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Review

Membrane separations using molecularly imprinted polymers

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Abstract

This review presents an overview on the promising field of molecularly imprinted membranes (MIM). The focus is onto the separation of molecules in liquid mixtures via membrane transport selectivity. First, the status of synthetic membranes and membrane separation technology is briefly summarized, emphasizing the need for novel membranes with higher selectivities. Innovative principles for the preparation of membranes with improved or novel functionality include self-assembly or supramolecular aggregation as well as the use of templates. Based on a detailed analysis of the literature, the main established preparation methods for MIM are outlined: simultaneous membrane formation and imprinting, or preparation of imprinted composite membranes. Then, the separation capability of MIM is discussed for two different types, as a function of their barrier structure. Microporous MIM can continuously separate mixtures based on facilitated diffusion of the template, or they can change their permeability in the presence of the template ("gate effect"). Macroporous MIM can be developed towards molecule-specific membrane adsorbers. Emerging further combinations of molecularly imprinted polymers (MIPs), especially MIP nanoparticles or microgels, with membranes and membrane processes are briefly outlined as well. Finally, the application potential for advanced MIM separation technologies is summarized.

Keywords: Reviews; Membrane separations; Molecularly imprinted polymers

Contents

Abbreviations: 9-EA, 9-ethyl adenine; AA, acrylic acid; AMPS, 2-acrylamido-2-methyl-1-propane sulphonic acid; As, adenosine; BFA, boc-phenylalaninanilid; Boc, *tert*-butyloxycarbonyl; CA, cellulose acetate; Caf, caffein; CBZ, carboxybenzoyl; *co*, ... *co* {polymer}; DBD, dibenzodioxin; DBF, dibenzofuran; DIDE, *tetrapeptide*: H-Asp(OcHx)-Ile-Asp(OcHx)-Glu(Obz)-CH_2; DPE, diphenylether; DTCS, *N*,*N*-diethylaminodithiocarbamoylmethylstyrene; EDMA, ethylenglycol dimethacrylate; FFE, *tripeptide*: H-Phe-Phe-Glu(Obz)-CH_2; *g*, ... graft {polymer}; Gs, guanosine; HEMA, 2-hydroxyethyl methacrylate; MAA, methacrylic acid; MBAA, *N*,*N*′-methylene bisacrylamide; MIM, molecularly imprinted membrane; MIP, molecularly imprinted polymer; PAN, polyacrylonitrile; PI, phase inversion; PP, polypropylene; PSf, polysulfone; PVDF, polyvinylidene fluoride; SPE, solid-phase extraction; St, styrene; Tho, theophylline; TRIM, 1,1,1-(trishydroxymethyl)propane trimethacrylate; Trp, tryptophan; Tyr, tyrosine

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1. Membrane separations—state-of-the-art

A membrane is an interphase between two adjacent phases acting as a selective barrier, at the same time organizing a system into compartments and regulating the transport between the two compartments. The main advantages of membrane technology as compared with other unit operations in (bio)chemical engineering are related to the unique separation principle, i.e. the transport selectivity of the membrane. Furthermore, separations with membranes do not require additives, and they can be performed isothermally and at very competitive energy consumption. Finally, both upscaling and downscaling of membrane processes as well as their integration into other separation or reaction processes are easy.

Within the last few decades, a very dynamic technical development had lead to a large variety of membranes along with various optimized separation processes [1,2]. Synthetic separation membranes can be classified according to different criteria:

- *Membrane materials*: Organic polymers, inorganic materials (oxides, ceramics, metals), organic–inorganic composite materials.
- *Membrane cross-section morphology*: Symmetric (relatively thick—50–500 μm—and even barrier from one material; cf. Fig. 1a), asymmetric (thin—up to a few μm—layer ontop of a support, both from the same material; cf. Fig. 1b), thin-layer or mixed matrix composite, bi- or multilayer.
- *Preparation method*: Phase inversion of polymer solution of (solvent evaporation or thermally induced “dry PI”, non-solvent induced “wet PI”), sol–gel process towards inorganic or organic–inorganic material, interface reaction towards thin-layer composite, stretching, extrusion, track-etching, micro-fabrication.
- *Membrane shape*: Flat-sheet, hollow fibre, hollow capsule.

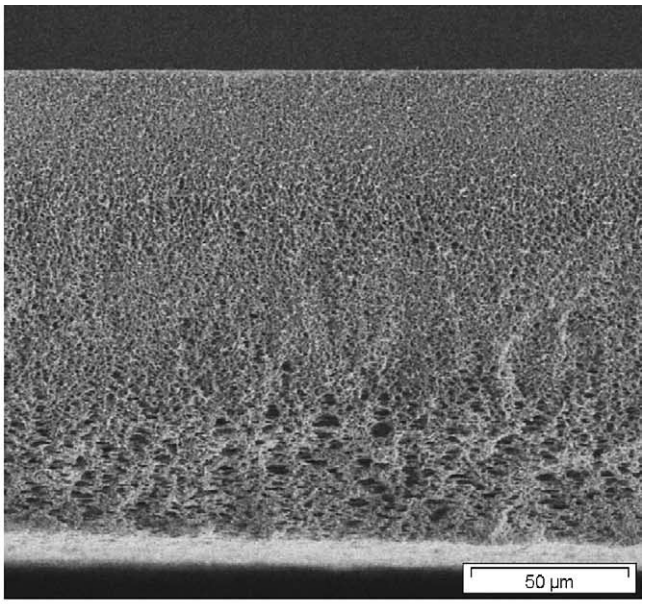
All technically implemented membrane processes are based on passive transport driven by a gradient in chemical potential. Depending on the barrier pore structure, the main separation mechanisms are solution–diffusion [3] or sieving [4]. Typically, the implementation of continuos separation processes is straightforward. Combinations with other interactions, mainly electrostatic or affinity, are also possible. An overview is given in Table 1.

Membrane adsorbers [5] are a special case: on the one hand, typical membrane structures improve the separation performance significantly in comparison with conventional adsorber materials such as particles; on the other hand, the separation ability under constant feed conditions is limited by the adsorber capacity, making truly continuos processes complicated or impossible.

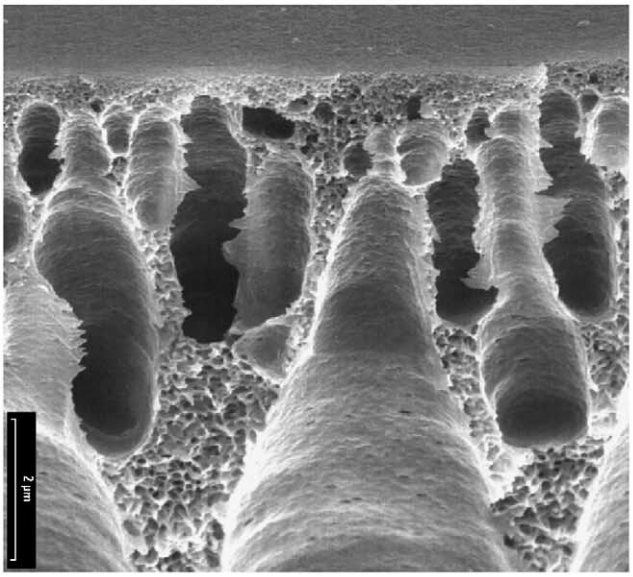
The success of membrane technology has now been impressively demonstrated for large scale industrial applications [2]. The major examples are water purification by reverse osmosis and blood detoxification by dialysis or ultrafiltration. Other applications have been realized, especially in the food and pharmaceutical industry as well as the process and waste water treatment. Membranes have also gained great importance in bioseparations, especially in the life sciences [6]. Many very specialized applications exist, often as a key step for complex and complicated analytical tasks in genomics and proteomics. Parallelization of separations has been implemented via 96- or 384-well membrane-filter

Table 1
Classification of membranes and membrane processes for separations via passive transport

Membrane barrier structure	Trans-membrane gradient		
	Concentration	Pressure	Electrical field
Non-porous	Pervaporation	Gas separation Reverse osmosis	
Microporous Pore diameter $d_p \leq 2$ nm	Dialysis	Gas separation Nanofiltration	Electrodialysis
Mesoporous Pore diameter, $d_p = 2$ to 50 nm	Dialysis	Ultrafiltration	Electrodialysis
Macroporous Pore diameter, $d_p = 50$ to ~500 nm		Microfiltration	



(a)



(b)

Fig. 1. Synthetic separation membrane morphologies visualized by scanning electron microscopy: (a) symmetric macroporous membrane for microfiltration or as base material for membrane adsorption—here made from polypropylene (Membrana GmbH, Wuppertal), (b) asymmetric membrane for ultrafiltration or as base material for composite membrane (layer topology also relevant for nanofiltration, reverse osmosis, pervaporation or gas separation)—here made from polyacrylonitrile (GKSS, Geesthacht).

plates equipped with microfiltration, ultrafiltration or adsorber membranes. Finally, the integration of membranes into lab-on-a-chip systems has just started [7]. Serving all these needs will require innovative research and development towards improved membrane materials and processes.

The development of synthetic membranes had always been inspired by nature, in particular by the fact that the selective transport through biological membranes is enabled by highly specialized macro- and supramolecular assemblies based on and involved in molecular recognition. Hence, for the development of a next generation of highly selective membranes, synergies between the achievements of synthetic membranes and the “bio-inspired” concept of molecular imprinting are of particular interest.

This review will provide an overview on the promising field of molecularly imprinted membranes (MIM). After the first review on that topic written 5 years ago [8], significant progress has been made. Consequently, the relevance of membranes as a special format for molecularly imprinted polymer (MIPs) has been highlighted in a few other recent reviews [9–11]. Here, we will discuss the state-of-the-art based on a comprehensive analysis of the research literature with a particular focus onto separations via membrane transport selectivity. Emerging further combinations of MIPs with membranes and membrane processes will be briefly outlined as well.

2. Novel separation membranes with improved selectivity

Many technically challenging and commercially attractive separation problems can not be solved with existing membranes, because the typically achieved separations of complex mixtures are only fractionations into substance groups. Novel membranes with high selectivities, for example for toxins, chiral drugs or complex biomolecules, are required. The only examples for truly molecule selective membrane separations in practical applications are porous bioaffinity membrane adsorbers with immobilized biomolecules, used in membrane filtration modules via chromatography or bind-wash-eluted protocols (e.g.: [5,12]). Carrier membranes for substance-specific separations had been intensively investigated; however, for liquid membranes with mobile carriers, the stability of membrane performance is still the main obstacle for technical implementation [13]. The immobilization of carriers in suited polymer membranes could be an alternative (e.g.: [14]. Furthermore, a membrane selectivity which can be switched by a stimulus or membranes which can adapt to the process conditions would be highly attractive. Many examples for such “smart” membranes have been described in the scientific literature (e.g.: [15,16]).

The aim of current membrane development are specialized, “tailor-made” membranes with a high selectivity and/or flux along with a sufficient stability of membrane performance. For example, porous membranes, functioning according to a sieving mechanism, should have a very narrow pore size distribution, a high porosity and a minimal tortuosity. In addition, minimizing the thickness of the membrane barrier layer will be essential.

Active research is devoted to highly specific membrane separations based on molecular recognition in the nanospace; two recent examples may serve as an illustration.

"Nanotubule" membranes with well-defined transmembrane pores having a diameter of a few nm had been developed [17]. The preparation had been based on controlled deposition of gold layers on the porewalls of track-etched membranes having pore sizes of about 10 nm. In combination with self-assembled functional monolayers on the thus obtained nano-tubules, selective membrane separation could be achieved using size and affinity selection of discrete molecules. "Supramolecular channel" membranes with pores mimicking biological ion-channels had been described [18]. The approach had been based on the gelation of solutions by string-like supramolecular assemblies of functional gelator molecules, the subsequent fixation of these gels by an in situ polymerization followed by the removal of the gelator fibres yielding pore channels predetermined by size and shape of the template. Promising ion selectivities could be achieved via that approach.

In conclusion, innovative principles for the synthesis and/or preparation of membranes with improved or novel functionality are focussed onto optimized membrane morphologies. The most promising recent approaches include self-assembly or supramolecular aggregation as well as the use of templates (molecules, micelles, particles, nanostructured matrices) for creating well-defined and selective trans-membrane transport pathways.

3. MIM preparation strategies and morphologies

A MIM is a membrane either composed of a MIP or containing a MIP. A high membrane performance depends on a well-defined membrane morphology with respect to barrier pore size (cf. Table 1) and layer topology, especially the thickness of the barrier layer (cf. Fig. 1). A general problem of the "conventional" MIP technology is the simultaneous and random creation of the imprinted sites along with the formation of the polymer matrix including it's pore structure. As a consequence, random distribution and uneven accessibility of receptor sites in the volume of a MIP material are characteristic for the state-of-the-art [19].

Three main strategies can be envisioned for the preparation of MIM:

(1) sequential approach—preparation of membranes from previously synthesized "conventional" MIPs, i.e. particles,
(2) simultaneous formation of MIP structure and membrane morphology,
(3) sequential approach—preparation of MIPs *on* or *in* support membranes with suited morphology.

3.1. Sequential approach from presynthesized MIPs towards MIM

Only few attempts towards processing presynthesized MIPs to separation membranes had been reported yet. A promising example is the arrangement of MIP nanoparticles as a filter cake between two microfiltration membranes; these flat-sheet filters had been evaluated with respect to their flow and binding, i.e. adsorber, properties [20,21]. Embedding MIP particles into a suited porous polymer matrix, in analogy to already commercially established "membrane-SPE discs", could be an alternative. Using very small MIP nanoparticles or MIP microgels would open further possibilities for the design of composite membranes (cf. Section 5).

3.2. Simultaneous formation of MIP sites in and morphology of self-supported MIM

Self-supported flat-sheet membranes should be at least 10 μm thick in order to have sufficient stability. Therefore, when using simultaneous MIM preparation, the control of film thickness, e.g. by solution casting or using moulds, is essential. Also, when established MIP synthesis protocols shall be applied, the "synchronization" of imprinting and film solidification are of critical importance for MIM shape, structure and function. Two main routes towards MIM had been used, the "traditional" in situ crosslinking polymerization and the "alternative" polymer solution phase inversion, both in the presence of templates. In contrast to other MIP formats, the synthesis of inorganic MIM for separation, e.g. via sol–gel processes, had not yet been reported.

3.2.1. In situ crosslinking polymerization

In an early study, the crosslinking copolymerization of a mixture of acrylamide and acrylates including a photo-isomerizable functional acrylate yielded a MIM with a "poor mechanical stability", obviously due to the swollen structure [22]. In an attempt to directly adapt established MIP preparations to the synthesis of flat-sheet membranes, free-standing but brittle MIM had been obtained by thermally initiated in situ cross-linking copolymerization of one of the "standard" monomer mixtures (MAA/EDMA) [23]. Scanning electron microscopy studies revealed a regular porous structure built up by 50–100 nm diameter polymer nodules. A significant improvement had been achieved by using an oligourethane–acrylate macromonomer in in situ imprinting polymerization mixtures in order to increase the flexibility and mechanical stability of the membranes; self-supported MIM with a thickness between 60 and 120 μm had been prepared [24]. A step towards a higher membrane permeability was the use of a macromolecular pore former (polyester) along with a cross-linking copolymerization of styrene monomers [25]. Based on scanning electron microscopy and permeation data, it was speculated that "trans-membrane channels" had been obtained, induced by the removal of the polyester from the MIM.

3.2.2. Polymer solution phase inversion (PI)

Polymer solution film casting and subsequent phase inversion, the main approach towards technical polymeric

Table 2
Microporous MIP membranes prepared via in situ polymerization and their separation performance in diffusion experiments

Monomer mixture	Template	Membrane thickness (μm)	Source concentration (μmol/l)	Solvent	Flux (nmol/cm^2 h)	Permselectivity[a]	Reference
Self-supported symmetric membrane							
EDMA/MAA	9-EA	Not given	76	$CHCl_3$/MeOH, 94/6	0.2	$\alpha_{As/Gs} \sim 3.4$	[23]
PSt/DVB/vinylbenzoat + polyester (porogen)	UO_2^{2+}	100	200	H_2O	2.7	α (UO_2^{2+}/Ni^{2+}) > 100	[25]
Pore-filled composite membrane							
TRIM/MAA	CBZ-L-Tyr	160 (filled support)	2000	$CHCl_3$/MeOH, 50/50	117	$\alpha_{l/D} \sim 3.4$ (from single solute)	[45]
Thin-layer composite membrane							
EDMA/MAA	Tho	~0.05 (film on/in support)	10	MeOH	17	$\alpha_{Tho/Caf} \sim 2.6$	[46]
			1			$\alpha_{Tho/Caf} \sim 5.0$	
	Caf		10		18	$\alpha_{Caf/Tho} \sim 3.0$	

[a] From mixed solute experiments.

membranes (cf. Table 1), can also be applied for molecular imprinting (see Tables 2 and 3). Instead of an in situ polymerization, the solidification of a polymer is used. In the first work on that road, Yoshikawa et al. had used polystyrene resins with peptide recognition groups, in a blend with a matrix polymer, for the MIM formation via a "dry PI" process, i.e. the polymer solidification was achieved by solvent evaporation [26–31]. Remarkably, the permeability was much higher for the MIM as compared with the blank membranes. Alternatively, Kobayashi et al. had used functional acrylate copolymers for a "wet PI" process yielding asymmetric porous MIM [32–34]. In that case, the polymer solidification was achieved by a precipitation induced via contact with a non-solvent. The copolymer material and methodology had recently successfully been adapted by another group [35].

In the meantime, the polymer selection for phase inversion imprinting had been extended to most of the commonly used membrane materials, e.g. cellulose acetate [36], polyamide [37,38], polyacrylonitrile [38] and polysulfone [38–40]. The formation of porous MIM from a compatible blend of a matrix polymer—for adjusting a permanent pore structure—and a functional polymer—for providing binding groups—could provide even more alternatives [41]. Furthermore, polyethyleneglycol as pore former in the polymer blend casting solution had been successfully used to increase the membrane permeability [41].

A "hybrid" approach of in situ polymerization and "wet PI" had been recently reported: The polymerization of functional monomers had been performed in the presence of the template, and the resulting solution of *linear* copolymers, either P(AN-co-AA) or P(AN-co-MAA), with the associated template had then been directly used for film casting/immersion precipitation towards porous MIM [42]. However, the membranes had only been characterized in batch sorption experiments.

It is remarkable, that most MIM prepared via phase inversion imprinting had at least acceptable binding performance in aqueous media. However, such MIM lost their "template memory" when exposed to a too organic environment where swelling and chain rearrangement seemed to "erase" the imprinted information [31]. However, it should be noted, that even if the PI should be most suited for the preparation of separation membranes, the adaptation of the process to the preparation of MIM is complicated because the conditions required for an optimal formation of MIP sites may not be compatible with the ones for obtaining an optimal pore structure. Furthermore, the type of pore structure—e.g. symmetric macroporous or microporous (cf. Fig. 1a) versus asymmetric (cf. Fig. 1b)—will have decisive impact onto MIM separation performance (cf. Section 4).

In conclusion, all simultaneous preparations share the same major problem, that MIP sites and membrane morphology are formed in the same step from the same building blocks, either monomer or polymers. Therefore, the limited accessibility of imprinted sites due to a random distribution inside and on the surface of the bulk polymer phase remains a

Table 3
Microporous MIP membranes prepared by "dry phase inversion" and their separation performance (source solute concentration 1 mmol/l, solvent water/ethanol 50/50)

Matrix	Functionality	Template	Thickness (μm)	Separation by	Flux (nmol/cm² h)	Permselectivity[a]	Adsorption selectivity	Reference
PAN-co-St	PSt-DIDE	Boc-L-Trp	~145	Diffusion	~5	$\alpha_{D/L}$ ~ 1.4	L > D	[26]
	PSt-DIDE	Boc-L-Trp	~145	Electrodialysis Diffusion	~3 <1	$\alpha_{L/D}$ ~ 6.0 $\alpha_{L/D}$ ~ 0.8	L > D	[28]
	PSt-FFE	Boc-L-Trp	~140	Electrodialysis	0.3	$\alpha_{L/D}$ ~ 4.6	L > D	[30]
	PSt-DIDE	9-EA	~145	Diffusion	~0.75	$\alpha_{Gs/As}$ ~ 1.2	As > Gs	[29]
CA		9-EA	~110	Diffusion	~0.8	$\alpha_{Gs/As}$ ~ 1.2	As > Gs	
PSf		9-EA	~105	Diffusion	~0.75	$\alpha_{Gs/As}$ ~ 1.2	As > Gs	
PSf-COOH		Boc-D-Glu Boc-L-Glu	Not given	Electrodialysis	~5	$\alpha_{D/L}$ ~ 1.2 $\alpha_{L/D}$ ~ 1.2	D > L L > D	[39]
CA		D-Glu L-Glu	105	Electrodialysis	10	$\alpha_{D/L}$ ~ 2.3 $\alpha_{L/D}$ ~ 2.3	D > L L > D	[36]

[a] From mixed solute experiments.

major unsolved problem. Furthermore, the problem of combining a high yield of MIP sites with a pore structure suited for efficient membrane separation had not yet been solved.

3.3. Preparation of composite MIM

Advanced molecular separations, e.g. via reverse osmosis, nanofiltration, pervaporation or membrane adsorption, are performed using composite membranes, where an optimized porous support membrane is functionalized with a suited thin selective layer. Analogously, the preparation of MIP composite membranes should allow to adjust membrane pore structure and MIP recognition sequentially and by two different materials.

In the earliest attempts, established MIP synthesis mixtures, e.g. MAA/EDMA, had been polymerized in mm-thick glass filters to fill their pores [8,43,44]. Later, reaction mixtures had been casted into the pores of a symmetric microfiltration membrane and a cross-linking copolymerization of a functional polyacrylate had been performed [45] (cf. Table 2). In both cases, thick symmetric MIM had been obtained, with the mainly meso- and microporous MIPs filling all pores of the support material.

Thin film MIP composite membranes, with a minimized thickness of the MIP layer acting as selective barrier, should enable a much higher membrane permeability. With that intention, in situ photoinitiated crosslinking copolymerization of a MAA/EDMA mixture had been performed on top of an asymmetric 20 nm pore size alumina membrane [46] (cf. Table 2). Also, a cellulosic dialysis membrane had been used as matrix for a two-step grafting procedure yielding a MIP by in situ copolymerization in the thin mesoporous barrier layer of the base material [47].

Macroporous composite membranes, evenly functionalized with thin MIP layers, had been developed to achieve high performance MIM adsorbers [8,48–51] (see Table 4). The structure of the base membrane can be used as a means to adapt both pore size—permeability—as well as internal surface area—binding capacity—to the desired application. Using a coated photoinitiator, a photo-initiated cross-linking graft copolymerization yielded very thin MIP films which were covalently anchored and covered the entire surface of the base membrane [49]. Based on the results of surface and pore analyses, the thickness of MIP layers with the highest affinity and selectivity was below 10 nm [11]. Moreover, it had been discovered that a previously prepared thin hydrophilic layer on the support membrane can have two functions [50]: (i) matrix for the crosslinking polymerization and limiting monomer conversion to "filling" the layer thus forming an interpenetrating polymer network, (ii) minimizing non-specific binding during SPE. A superior MIM performance, especially a high template specificity, could be achieved using this advanced composite structure.

In conclusion, the sequential approach will allow to use the base membrane pore structure (barrier pore size) and layer topology (symmetric versus asymmetric) as well as the location of the MIP—on top of ("asymmetric") or inside ("symmetric") the support membrane (cf. Fig. 1)—to prepare different MIM types, with the MIP either as selective barrier or transport phase or as an affinity adsorber layer (cf. Section 4).

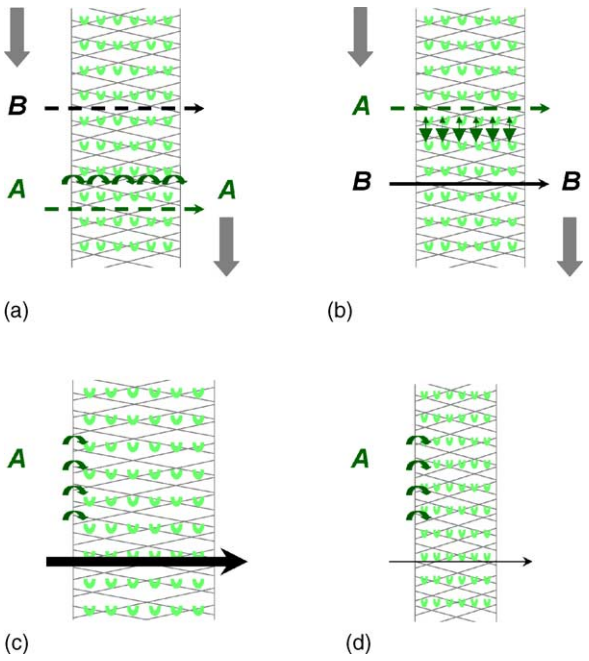
4. MIM separations

4.1. Overview on MIM separations

The template binding to MIP sites in a MIM can be coupled with a selective transport through the MIM thus enabling a membrane separation. The transport pathways in a polymer membrane can be either the free volume between polymer chains, the solvent fraction of a swollen polymer gel or connected pores in a solid polymer (cf. Section 1). Two major mechanisms for selective transport

Table 4
Macroporous MIP membrane adsorbers—preparation and filtration separation performance

Preparation	Matrix	Functionality	Thickness (μm)	Template	Feed concentration in water (μmol/l)	Flux (l/m^2 h) (pressure)	Binding selectivity	Binding capacity (*conditions*)	Reference
Asymmetric membrane									
Wet PI	PAN-co-AA (10% AA)		100	Tho	3.6	5.6 (2.5 kPa)	$\alpha_{Tho/Caf} > 50$	0.52 μmol/g (*recycle*)	[33]
Wet PI	PAN-co-AA (16.6% AA)		500 (casted film)	Naringin	6.7	19 (n.d.)	n.d.	0.13 μmol/g (*recycle*)	[35]
Wet PI	Nylon		30	L-Glutamin	10	2.9 (1.0 kPa)	$\alpha_{l/d} = 3.5$	3.5 μmol/g (*recycle*)	[37]
Wet PI	PSf		80	DBF	250	1.2 (1.0 kPa)	$\alpha_{DBF/DBD} = 3.5$ $\alpha_{DBF/DPE} = 3.5$	102 μmol/g (*24 h*)	[40]
Wet PI	Sulfonated PSf/CA blend		250	Rhodamin B	18	1000 (0.3 kPa)	n.d.	50 nmol/cm^2 = 10 μmol/g (*1 step: ≤10 min*)	[41]
Asymmetric composite membrane									
Photo-graft-copolymerization	PAN-co-DTCS	MAA/MBAA	100	Tho	3.6	3.3 (2.0 kPa)	$\alpha_{Tho/Caf} = 5.9$	32 nmol/cm^2 (*recycle*)	[48]
Symmetric composite membrane									
Photo-graft-copolymerization	PP	AMPS/MBAA	150	Desmetryn	10, 1000	120 (≪0.1 kPa)	Group specific	25 nmol/cm^2, 128 nmol/cm^2 (*1 step: ≤10 min*)	[49]
Photo-graft-copolymerization	PVDF precoat	AMPS/MBAA	125	Terbumeton	10	120 (≪0.1 kPa)	$\alpha_{Terbumeton/Atrazin} = 15$	13 nmol/cm^2 (*1 step: ≤10 min*)	[50]
Photo-polymerization	PVDF; PVDF precoat	AMPS/MBAA	125	Desmetryn	10	120 (≪0.1 kPa)	n.d.	13 nmol/cm^2 as Δ (MIP-blank) (*1 step: ≤10 min*)	[51]



Scheme 1. Separation mechanisms for MIM as a consequence of the binding selectivity obtained by imprinting for a substance A: (a) transport of A driven by a concentration gradient is facilitated via binding/desorption to neighboured MIP sites, while the non-specific transport of another substance B by diffusion is hindered by the micropore structure of the membrane ("fixed carrier" membrane), (b) transport of A is retarded either by binding or binding/desorption to MIP sites on the surface of trans-membrane pores, while another substance B which has no specific interactions with the membrane surface will be transported by diffusion or convection (membrane adsorber), (c) the MIM permeability is increased, e.g. due to an increase of membrane (barrier) swelling as a consequence of A binding to MIP sites, (d) the MIM permeability in deceased, e.g. due to a decrease of membrane (barrier) swelling as a consequence of A binding to MIP sites.

can be regarded (see Scheme 1):

(i) facilitated permeation driven by preferential sorption of the template due to affinity binding—slower transport of other solutes,
(ii) retarded permeation due to affinity binding—faster transport of other solutes, until a saturation of MIP sites with template is reached.

In case (i), depending on the membrane structure as well as MIP site concentration and distribution, transport can occur via carrier-mediated ("facilitated") transport, in real membranes coupled with diffusion [52]. Due to the coupling with non-selective diffusion, separation selectivity can only be achieved for relatively small diameters of transmembrane pores. Note, that most synthetic carrier membranes based on facilitated transport are liquid membranes [13], i.e. they have a non-porous barrier structure. In case (ii)., due to the saturation behaviour, separation efficiency will be mainly determined by MIP binding capacity. Because selectivity is caused by specific adsorption, those MIM can be considered as membrane adsorbers [5].

Moreover, the template binding can also change the barrier properties of the MIM, e.g. via an altered membrane swelling (cf. Scheme 1). Obviously, the magnitude of such effects will also depend very much on the barrier pore size. For conventional synthetic membranes functioning according to the solution–diffusion mechanism (cf. Section 1), such phenomena are well-known: The sorption of the preferred solute in the membrane will lead to a swelling thus also enabling the transport of other less preferred solutes, causing a reduced membrane separation selectivity [3]. With MIM, however, the effect will be specific with respect to the imprinted site receptor function: The resulting response, a changed membrane permeability, can be used for separation but also as a transducer in a sensor system or for controlled release through a membrane (for more details cf. [11]).

Hence, for tailoring and optimizing MIM function, it is critically important to control the affinity of MIP sites along with their density in the membrane and to create a well-defined membrane pore morphology. With mainly meso- and microporous MIM, template binding to imprinted sites can either change the pore network thus altering membrane permeability in general ("gate effect") or the permeation rate is controlled by the interaction with the micropore "walls" (cf. Tables 2 and 3). In MIM with trans-membrane macropores, non-selective transport by diffusion or convection can only be compensated by binding to accessible imprinted sites, causing a retardation which can be used in membrane adsorbers (cf. Table 4). This overview supported by the examples in the Tables will be further discussed and classified in the following sections.

4.2. Microporous MIM–MIP as barrier or transport phase

4.2.1. Gate effect

Early studies with thick pore-filling MIP composite membranes (cf. Section 3.3) indicated an alteration of MIM permeability/conductivity due to binding of the template [8,43]. The opposite behaviour of non-covalently and covalently imprinted membranes [44] was explained by the effect of template binding onto MIP swelling; e.g. a strong shrinking due to binding of template to the covalently imprinted material could be detected even macroscopically. For the non-covalently imprinted materials, the possible reasons were less clear. Studies with much thinner self-supported MIM via in situ polymerization provided clear evidence for this "gate effect". A most remarkable template specificity could be observed: The conductivity reponse to the template atrazine was more than six times higher than for other triazine herbizides [24]. With thin-film composite membranes an effect of template binding onto substance transport was detected directly: The diffusive rate of another solute (creatinine) increased 1.23-fold in the presence of the template (theophylline) while without any additive or in the presence of caffein the fluxes were the same [47].

4.2.2. Facilitated or retarded template transport

Self-supported or composite MIM prepared by in situ polymerization with different templates showed all a similar diffusive transport behaviour because a faster transport of the template could be observed. However, only in one study a facilitated transport via "fixed carrier" MIP sites had been verified by the increase of transport selectivity with decreasing solute concentration [46] (cf. Table 2). The remarkably high selectivities and permeabilities for MIM prepared with a polymer porogen [25], will definitely need further verification (cf. Table 2). Membranes prepared via phase inversion imprinting showed a more complex transport behaviour, especially as a function of the applied driving force for transport (cf. Table 3). The MIM behaviour—for dialysis and electrodialysis—was summarized in a phenomenological relationship where the flux monotonically increased with the difference in chemical potential while the selectivity was around 1 at about 20 kJ/mol (corresponding to a concentration difference of 1 mmol/l), showed a pronounced maximum in the range of 200 kJ/mol and levelled off again to about 1 at very high (electrical) potential values [28].

4.2.3. Mechanisms for transport and selectivity

A detailed pore morphology analysis had not yet been performed for the MIM with mainly meso- and microporous barrier. The conclusions from permeability and other data for MIM and blank membranes [11,26,44,46] can be summarized as follows:

- no large transmembrane pores exist in MIM and blank membranes (the membranes described by Kimaro et al. [25], were additional pores had been created with help of a pore former, are an exception; however, in these MIM the large pores represented only very low surface and volume porosities),
- imprinting creates a specific micropore fraction in MIM which is not present in the blank membranes,
- imprinting can contribute to the connectivity of pores.

A *static model* to explain MIM transport selectivity will be based on affinity binding to the "walls" of *permanent pores* what could either facilitate or retard the transport of the template. The critical parameters are the affinity and the density of imprinted sites: With increasing site density, the contribution of facilitated transport via "fixed carrier" sites [52] will increase. When the imprinted sites are mainly located in very small pores (diameter of a few nm) this precondition will be fulfilled.

A *dynamic model* considering the *adaptation of the micropore structure* to environmental conditions due to interactions with solutes—in particular the template—might be much more realistic for understanding liquid separation with MIM. Solid porous polymers, prepared via in situ crosslinking polymerization or phase inversion, have a structural flexibility as a function of their solvation. For MIPs, significant template-induced polymer shrinking or swelling have been observed, and the "gate effect" for MIM had been confirmed with charged and uncharged spezies. Therefore, its possible impact onto other permeation data should be (re)analyzed. Nevertheless, facilitated transport could also occur in the framework of the dynamic model, but the carrier sites may have a certain mobility.

In conclusion, microporous MIM's permselectivity is based on preferential and reversible binding and exchange between template and MIP sites in the membrane thus providing pathways for selective trans-membrane transport. However, the different behaviour of membranes from different materials and preparation methods, imprinted for various templates and studied under various conditions, demonstrates the need for further detailed investigations of membrane structure as well as detailed transport characterization of well-defined membranes from controlled preparations, with a particular focus on dynamic effects onto micropore structure.

4.2.4. Performance of microporous MIM

Microporous MIM performance must be compared with established membranes for molecular separations, mainly for ultrafiltration, dialysis, nanofiltration or reverse osmosis (cf. Table 1). With state-of-the-art membranes, a continuos separation of two isomers with a permselectivity of 6 (cf. Table 3) can not be achieved. If the fluxes through MIM could be increased without compromising the selectivity and if this performance could be maintained for a long time under technical conditions, such novel materials could immediately gain practical relevance. Imprinting efficiency, membrane morphology and separation conditions can be further optimized in order to improve the selective flux. It is most promising that significant binding and transport selectivities can also be achieved by imprinting with rather common functional polymers [36–38,40,41]. In terms of membrane morphology, the potential of thin-layer composite MIM for increasing permeability has already been indicated [46,47]. Imprinting efficiency and membrane morphology can most efficiently be addressed by tailored composite membranes, i.e. using the sequential preparation approach. An example is filling the straight and regular pores of thin track-etched membranes (cf. [18]) with MIPs [53]. Also, the evidence for a positive impact of a higher driving force onto flux *and* selectivity is most interesting [9,28]. In conclusion, advanced MIM which enable a continuos and truly molecule-selective separation based on affinity interactions seem to be feasible and could have a very large application potential.

4.3. Macroporous MIM–MIP as affinity adsorber layer

With macroporous membranes, molecular separations can only be achieved via interactions with the membrane material. Convective flow through the membrane can be used as means to improve separation performance via elimination of diffusion resistances. The advantages of membranes in comparison with other adsorbers such as beads are a high

selective binding capacity at a high throughput [5,54]. With MIM, the molecule selectivity could be tailored by the binding affinity of imprinted sites, i.e. the efficiency of molecular imprinting. However for MIM as for any other membrane adsorber, pore morphology is of major importance: The micropore fraction will determine the binding capacity, and a connected macropore fraction will be essential for efficient transmembrane transport and elimination of diffusion resistance.

4.3.1. MIP particle composite membranes

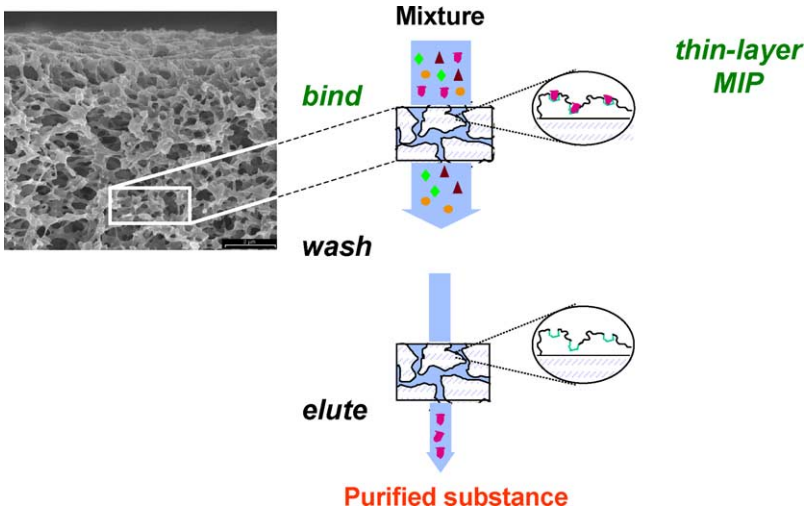
MIP particle composite membranes (cf. Section 3.1), with a macroporous void fraction and a rather symmetric layer topology, had been studied as adsorbers. Especially, the use of monodisperse particles is very promising because a rather even flow distribution could be achieved. However, permeabilities and binding site accessibility were relatively low so that the binding studies had been performed by recirculating the analyte solution through the membrane for many hours in order to achieve the plateau values; but the finally achieved binding capacities for the chiral template BFA (50 μmol/g nanoparticles, measured at a BFA concentration of 50 μmol/l) were quite high [21].

4.3.2. MIM adsorbers prepared via "alternative imprinting"

MIM adsorbers prepared via "alternative imprinting" (cf. Section 3.2) showed in some cases very impressive binding selectivities. However, most of these data had been obtained for single solutes only, i.e. real selectivities under competitive conditions are still missing. Furthermore, experiments had been done at very low flow rates, including extensive recirculation, where the intra-membrane transport occurred mainly via diffusion [33,35,40] (cf. Table 4). The reason was the asymmetric pore structure with a mesoporous skin layer (cf. Fig. 1), created by the immersion step, which largely reduced the membrane permeability [33,40]. The very high binding capacities for DBF on imprinted PSf had been measured at a comparatively high concentration (cf. Table 4), but special binding mechanism—via a CT complex between DBF and PSf—had also been discussed [40]. A largely improved MIM permeability could be obtained by adapted PI conditions for a polymer blend, and significant specific binding had been achieved during one very fast filtration step [41]; the binding capacity achieved in one filtration step of less than 10 min was higher than for most other phase inversion MIM in many hours contact time (cf. Table 4). Nevertheless, further work is necessary to achieve an acceptable membrane adsorber performance for phase inversion MIM.

4.3.3. Thin-layer MIP composite membranes

Due to the macroporous structure of the support microfiltration membrane, thin-layer MIP composite membranes (cf. Section 3.3) for herbicides could be characterized at very high flow rates [49–51] (cf. Table 4): The *dynamic* binding capacities obtained in one fast filtration step (less than 10 min.; i.e. without any recirculation!), normalized to the amount of functional polymer, were similar to the *static* binding capacities for the best phase inversion MIM [33]: For example, the thin-layer MIP PVDF composite membranes had a degree of grafting of 340 μg/cm^2 [50], so that the observed 13 nmol/cm^2 MIP-specific binding capacity (measured at a terbumeton concentration of only 10 μmol/l!) correspond to 38 μmol/g. For the advanced composite MIM a very high selectivity, e.g. a separation factor of 15 for terbumeton versus atrazin, had been achieved [50].



Scheme 2. Application of macroporous thin-layer MIP composite membrane adsorbers for SPE: The separation selectivity is based on the affinity of the imprinted sites; a high binding capacity and a high membrane permeability, respectively, can be adjusted by selecting a suited pore structure (internal specific surface area and average membrane pore size, respectively) of the base membrane. Note, that the small bed volume of the membrane or membrane stack in comparison with adsorber particles also allows a faster equilibration and the elution with smaller volumes so that the target compound can be obtained very fast (if desired in seconds) and in a concentrated form.

Furthermore, quantitative template recovery by elution from the MIM was possible, and the MIM were reusable in several subsequent bind-wash-elute cycles [49] (see Scheme 2). Currently, the main objective is further improving the MIM binding capacities [53]. The high MIM permeabilities would enable an efficient isolation or removal of a dilute valuable or toxic compound from a very large volume.

4.3.4. Performance of macroporous MIM

Performance of macroporous MIM should be discussed in the context of affinity membrane adsorbers which itself directly compete with other affinity materials, either established, e.g. particles, or alternative ones, e.g. monoliths [54]. For the first high-flux composite MIM [49–51], binding selectivities are promising but the capacities must still be improved. When compared with commercial affinity membranes using, e.g., ion-exchange groups [5], MIM—due to the higher spatial order of functional groups in the imprinted sites on the accessible surface—will per se have somewhat lower capacities. However, when compared with membrane-immobilized proteins [12], receptor site density may even be higher for MIP layers. In order to achieve the performance goals, further improvements of the (sequential) preparation of composite MIM will be the most effective approach. Hence, tailored materials for MIM-SPE could already be envisioned (cf. Scheme 2). Further applications, e.g. in membrane chromatography [5,54] or in lab-on-a-chip devices [7], will follow.

5. Combination of novel MIP formats with membrane separations

Active development is devoted to the synthesis of MIPs as nanoparticles [21,55–57] or even microgels [58,59]. With small particles of well-defined morphology in a colloidal dispersion, the specific binding capacity of MIPs can be increased significantly. Ultimately, with microgels not only the function of the binding site but also the three-dimensional structure of biomacromolecules can be mimicked, because the MIP microgels have a molecular weight in the same range as that of proteins. However, the handling of such small entities requires mechanisms which are suited for colloids or biomacromolecules. In that context, “conventional” separation membranes (cf. Table 1) become increasingly attractive.

In fact, during the first syntheses of MIP nanoparticles or microgels and during the evaluation of their binding properties, ultrafiltration has already been used as an alterative to (ultra)centrifugation for particle purification and separation [56].

Consequently, similar to the rapid development of affinity membrane processes for separation and reaction engineering [60,61], the integration of MIP particle and membrane technologies will be extended towards batch, semi-batch and continuos separator and reactor systems. Those systems will be either based on a rather simple combination of MIPs and membranes, for retaining nano-MIPs in the system by a membrane, or on the immobilization of nano-MIPs in membranes with suited transport properties. The latter composite membranes could be developed towards tailored separation membranes, e.g. using MIP microgels as fixed or even mobile carriers, or towards catalytically active membranes based on the immobilization of enzyme-mimicking MIPs.

6. Conclusions

The unique feature of MIM is the interplay of selective binding and transmembrane transport of molecules, making them potentially superior to state-of-the-art synthetic separation membranes already applied in various industries. Receptor and transport properties of microporous MIM can be based on template-specific binding sites in trans-membrane pores, which serve as fixed carriers for “facilitated” transport. Furthermore, template binding in microporous MIM can lead to a “gate effect” which either increases or decreases membrane permeability. Alternatively, MIM can also function as adsorbers, leading to a retardation of template transport followed by breakthrough once the binding capacity has been saturated. Finally, the development of nano-MIPs will facilitate other synergistic combinations with separation membranes for effective separations based on MIPs.

The existing data in the literature can be considered as the “proof-of-feasibility” for separations with MIM, but much further work will be necessary to really explore their potential. A better integration of the fundamental knowledge about membrane materials and technology from the last decades will provide guide-lines for the development of improved MIM with tailored and stable selectivities for diverse separations. These properties must be combined with a high membrane permeability. Therefore, significantly advanced preparation methods and a much more detailed structure characterization will be necessary in order to be able to rationally design permselective MIM.

The main problem in MIM preparation is to optimize MIP recognition and membrane transport properties at the same time. The most promising routes are innovative strategies based on novel materials, e.g. polymer blends, block copolymers or inorganic/organic composites, and the preparation of composite membranes. Towards improved composite membranes, surface functionalization—by self-assembly or controlled grafting—can be used for either coating the pore surface or a controlled filling of pores. Pore-filling applied to asymmetric ultrafiltration membranes, could ultimately enable the application of the MIP “gate effect” for efficient separations via “smart” membranes. Also, the use of presynthesized MIPs for composite membranes, either via creating filter beds from nanoparticles or via entrapment or other immobilization of nanoparticles or microgels in filter structures, should be explored in more detail.

Once MIM materials with attractive intrinsic properties will have been obtained, module and process design will be the next critical issues. In particular for separations by microporous MIM with low permeabilities, the preparation of hollow-fibre membranes could serve as a means to increase the membrane area per volume of a separation unit. For higher driving forces and long term operations, problems with concentration polarization and membrane fouling must be solved. All these challenges can be met by adapting the knowledge in "conventional" membrane technology [1,2]. Moreover, the integration of membranes, as separation media or for process intensification, in lab-on-a-chip systems is already underway [7].

Among first examples for real applications will be MIM adsorbers for the specific sample enrichment from large volumes by membrane SPE, and for the specific decontamination of large process streams. However, the already demonstrated ease of integrating separation membranes into high-throughput technologies, for example via 96- or 384-well membrane filter plates, will at the same time facilitate the use of substance-specific MIM or MIM libraries in screening applications. Other promising continuos separations are the resolution of enantiomers or the (by)product removal from bioreactors, both feasible either by electrodialysis or by dialysis. Controlled release or delivery from or through MIM, including fibres or capsules, will be another field of attractive potential applications. Targets could be drugs but also technically or environmentally interesting substances. Release from MIP-based depots could occur passively, with the MIM as barrier dictating the transport kinetics, but also triggered by a stimulus from the environment, e.g. via recognition of a specific signal molecule at an imprinted site (cf. [47]).

In a more general context, MIM can serve as model systems for cellular transmembrane transport and natural receptors. Applications in sensors can be immediately derived from those models. MIP films have already been adapted to various sensor and assay formats, fulfilling the minimum requirement—immobilization of the receptor—but also fitting to the need of various detection formats [62]. For the integration of transducer functions into MIP films, the use of membrane transport effects, e.g. the "gate effect", may be especially beneficial for implementing improved detection specificity and signal amplification. Biocompatibility of materials in contact with cells or tissue, relies on specific molecular recognition processes, especially at the interfaces, and imprinted surfaces are expected to play a key role in this field in the future [63]. Thin-layer MIP composite membranes for the recognition of proteins [53], but also for cell-specific recognition based on surface-marker structures or cell shape could also be envisioned. Ultimately, catalytic MIM, integrating and organizing separation and reaction in space and time, have a great perspective as key elements for advanced "bio-mimetic" processes in chemical and biochemical reaction engineering [64].

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