrane separation

1 Introduction

Chirality refers to the property of a compound by which its molecular structure and its mirror image cannot be superimposed. Many organic compounds possess this chiral property (Pinto et al., 2020; Zhang et al., 2021; Zhu et al., 2023). The significance of chiral molecules extends to the domains of life sciences, chemistry, pharmaceuticals, food, and the environment (Yoo and Park, 2019; Matencio et al., 2020; Lu et al., 2021b). Drugs with chiral structures are referred to as chiral drugs. In chiral drugs, the molecule's stereo configuration results in two asymmetric isomers, namely the left-handed (levorotatory) and right-handed (dextrorotatory) forms (Sanganyado et al., 2017; Bewley et al., 2023; Yu et al., 2023). The stereoisomeric nature of chiral drugs has a profound effect on their activity, metabolic pathways, effectiveness, and safety. Effective separation and purification of chiral drugs are crucial because the left-handed and right-handed enantiomers may exhibit different pharmacological activities and side effects (Song et al., 2020; Li et al., 2023). Chiral drugs with single optical activity usually have more defined therapeutic targets and higher efficacy, and cause fewer adverse reactions. Chiral drugs play an important role in the treatment of cardiovascular diseases, antibacterial drugs, and anticancer drugs. In addition, chiral molecules can be used as precise diagnostic tools to help accurately detect disease through unique biomolecular interactions. Chiral drug separation has become an important research area in the pharmaceutical industry and clinical medicine, with the goal of improving the efficiency, quality, and safety of pharmaceutical processes and providing better treatment outcomes for patients.

Through chiral separation technology, a single enantiomer with a therapeutic effect can be isolated,

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preventing the side effects of ineffective or harmful isomers and thus improving drug efficacy. More interestingly, chiral drug separation technology helps in studying the differences in the absorption, metabolism, and other processes of chiral drugs, so as to optimize drug dosage. Common techniques for separating chiral drugs involve high-performance liquid chromatography (HPLC) (Ali et al., 2018; Yu XX et al., 2020, Yu YY et al., 2020; Lv et al., 2022), gas chromatography (GC) (Köhler et al., 1992; Zhang et al., 2015; Cui et al., 2020; Tang et al., 2022; Huang et al., 2023), and crystal chemistry methods (Zhao et al., 2014; Leek et al., 2017; Zeng et al., 2021, 2022). Nevertheless, these traditional techniques frequently necessitate costly chiral stationary phases, solvents, and equipment, thereby augmenting the expense and intricacy of separation. In addition, their applications are somewhat limited due to issues such as inefficient separation, complicated operations, and a detrimental effect on the environment. Hence, the pursuit of novel, effective, economical, and eco-conscious approaches for chiral drug separation has emerged as a prevailing area of research.

Chiral drug separation membranes are emerging separation techniques that offer advantages such as high separation efficiency, good selectivity, and controllability, that overcome the limitations of traditional methods. With the expansion of the global pharmaceutical industry, there is a concurrent increase in demand for chiral separation membranes. Companies operating in the membrane separation technology market can achieve cost-savings by implementing this technology, while simultaneously mitigating non-compliance risks, thereby playing a pivotal role in enhancing the economic efficiency of the pharmaceutical sector. Based on their morphology, chiral membranes are typically categorized as liquid or solid membranes (Petrusová et al., 2023). Liquid membranes take advantage of specific disparities to induce varying movement rates of enantiomers, thereby attaining chiral separation (Dżygiel and Wieczorek, 2010). However, these membranes have poor mechanical stability and durability, limiting their application and industrial-scale production (Gössi et al., 2018). With the advancement of research in new surfactants and emulsion-breaking techniques, though, liquid-membrane technology has evolved from the theoretical stage to industrial production. In contrast, solid membranes have already met the requirements of industrial production in terms of stability. Solid membranes utilize the differential affinity of their internal or external chiral sites for the isomers, resulting in the selective passage of different enantiomers across the membrane under various driving forces such as concentration gradient, pressure difference, and potential difference (Liu TQ et al., 2021). Despite the significant advantages of solid-film technology, such as simplicity and cost-effectiveness, there are still several practical challenges, especially the balance between flux and separation efficiency.

While there have been many studies on chiral drug separation membranes, there are few related reviews, possibly due to the wide range of disciplines and materials involved. This paper systematically introduces the separation mechanisms of chiral drug separation membranes and provides an overview of the design and construction of separation membranes from a material perspective (Fig. 1). In addition, it presents thoughts on existing issues and future research directions, aiming to contribute to the development of the field of chiral drug separation membranes.

2 Significance of chiral drug separation membranes

2.1 Enhancement of separation efficiency

Chiral drugs are pharmaceutical compounds that exist in two mirror-image forms, known as enantiomers: left-handed (levorotatory) and right-handed (dextrorotatory) enantiomers. Separating and purifying these enantiomers is crucial for obtaining highly pure drug products.

Using chiral drug separation membrane technology, pharmaceutical companies can now separate a drug's left-handed and right-handed enantiomers more efficiently. This technology exploits the different molecular interactions and physical properties of enantiomers to achieve separation in a more streamlined way, reducing production costs.

The increased availability of chiral drugs not only benefits pharmaceutical companies but also contributes to the supply of drugs in the market. Efficient separation and purification of chiral drugs ensure that high-quality pharmaceutical products are readily available to patients. This technology plays a significant role in advancing drug development and improving healthcare outcomes.

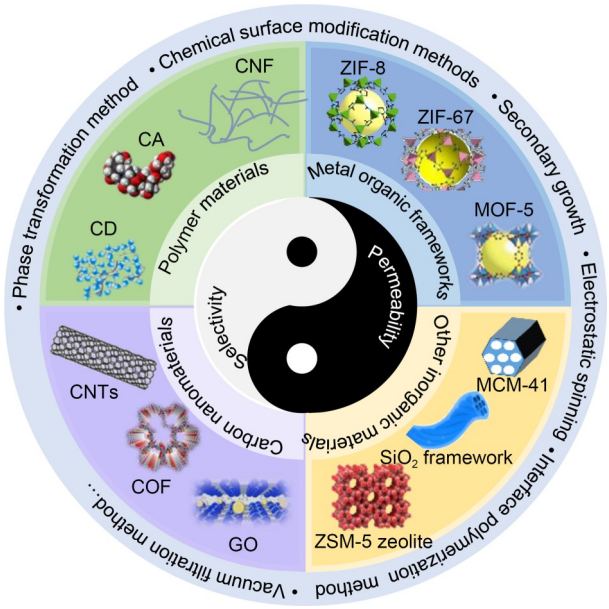

Fig. 1 Chemical structures of different chiral drug separation membranes, and related construction methods. CNF: cellulose nanofiber; CA: cellulose acetate; CD: cyclodextrin; CNTs: carbon nanotubes; COF: covalent organic framework; GO: graphene oxide; MOF: metal-organic framework; ZSM: zeolite socony mobil; ZIF: zeolitic imidazolate frameworks; MCM: mobil composition of matter

2.2 Improvement of drug safety

The left-handed and right-handed enantiomers of chiral drugs may exhibit different pharmacological activities and side effects. By employing chiral drug separation membrane technology, these chiral isomers can be effectively separated to obtain high-purity chiral drugs. The application of this technology helps to improve the therapeutic efficacy of drugs, reduce potential side effects, and enhance the safety and reliability of drug treatment. By obtaining pure enantiomers, pharmaceutical companies can ensure the consistency and reliability of drug treatment. The separation process enables the production of drugs with known and controlled therapeutic effects, reducing the variability in patient response to medication. This consistency enhances the efficacy of drug treatment and improves patient outcomes.

2.3 Promotion of new drug discovery and development

The market potential for chiral drugs is enormous, but traditional chiral separation methods face various limitations and challenges. Through continuous research and development of chiral drug separation membrane technology, separation efficiency and selectivity can be improved, providing new avenues for the development of innovative chiral drugs. Continuous research and development in this field allow for the exploration of new chiral separation materials and methods. Scientists can work towards developing membranes with enhanced separation efficiency and selectivity. This improvement enables a more precise separation of chiral isomers, leading to higher purity and quality in the production of chiral drugs.

3 Mechanism of chiral drug separation membranes

A chiral separation membrane is a thin film that can selectively separate chemical substances with different chiral properties. The separation mechanism of chiral membranes can be either facilitating transport or retarded transmission mechanism (Han et al., 2021; Petrusová et al., 2023). The mechanism of facilitated transport is that the chiral recognition site has a high affinity for a certain enantiomer and can accelerate its transmembrane transport. In this case, the presence of chiral recognition sites promotes the selective transmission of enantiomers (Noble, 1992; Zhang et al., 2017). The mechanism of retarded transmission is that the chiral recognition site has a strong binding affinity for an enantiomer, resulting in a longer residence time on the membrane, while the other enantiomer preferentially passes through the membrane and penetrates. In this case, the transmission rate of different enantiomers is different through the retarded transmission mechanism, which leads to the separation of enantiomers (Gu et al., 2020).

In general, chiral films based on the facilitating transport mechanism are described as diffusion-selective, while chiral films based on the retarded transmission mechanism are identified as adsorption-selective. However, most chiral separation processes involve selective adsorption and diffusion (Zhu et al., 2023). Thus, a membrane that exhibits diffusion selectivity may have adsorption selectivity for one enantiomer and diffusion selectivity for the opposite enantiomer, which means that the permeation selectivity of enantiomers is primarily determined by the main transport process (Xie et al., 2008).

3.1 Facilitating transport mechanism

A chiral separation membrane is equipped with a chiral recognition site, enabling it to selectively engage with particular chiral compounds. This interaction can be achieved through forces such as electrostatic interactions, hydrogen bonds, or van der Waals forces. The chiral recognition site exhibits a strong attraction towards an enantiomer and can accelerate the transmembrane transport of the enantiomer (Rea et al., 2019; Suttipat et al., 2020; Xu et al., 2022). In contrast, the affinity for another enantiomer is lower and the transfer rate is slower. By facilitating the transport mechanism, the chiral separation membrane can selectively separate different enantiomers.

Zhou et al. (2020) prepared a polyimide film substrate and subsequently combined the chiral selector cyclodextrin with m-phenylenediamine monomer, which was then incorporated into the selective layer for interface polymerization. Using racemic amino acids as model chiral selectors, enantiomeric selectivity of 1.55 and 0.60 was observed under two different operating modes driven by the concentration gradient and pressure gradient, respectively. The concentration-driven mode demonstrated the mechanism of facilitating transport separation. Some chiral metal-organic framework (MOF) membranes have also used the facilitating transport mechanism. For example, Kang et al. (2013) prepared enantiopure MOF membranes (Ni_2(L-asp)$_2$(bipy)) by the in situ growth method on nickel mesh. R-2-methyl-2,4-pentanediol (R-MPD) was preferentially transported due to its specific interaction with the MOF membrane (Fig. 2a). By combining the MOF with polyvinylidene fluoride (PVDF) polymer through an impregnation and precipitation method, a CD-MOF/PVDF composite membrane for chiral amino acids was formed for the first time (Ye et al., 2023). D-phenylalanine (D-phe) and L-phenylalanine (L-phe) diffused into the membrane, creating a concentration gradient as the driving force. L-phe, which exhibited strong binding affinity to the CD-MOF, was adsorbed in the PVDF membrane matrix, while D-phe selectively penetrated through the membrane, achieving chiral separation (Fig. 2b).

Chiral membranes enable facilitated transmembrane transport, with their permeation flux being inversely proportional to their enantiomeric selectivity. As the driving force increases, chiral molecules induce convection on the membrane, resulting in a rapid decrease in enantiomeric selectivity (van der Ent et al., 2001; Weng et al., 2015). Therefore, chiral membranes based on facilitated transport mechanisms may be more suitable for practical applications.

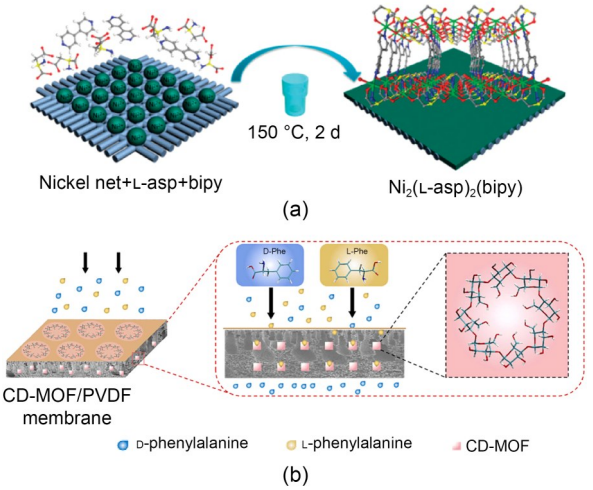

Fig. 2 (a) Schematic diagram of homochiral MOF membrane preparation by in situ growth on nickel mesh (reprinted from (Kang et al., 2013), Copyright 2013, with permission from Royal Society of Chemistry); (b) chiral separation mechanism of a CD-MOF/PVDF membrane (reprinted from (Ye et al., 2023), Copyright 2023, with permission from Elsevier)

3.2 Retarded transport mechanism

The retarded transport mechanism is also an important mechanism of chiral membrane separation. In this mechanism, the chiral separation membrane produces a specific binding effect with the chiral compound through the chiral recognition site. The chiral recognition site has a strong binding affinity for an enantiomer, resulting in the enantiomer staying on the membrane for a long time. Corresponding to this is another enantiomer, which has a relatively weak bond to the chiral recognition site and therefore a faster transmission rate (Ulbricht, 2004; Xie et al., 2008). Through the retarded transport mechanism, the chiral separation membrane can realize retarded separation of enantiomers.

Enantiomeric separation membranes based on graphene oxide (GO) have been shown to use transport mechanisms that either facilitate or retard, depending on the choice of chiral selectors. Gong et al. (2022) used a dipeptide as a chiral selector for separating racemes because it had a longer molecular length than a single amino acid as well as two chiral centers, and was more likely to penetrate the interlayer space

of the GO membrane. Compared to traditional chiral separation membranes, the dipeptide-modified GO membranes exhibited a maximum separation factor of 1.85, with a 1–3 order-of-magnitude increase in throughput, especially when the transport mechanism shifted from facilitation to retardation compared to previously reported GO membranes (Fig. 3a). Similarly, Li XX et al. (2021) chose mono-(6-amino-6-deoxy)-β-cyclodextrin (β-CD) as the chiral selector for separation of racemes in the base GO membrane. The enantioselective affinity of β-CD to L-enantiomers is much stronger than that of D-enantiomers, so this β-CD-modified GO membrane (β-CD-GOM) exhibited a retarded transport mechanism (Fig. 3b). It had excellent enantioselectivity, and the enantiomer excess (ee%) value was close to 100%.

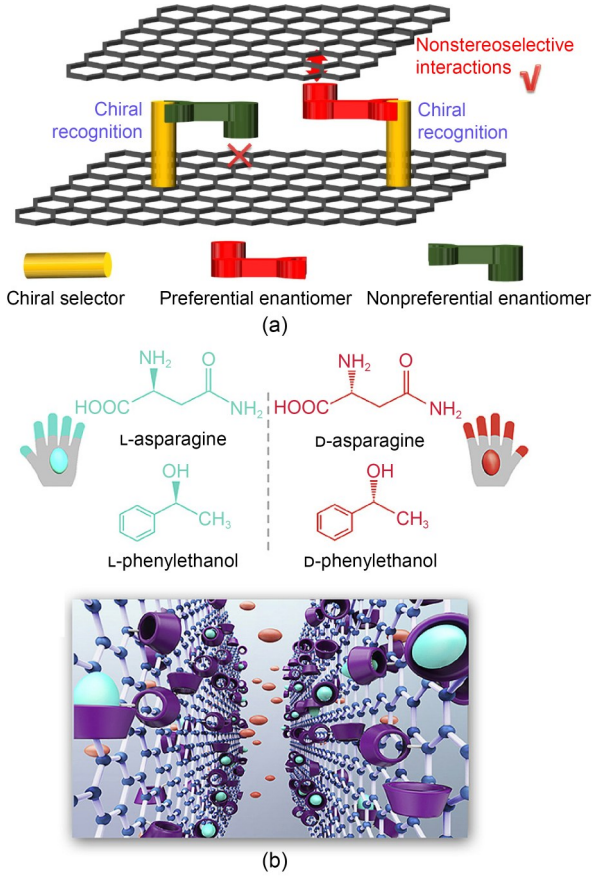

Fig. 3 Stylized illustration of (a) an L-Glutamate dipeptide modified graphene oxide (L-Glu-Glu-GO) composite membrane (reprinted from (Gong et al., 2022), Copyright 2022, with permission from Elsevier); (b) β-cyclodextrin modified graphene oxide (β-CD GO) composite membranes (reprinted from (Li XX et al., 2021), Copyright 2021, with permission from Elsevier)

Overall, chiral separation membranes based on the retarded transport mechanism, particularly those utilizing GO as a platform, offer enhanced enantioselectivity and improved separation performance. These membranes hold great potential for various practical applications requiring the separation of enantiomers, such as pharmaceutical production and chemical synthesis.

4 Design and construction of chiral drug separation membranes

To achieve efficient and selective separation of chiral pharmaceuticals, designers need to select appropriate membrane materials, regulate polymer structures, and incorporate suitable functional groups or employ molecular imprinting techniques. When designing chiral pharmaceutical separation membranes, the selection of suitable materials is crucial. These materials should possess good chiral selectivity and separation efficiency, and their mechanical properties, chemical stability, and reusability should also be considered.

4.1 Selection and design of membrane materials

4.1.1 Polymer-based chiral membranes

When the structure and composition of polymers are precisely controlled, polymer-based chiral separation membranes can selectively control chiral separation (Zhang YF et al., 2020; Vedovello et al., 2022a). The affinity of chiral molecules can be adjusted by changing the key parameters of the polymer, such as the three-dimensional configuration, porosity, or surface functional groups, to achieve efficient separation and enrichment of chiral molecules. In addition, a wide variety of materials for polymer-based chiral separation membranes can be flexibly selected and customized according to the requirements of a specific application.

Some polymer materials, such as cellulose (Conley et al., 2017; Gaálová et al., 2020; Lu et al., 2022; Wang et al., 2023; Zhao et al., 2024), alginates (Guo et al., 2020; Xu et al., 2023), chitosan (Tang et al., 2018; Zhang GH et al., 2019), and poly(γ-methyl glutamate) (Halmschlag et al., 2019), already have chiral recognition sites and can be directly used to prepare chiral separation membranes. For example, enantiomer-selective membranes prepared from nitrocellulose can be used to study the flux and permeation selectivity of D,L-tyrosine (Jiang et al., 2012). Cross-linked

enantiomer-selective membranes prepared from sodium alginate and chitosan can be used to study the permeation selectivity of membranes for separating tryptophan and tyrosine. As the degree of crosslinking increases, the membranes exhibit higher enantiomeric selectivity (Kim et al., 2003).

To further improve the chiral selectivity of polymer films, chiral recognition sites can be increased by modifying chiral selectors or molecular imprinting. Common chiral selectors include cyclodextrin (CD) (Huang et al., 2022; Qiu et al., 2022), amino acid (Yang and Sun, 2022), and bovine serum albumin (Liu et al., 2023a), which are fixed and modified on the pore surface or polymer matrix by means of impregnation and grafting. As shown in Fig. 4a, Ke et al. (2021) prepared chiral polyester composite film by covalently bonding CDs with commercial cellulose acetate film using trichloropropane as the crosslinking agent. They investigated the effects of modification conditions such as reaction temperature, concentration of trichloropropane

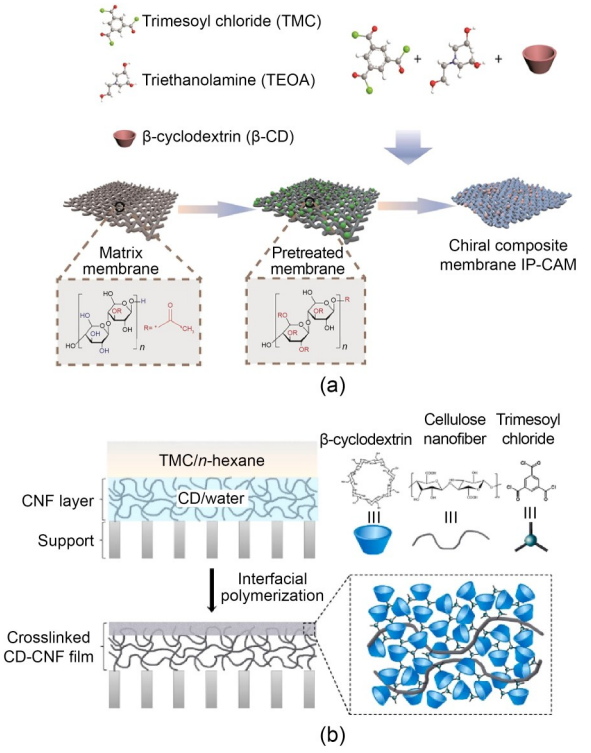

Fig. 4 Schematic illustration of (a) the preparation process for chiral composite membrane (reprinted from (Ke et al., 2021), Copyright 2021, with permission from Elsevier); (b) interfacial polymerization between CD (β-CD as an example), CNF, and trimesoyl chloride (TMC) and the structure of the crosslinked β-CD TMC CNF composite membrane (reprinted from (Lu et al., 2022), Copyright 2022, with permission from Elsevier)

solution, and organic additives on enantiomer separation. Enantiomer separation of (RS)-warfarin and (RS)-nefopam was achieved. Lu et al. (2022) prepared cyclodextrin-nanocellulose composite membranes by interfacial polymerization using CD molecules as the reaction monomer, nanocelluloses (CNF) as the support structure, and 1,3,5-benzoyl chloride as the crosslinking agent, and the result was excellent chiral molecular resolution performance with an ee% of 100%. CD molecules have a large number of chiral recognition sites and intrinsic micropore structures, and 1,3,5-benzoyl chloride crosslinked CDs films simultaneously achieve efficient recognition and transport of chiral molecules (Fig. 4b).

Furthermore, in this field, molecularly imprinted membranes, which are constructed based on the interaction between imprinting molecules and functional monomers to form molecular recognition cavities, also play an important role. These membranes can achieve highly selective recognition of target molecules. Li et al. (2018) prepared an enantiomer-selective membrane with high permeation selectivity and flux by using acetic-acid cellulose containing imprinting molecules to coat ZrO_2-modified alumina templates, achieving an ee% of 94.5%. Molecularly imprinted membranes exhibit specific recognition at the molecular level and have good operational stability (Fig. 5). However, there are still challenges such as high preparation costs and limited selectivity imposed by template molecules, leaving room for further development.

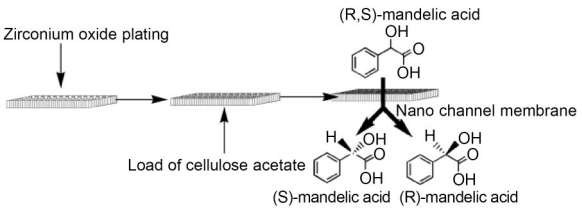

Fig. 5 Schematic diagram of preparation and separation of molecularly imprinted nanochannel membranes (reprinted from (Li et al., 2018), Copyright 2018, with permission from American Chemical Society)

4.1.2 Metal organic frameworks-based chiral membranes

Polymer-based chiral separation membranes can control separation efficiency when the composition and structure of the polymer material are adjusted to meet the separation demands of different chiral molecules. However, some chiral molecules can exhibit strong affinity for polymer-based chiral separation

membranes, leading to decreased separation efficiency and potential damage or degradation of the membrane material. In the past few years, MOFs and their derivatives have received significant attention in terms of chiral drug separation due to their well-defined and tunable pore size, high surface area, and excellent adsorption properties (Duerinck and Denayer, 2015; Das et al., 2018; Ma et al., 2022). These MOFs can obviate the limitations of polymer membranes by providing stability, as well as improved selectivity and efficiency through precise control over pore structure and surface properties. Overall, MOFs and their derivatives have emerged as a significant research focus in the field of chiral drug separation, providing new opportunities for the development of highly efficient and selective chiral separation membranes (Han et al., 2018; Huang et al., 2020; Liu YH et al., 2021; Lu et al., 2021a; Chen et al., 2022).

Navarro-Sánchez et al. (2017) developed a chiral Cu(II) 3D MOF based on the tripeptide Gly-L-His-Gly (GHG), aiming to achieve enantioselective separation of phenylpropanolamine and ephedrine. Monte Carlo simulations revealed that the chiral recognition was related to the preferential binding of one enantiomer. The team attributed this to the formation of stronger or additional hydrogen bonds with the framework, which resulted in more energetically stable diastereomeric complexes. This study is the first example of using MOFs for the separation of chiral polar drugs (Fig. 6a). Chan et al. (2018) prepared a chiral separation membrane (L-His-ZIF-8) by incorporating the natural amino acid L-histidine (L-His) into the ZIF-8 framework. The results showed that the membrane exhibited good chiral selectivity for racemic 1-phenylethanol, with an ee% of 76% (Fig. 6b). Additionally, the combination of magnetic nanoparticles with MOFs has shown promising results in enantioselective separation due to the large surface area per unit volume and strong magnetic response. As shown in Fig. 6c, functionalized homochiral MOFs were prepared by the team, combining magnetic Fe_3O_4/SiO_2 nanoparticles with homochiral MOF [Zn_2(bdc)(L-lac)(dmf)](DMF) (ZnBLD), and applied for the efficient enantioselective capture of chiral drug intermediates. Under optimized conditions, the ee% value of methyl phenyl sulfoxide (MPS) reached 85.2% within 3 min (Chang et al., 2015).

In the separation and extraction of chiral drugs, host-guest interactions mediated by MOFs have increased ee%, selectivity, and resolution. However, further research is still needed to improve the functional binding sites, and thus enhance the performance of chiral membranes.

4.1.3 Carbon-nanomaterial-based chiral membranes

In 1991, a new carbon structure composed of coaxial multi-layer hollow walls, known as carbon nanotubes (CNTs), was first discovered (Iijima, 1991). CNTs exhibit high mechanical strength, conductivity, and chemical stability, along with unique chiral structures and pore properties which give them distinctive advantages in chiral separation (Hemasa et al., 2017; Soleymani et al., 2017). However, the synthesis of pure and high-quality CNTs and their assembly into regular membrane structures remain technical challenges. For instance, Gogoi et al. (2020) employed a strategy involving covalent functionalization of hydrophobic single-walled carbon nanotubes (SWCNTs) with chiral selective –COOH groups, followed by acylation termination with D-tryptophan as a chiral probe. The functionalized SWCNTs were assembled into thin-film nanocomposite membranes using the reverse osmosis method. During the separation of the racemic mixture of tyrosine, the D-isomer preferentially adsorbed onto the membrane while the L-isomer exhibited selectivity in membrane transport, resulting in a high ee% of 98.86%. This example highlights the potential of functionalized CNTs in chiral separation, an area where further research and technological advancements could significantly enhance the performance and stability of CNT-based chiral separation membranes, paving the way for broader practical application.

Graphene materials, which are characterized by unique layered nanostructures, excellent strength, and large specific surface area, have garnered widespread attention and become excellent candidates for separation, adsorption, and support applications (Novoselov et al., 2004; Wang et al., 2019; Pan et al., 2020; Ren et al., 2021). However, graphene's tendency to aggregate and its non-chirality limit its applications in chiral separation. Through chiral modification, the layered structure of graphene acquires chiral elements, thus making it chiral selective. To address these issues and introduce chiral functionality, researchers have begun to modify graphene materials with chiral elements. The resulting chiral graphene materials have shown great potential for enantiomeric separation.

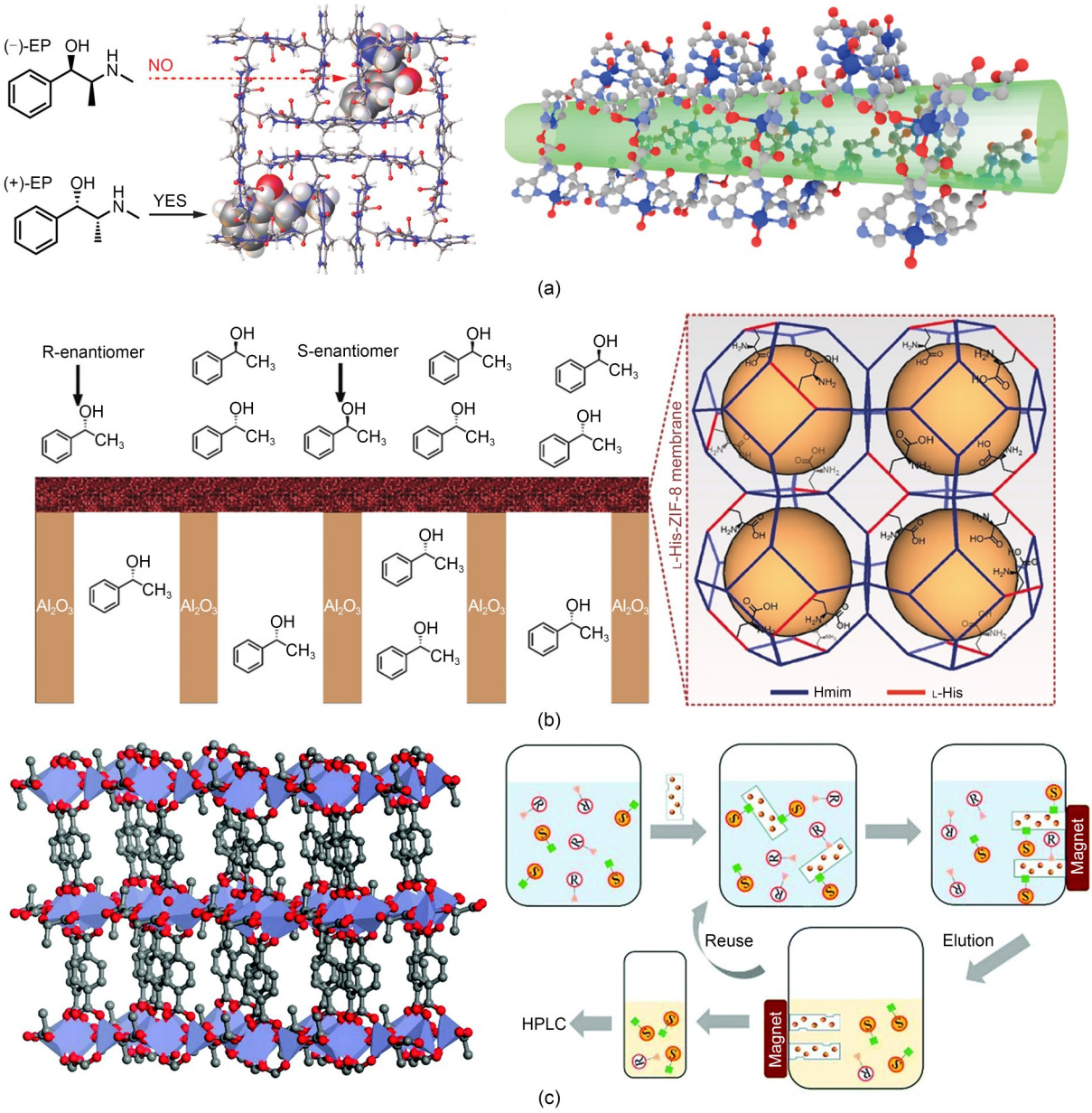

Fig. 6 (a) Schematic diagram of Cu(GHG) for chiral recognition and identification (reprinted from (Navarro-Sánchez et al., 2017), Copyright 2017, with permission from American Chemical Society); (b) schematic representation of a homochiral L-His-ZIF-8-membrane for separating the R-enantiomer of 1-phenylethanol from the S-enantiome (reproduced from (Chan et al., 2018), Copyright 2018, with permission from John Wiley and Sons); (c) schematic diagram of "enantioselective fishing" process performed using Fe_3O_4@SiO_2-ZnBLD (reproduced from (Chang et al., 2015), Copyright 2015, with permission from Royal Society of Chemistry)

Liu JL et al. (2021) prepared a novel chiral separation membrane by modifying GO with L-cysteine and obtained ee% of 43.60%, 44.11%, and 27.43% for isomers of alanine, serine, and tyrosine, respectively, in racemic mixtures under isobaric conditions. This membrane has practical value in the field of enantiomeric separation (Fig. 7a). In a further study in 2023, an ultra-high and stable permeance membrane (GALC) was designed and prepared using GO as the substrate and L-cysteine (L-Cys) modified gold nanoparticles (ALCs) as the functional units. The metal nanoparticles prevented the collapse of GO flakes and improved the stability of the membrane. The chiral separation membrane exhibited high enantiomeric selectivity for penicillamine enantiomers, with a chiral separation factor of 1.83 and a permeation rate of 21.7 L/(m^2·h·bar) (Liu JL et al.,

2023b) (Fig. 7b). The research results will contribute to the development of two-dimensional membrane materials for nanofiltration and chiral separation, particularly for use in environmental remediation and the pharmaceutical industry. Grafting chiral selectors and adjusting the interlayer spacing can improve both flux and selectivity to some extent. Moreover, special structures such as vortices can be formed through distortion superimposition to induce chirality. Tan et al. (2020) synthesized porous graphene with controllable nanopores directly from graphite using a one-pot method, and filtered it onto ultrafiltration membranes to form porous graphene membranes for selective separation of L/D-phenylalanine, achieving a separation factor of 4.76 (Fig. 7c). In summary, graphene materials can acquire chirality through various methods, overcoming the trade-off between selectivity and permeability in traditional chiral separation membranes. However, further research is needed on how to effectively increase the number of active sites and adjust the interlayer spacing.

Covalent organic frameworks (COFs) are a class of crystalline materials composed of organic molecules connected by covalent bonds. They typically possess highly controllable pore sizes, shapes, and chemical environments, making them suitable for a wide range of applications in adsorption, storage, separation, and catalysis (Liu et al., 2017; Chen et al., 2021; Li H et al., 2021; Zhao et al., 2023; Wang Y et al., 2024). To enhance solvent penetration and address the trade-off between permeability and selectivity, our team designed a microporous nanocomposite membrane with multiple complex transport channels, using an inherently microporous polymer (PIM) with precisely twisted repulsive pores as a matrix, as well as a covalent organic framework (COF) with uniform one-dimensional channels as a porous nanomaterial (Guo et al., 2022).

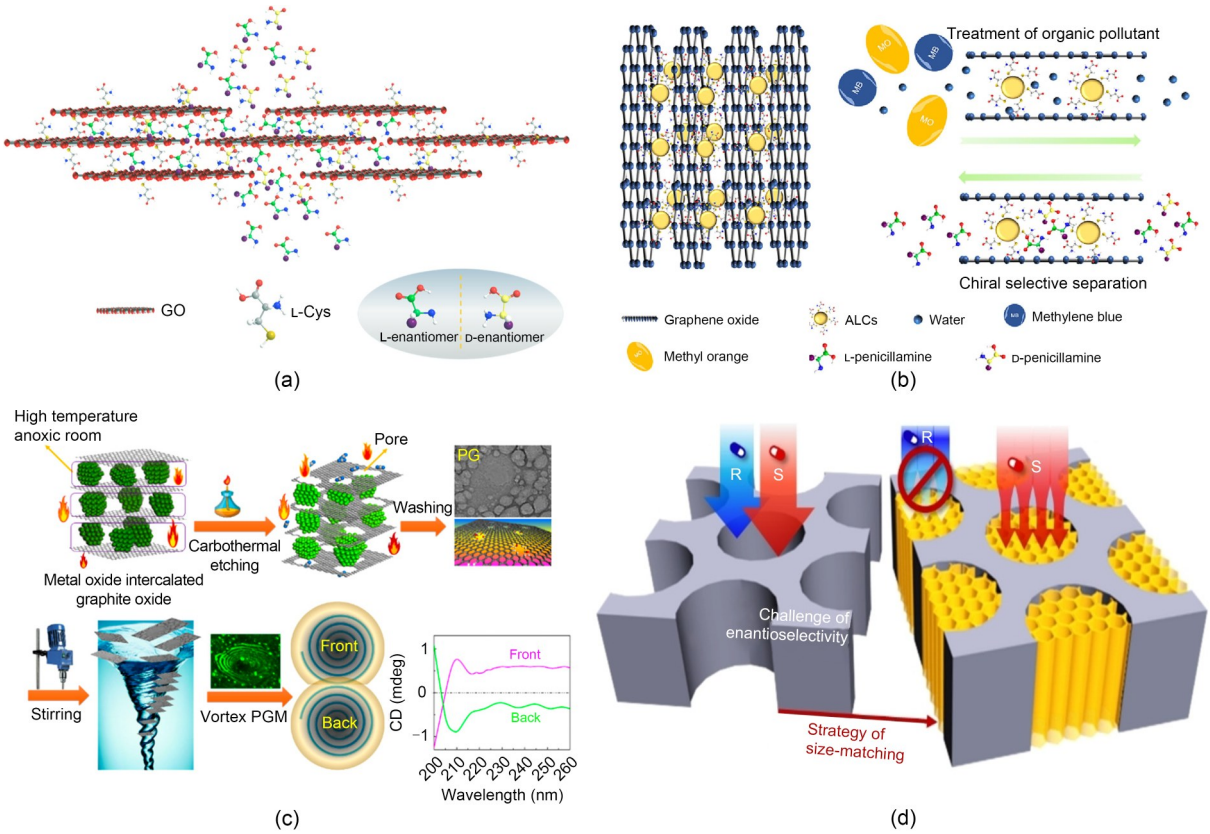

Fig. 7 Schematic diagram of (a) enantiomer separation in GO-Cys membrane (reprinted from (Liu JL et al., 2021), Copyright 2021, with permission from American Chemical Society); (b) GALC membranes for selective separation (reprinted from (Liu JL et al., 2023b), Copyright 2023, with permission from Elsevier); (c) synthesis of PGM with vortex structures (reprinted from (Tan et al., 2020), Copyright 2020, with permission from American Chemical Society); (d) L-tyrosine-functionalized covalent organic framework (L-Tyr-COF) packed nanochannel membranes (reprinted from (Zhang et al., 2022), Copyright 2022, with permission from John Wiley and Sons)

This composite membrane opens a new door for the application of COF in the pharmaceutical industry. In addition, the chiral COF (CCOF) is a functionalized COF in which the chiral selector is modified on the original skeleton of the COF to give it chiral separation properties. As shown in Fig. 7d, Zhang et al. (2022) filled nanochannels with in-situ-synthesized L-tyrosine-functionalized COFs (L-Tyr-COFs). The filled L-Tyr-COFs reduced the pore size of the channels, matched the enantiomer of Nafupramide, and enhanced enantioselectivity, thereby achieving high selectivity (ee%=94.2%) and high throughput (1.33 mmol/(m^2·h)) in enantiomeric separation. Chiral COF fillers possess advantages such as enantioselectivity, flux, versatility, and recyclability. It should be noted that COF materials are still at the research and development stage, requiring further research and optimization for different application fields.

4.1.4 Other inorganic-materials-based chiral membranes

Inorganic carbon materials have made great contributions to the separation of chiral drugs, and other inorganic materials such as polycrystalline zeolite and alumina also play different roles in this field. Polycrystalline zeolite has a highly ordered pore structure and excellent adsorption and separation performance (Shi et al., 2021). Vedovello et al. (2022b) grafted Pirkle chiral selectors onto a silicon-based mesoporous array (MCM-41) to prepare chiral nanocomposites, which resulted in a good separation factor (α=1.28). The membrane was more permeable to (R)-Pirkle's alcohol than to (S)-Pirkle's alcohol. Inspired by supramolecular templates for chiral transcription nanoparticles, Huang et al. (2022) super-assembled chiral transcript mesoporous silica on a porous anodic alumina carrier, achieving high throughput and high separation factors (e.g., 7.52 for L-arginine) (Fig. 8). In general, compared with chiral separation membranes made of organic materials, research on and application of chiral separation membranes based on inorganic materials are still in the developmental stage.

4.1.5 Mixed matrix membrane

Mixed matrix membranes, also known as composite matrix membranes, are membrane materials composed of two or more different materials mixed in certain proportions. These various materials can be polymers, inorganic materials, or their combinations. Mixed matrix membranes typically exhibit superior performance and comprehensive characteristics, because they combine the advantages of different materials.

For example, due to the difficulty of crystallizing chiral MOF membranes on porous substrates without defects, only a small number of high-quality homochiral polycrystalline MOF membranes have been prepared. Lu et al. (2019) successfully introduced chirality into non-chiral MIL-53-NH_2 nanocrystals through synthesis and modification using amino acids (L-histidine and L-glutamic acid). Subsequently, they embedded MIL-53-NH-L-His and MIL-53-NH-L-Glu nanocrystals into a polyethersulfone (PES) matrix to form enantioselective mixed-matrix membranes (MMMs). These MMMs exhibited outstanding enantioselectivity towards 1-phenylethanol, with an ee% reaching up to 100% (Fig. 9a). By combining the two materials, an effect of "1+1>2" was achieved. The successful application

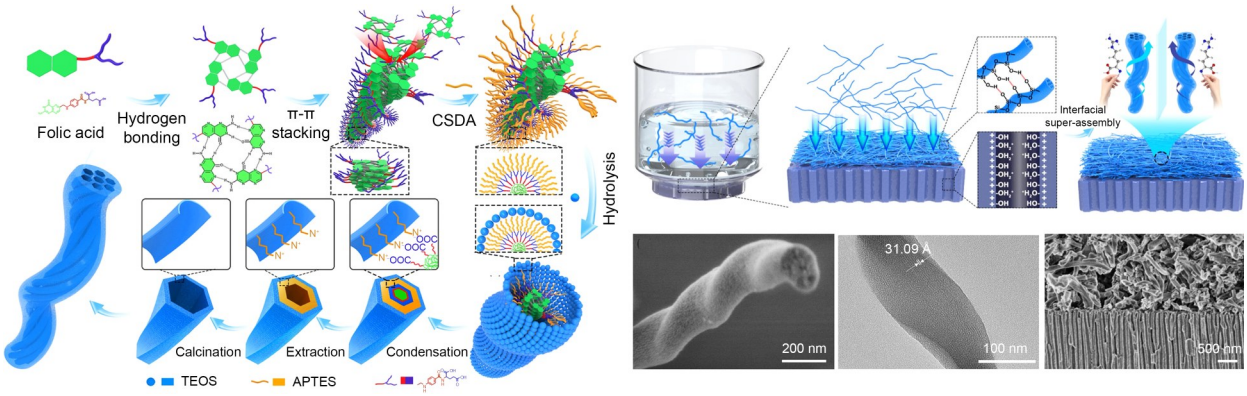

Fig. 8 Fabrication process of the chiral mesoporous nanofibers of CMS (reprinted from (Huang et al., 2022), Copyright 2022, with permission from American Chemical Society). TEOS: tetraethoxysilane; APTES: 3-aminopropyl triethoxy silane; CSDA: co-structure-directing agent

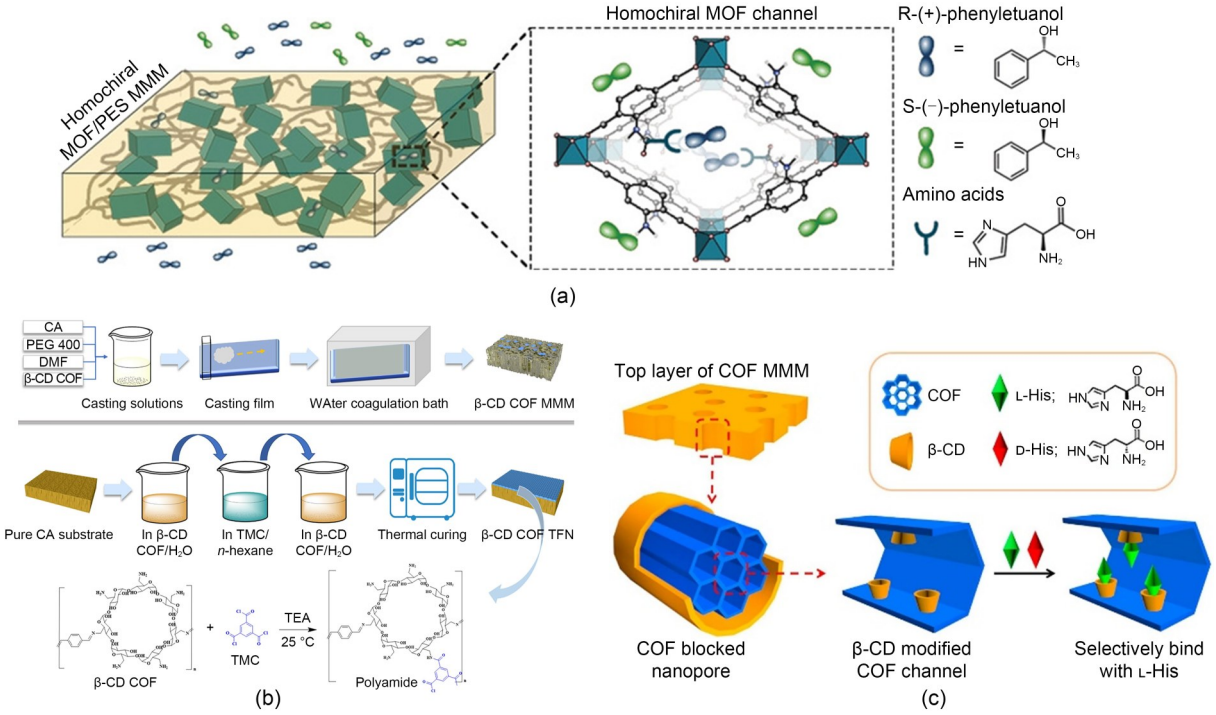

Fig. 9 (a) Selective permeation of R-(+)- and S-(−)-1-phenylethanol through the MIL-53-NH-L-His channel (reprinted from (Lu et al., 2019), Copyright 2019, with permission from John Wiley and Sons); (b) schematic of the preparation procedure of β-CD COF MMM, and β-CD COF TFN (reprinted from (Luo et al., 2022), Copyright 2022, with permission from Elsevier; TEA: triethylamine); (c) operation principle of the Chiral CD COF MMM System (reprinted from (Yuan et al., 2019), Copyright 2019, with permission from American Chemical Society)

of this method provides new ideas and approaches for designing efficient MMMs for chiral molecule separation. Luo et al. (2022) prepared two types of β-CD covalent organic framework (β-CD COF) membranes, as shown in Fig. 9b, including β-CD COF mixed-matrix membranes (β-CD COF MMM) and β-CD COF thin-film nanocomposite membranes (β-CD COF TFN), by physically and chemically modifying cellulose acetate matrices with β-CD COF as a chiral selector. The β-CD COF TFN membrane exhibited the best enantioselectivity and comparable solute flux (flux=1.9–5.4 nmol/(cm^2·h)) for D,L-tryptophan (ee%=100%), (RS)-mandelic acid (ee%=58.1%), D,L-phenylalanine (ee%=36.3%), and (RS)-propranolol (ee%=18.0%). Yuan et al. (2019) developed selective transport of amino acids in COFs by modifying them with chiral β-CD, resulting in the formation of independent MMMs.

In the field of chiral drug separation, MMMs offer the potential for selective separation of chiral molecules by tuning the material composition and structure. However, several challenges still exist in the practical application of MMMs. Firstly, their selectivity relies primarily on the interactions between polymers and organic molecules. However, due to the complexity of these intermolecular interactions, the selectivity of MMMs is often limited. Secondly, the fabrication of MMMs typically requires precise control of the content and composition of materials, which demands advanced techniques and processing conditions. This complexity and cost associated with the fabrication process hinder the large-scale production and widespread application of mixed-matrix membranes. Thirdly, precise control of filler distribution and arrangement within these membranes is still difficult.

In the future, in alignment with the requirements of contemporary sustainable development, the materials utilized for chiral drug separation membranes will progressively evolve towards environmental friendliness. The incorporation of novel biodegradable or recyclable materials will mitigate their environmental impact.

4.2 Design and control of membrane structures

4.2.1 Dense membranes

In the preparation and application of chiral drugs, separation and purification of drug enantiomers are

crucial. Dense membranes with excellent chiral selectivity and permeability performance provide strong support for the efficient separation of chiral drugs. Reverse-osmosis (RO) membranes are dense membranes commonly used for the separation of chiral drugs. RO membranes utilize pressure differentials to allow solvents to pass through the dense membrane from the high concentration side, achieving separation and purification of drugs. By adjustment of the osmotic pressure and membrane selectivity, RO membranes can effectively separate chiral drugs, enhancing their purity and quality. Son and Jegal (2007) used a conventional interfacial polymerization method to incorporate the target molecule (D-serine), piperazine (PIP), along with trimesoyl chloride (TMC), into the active layer on the surface of polysulfone ultrafiltration membranes to create a membrane with chiral spaces. After the formation of the polyamide composite membrane, the target molecule in the active layer was removed to prepare a molecularly imprinted composite membrane. Optimal separation results were obtained under an operating pressure of 1 bar.

Additionally, since the last century, some natural chiral polymers such as cellulose and its derivatives, proteins, and traditional synthetic chiral organic polymers like chiral polyphenylene, have been prepared as membranes for chiral separation. In 1990, Maruyama et al. (1990) first used polyamino acids for chiral separation. Chen et al. (2020) synthesized poly(L-glutamic acid methyl ester), poly(L-glutamic acid ethyl ester), and poly(L-glutamic acid benzyl ester) with different molecular weights through the N-carboxylic anhydrides method. Among these acids, poly(L-glutamic acid ester) exhibited excellent film-forming properties and chiral separation ability.

The application of dense membranes provides efficient and sustainable processes for the separation and purification of chiral drugs, opening up new possibilities for the pharmaceutical industry and medical research. Through continuous research and innovation, further advancements in the development and application of chiral drugs will contribute to the progress of the pharmaceutical industry.

4.2.2 Porous membranes

Porous membranes have a relatively high porosity, and by controlling factors such as the pore size and surface chemistry of these membranes, selective separation of chiral drugs can be achieved. The performance of porous membranes is influenced by the modulation of pore structure, and the chiral selectivity is determined by the size of chiral substrates and the pore size of the membrane. Adjustable pore structure and diverse structural design provide a potential platform for enantiomeric separation applications. Wang et al. (2022) prepared chiral porous polymer membranes with chiral NH groups by crosslinking a single-component chiral polyelectrolyte with water molecules through hydrogen bonding. These chiral porous membranes can effectively achieve enantioselective separation of drug enantiomers through directional hydrogen-bonding interactions. Wang FMJ et al. (2024) prepared a homochiral porous organic cage-polymer film for enantioselective resolution using polyamide as the substrate for enantioselective separation of limonene racemates. The membrane exhibits high selectivity for enantiomers.

4.2.3 Multi-layered membranes

Multi-layered chiral drug separation membranes are typically composed of multiple layers, each with specific functions and characteristics. Some layers employ mechanisms such as adsorption, sieving, and reverse osmosis to selectively capture and separate the enantiomers of the target chiral drugs. Other layers may be designed to increase the mechanical strength and stability of the membrane, ensuring long-term separation performance. The combination of multiple layers in the membrane structure enables more efficient chiral drug separation.

In the selection of membrane materials, it is crucial to ensure high selectivity, high flux, and good stability. For example, Zhang YQ et al. (2019) utilized a porous chitosan membrane with excellent antibacterial activity and biocompatibility as a substrate to prepare a molecularly imprinted membrane with the AGET-ATRP process, using artemisinin as a template. The nanocomposite structure provided a relatively large specific area, while the silver decoration layer exhibited antibacterial effects, and the molecularly imprinted layer enabled recognition of the target molecule. As a result, the membrane demonstrated high adsorption capacity and permeation selectivity. In another study, researchers modified the surface of polyvinylidene fluoride (PVDF) with a multi-layer functional molecularly imprinted nanocomposite membrane (A-MINM) using a polydopamine (PDA), polyethyleneimine/mesoporous silica (PEI/MCM-41), and acteoside (ACT)

imprinting layer. The PEI/MCM-41 layer regulated the pore uniformity of the membrane surface and contained abundant amino groups, providing a platform for ACT imprinting to trigger imprinting polymerization and form the imprinting layer. The ACT imprinting layer had numerous ACT imprinting sites and cavities, allowing for specific recognition and efficient separation of ACT (Zhang et al., 2023) (Fig. 10).

The field of multi-layered chiral drug separation membranes is challenging but holds immense potential. Its further development will contribute to advances in pharmaceutical preparation, analysis, and biomedical sciences.

4.3 Preparation and construction technology

4.3.1 Self-assembly method

Self-assembly is one of the commonly used methods for preparing chiral drug separation membranes. By utilizing non-covalent interactions between chiral molecules, such as hydrogen bonds and van der Waals forces, chiral molecules are enabled to spontaneously form films in solution, with specific structures and functions. First, an appropriate chiral molecule, such as a chiral polymer or CD, is selected as the molecular assembly unit. Then, under specific solution conditions, the chiral molecules can self-assemble to form stable structures when various parameters are adjusted, such as solution concentration, temperature, and pH value. The formed chiral drug separation membrane can selectively recognize and transport chiral drug molecules during the separation process, and realize effective separation and enrichment of chiral drugs. By self-assembly of CDs in nanochannels, Zhang SY et al. (2020) prepared nanochannel membranes based on drug/metabolite transport (DMT) in cell membranes and used them for chiral transport and separation of chiral drugs such as naproxen. The self-assembly method is simple, flexible, and efficient, and has been widely used in the preparation of chiral drug separation membranes.

4.3.2 Surface modification method

The surface modification method involves introducing compounds or functional groups with chiral selectivity onto the membrane surface to achieve chiral separation through chemical bonding or physical adsorption. Surface modification methods include selectively introducing chiral selector molecules or ligands onto the membrane surface, which interact with chiral drugs through chemical bonding or physical adsorption to achieve chiral separation. Chiral selectors can be chiral molecules, chiral polymers, chiral materials, etc. Miao et al. (2017) modified polysulfone membranes with dopamine and surface-modified them with β-CD as the chiral selector. The membrane surface was completely coated with polydopamine, forming a monolayer of β-CD on the polydopamine coating. This method can be used for large-scale production of chiral separation membranes or other higher-performance chiral separation membranes. Additionally, it is possible to introduce chemically functional groups with chiral selectivity onto the membrane surface to interact with chiral drug molecules.

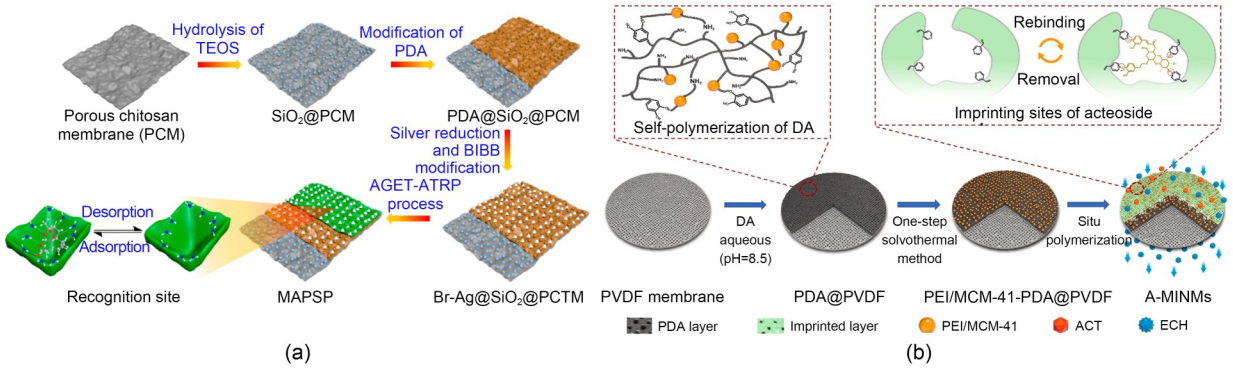

Fig. 10 Schematic illustration of (a) synthesis of MAPSP (reprinted from (Zhang YQ et al., 2019), Copyright 2019, with permission from American Chemical Society; MAPSP: MIP@Ag@PDA@SiO_2@PCM; ATRP: atom transfer radical polymerization; AGET: activators generated by electron transfer; 2-BIBB: 2-bromoisobutyryl bromide; PDA: polydopamine); (b) A-MINM preparation process (reprinted from (Zhang et al., 2023), Copyright 2023, with permission from Elsevier; PEI: polyethylenimine; ECH: echinoside; A-MINMs: acteoside is used as template molecule, and multilayer-functionalized of molecularly imprinted nanocomposite membranes are designed)

4.3.3 Interfacial polymerization method

The interfacial polymerization method involves dissolving two monomers with high reactivity in two immiscible solvents and conducting a polymerization reaction at the interface of the two phases to form a dense thin film. Qiu et al. (2023) combined three different amino acids with mono-6-deoxy-6-(3-benzylimidazolium)-β-cyclodextrin ([β-CD-BIM]) to synthesize three chiral ionic liquids: [β-CD-BIM][L-Cys], [β-CD-BIM][L-asp], and [β-CD-BIM][L-Lys]. These chiral ionic liquids were then introduced into cellulose acetate membranes by interfacial polymerization to prepare chiral composite membranes for enantiomer separation. Chen et al. (2023) introduced n-heptyl (6-amino-6-deoxy)-β-CD-functionalized carboxylate COF (TpBD-Am7CD) as a chiral functional material and prepared TpBD-Am7CD-stainless steel I-Net cellulose acetate membranes (COF/SSCAM) through interfacial polymerization. Due to the enantioselectivity and hydrophilicity of TpBD-Am7CD, COF/SSCAM exhibited higher excess rates of enantiomers for external racemic amino acids (ee%=100.00%); as well as higher solute permeation flux (3.7×10^{-6} (mol/(m^2·h)) compared to the support membrane. Chiral separation membranes prepared by the interfacial polymerization method can achieve selective adsorption and separation of chiral molecules. This method has the advantages of simple operation, wide applicability, and low preparation cost, and has been widely used in the field of chiral separation.

The choice of preparation and construction techniques for chiral drug separation membranes depends on the characteristics of the drugs, separation conditions, and application requirements. Therefore, the appropriate technique should be selected based on specific circumstances. With continuous advancements in scientific technology, the preparation and construction techniques for chiral drug separation membranes will continue to develop and improve, providing more options for the separation and purification of chiral drugs.

5 Current challenges and prospects of chiral drug separation membranes

5.1 Challenges

The endeavor of achieving high selectivity while maintaining high flux remains a challenge in chiral drug separation membranes. This means it is difficult to simultaneously improve both selectivity and permeability during membrane separation. In addition, achieving high selectivity for simultaneous separation of multiple chiral drugs in a mixture is a challenging task. During the process of chiral drug separation, the membrane can be affected by contaminants, deposits, and gases, leading to decreased separation efficiency and stability. Factors such as dehydration, deformation, and membrane-material aging during long-term use can also impact the performance and lifespan of a separation membrane. Over time, environmental impact and sustainability have emerged as critical factors in the assessment of chiral drug separation membrane technology. Achieving an environmentally friendly and sustainable chiral drug separation process has become a focal point, where both challenges and opportunities are present.

Chiral membrane materials, including chiral polymers, chiral graphene, and chiral MOFs, exhibit excellent separation performance for chiral drugs. However, they also have some limitations. For example, the stability of MOF materials needs further exploration, and the separation performance of graphene-based chiral membranes is influenced by interlayer spacing. Overall, most chiral drug separation membranes are still in the laboratory research stage.

5.2 Prospects

The selectivity of chiral drug separation membranes can be enhanced by deepening our understanding of chiral selectors, surface modifications, structural designs, and materials modification. Efforts must focus on improving chiral selectivity. Furthermore, the use of new technologies such as machine learning and high-throughput screening can accelerate the discovery and optimization of novel separation membranes, with the potential to further improve chiral selectivity. It is difficult to produce a chiral separation membrane that has high permeability, high selectivity, and high stability at the same time. Through interdisciplinary cooperation, for example between chemical engineering, materials science, and biology, it may be possible to promote the development of new membrane materials and achieve a balance of properties. The advancements in novel materials such as chiral mesoporous materials and chiral ionic liquids, along with the implementation of molecular imprinting technology, will further surmount the existing limitations of membrane technology in

separating chiral drugs. In the future, chiral drug separation membranes will contribute to green chemistry and sustainable development by offering high separation efficiency and high-throughput screening capabilities.

To tackle pollution-related issues, it is advisable to explore surface-modification techniques that would enable self-cleaning functions. By incorporating nanoscale structures or coating technologies, the accumulation of pollutants and deposits on the membrane surface can be reduced, thereby extending the lifespan of separation membranes. In addition, the key to improving the long-term performance of separation membranes lies in the development of more stable and durable membrane materials. Efforts should be made to enhance long-term performance and extend the lifespan of separation membranes. The development of membrane cleaning and recycling technologies to reduce the production of solid waste should also promote environmental protection.

Furthermore, it is essential to promote the industrial production of chiral drug separation membranes by strengthening process development and cost control, and by reducing production costs. This will facilitate the commercial production and application of separation membranes.

Overall, through comprehensive research into chiral selectors, surface modifications, and structural designs, as well as materials modification, the chiral selectivity of drug separation membranes can be significantly improved. The utilization of new technologies and the development of more durable and stable membrane materials, along with the promotion of industrial production, is crucial for the commercialization and widespread use of chiral drug separation membranes.

6 Conclusions

Chiral drug separation membranes represent a specialized class of membrane materials engineered for the separation of chiral compounds. These membranes enable effective separation of chiral isomers, offering advantages such as high selectivity, low energy consumption, and environmental friendliness compared to traditional separation methods. With the development of materials such as polymeric membranes, carbon nanomaterials, metal-organic frameworks, and other inorganic materials, the foundation for further advancements in chiral drug separation membranes has been laid, indicating promising prospects for their application. Continuous research efforts will drive the development of chiral drug separation membrane materials for practical applications and provide new insights for further studies.

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Author contributions

Jianyu WANG and Qindan CHU wrote the first draft of the manuscript. Chuanjie FANG and Baoku ZHU helped to organize the manuscript. Jianyu WANG and Liping ZHU revised and edited the final version.

Conflict of interest

Jianyu WANG, Qindan CHU, Chuanjie FANG, Baoku ZHU, and Liping ZHU declare that they have no conflict of interest.

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