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Polymer application for separation/filtration of biological active compounds

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Abstract:
Membrane technology is an important part of the engineer's toolbox. This is especially true for industries that process food and other products with their primary source from nature. This review is focused on ongoing development work using membrane technologies for concentration and separation of biologically active compounds, such as polyphenols and flavonoids. We provide the readers not only with the last results achieve in this field but also, we deliver detailed information about the membrane types and polymers used for their preparation.

Keywords: asymmetric polymeric membranes, polyimide, metal-organic frameworks
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1 Introduction

Bioactive compounds (BACs) from natural sources, extracted by appropriate solvent and further treated by membrane operations, are promising and intensively investigated area of scientific research in view of BAC separation or concentration. Polymer membranes, as well as the newer class of mixed matrix membranes (MMMs), are attractive for concentrating and/or selectively fractionating BACs contained in aqueous as well as non-aqueous extracts from different natural sources. A large number of potential applications are focused on their solvent resistancy and the ways to improve it, as can be seen in several review articles in the recent years [1–4]. Large areas for realization of these membrane separation techniques are the food industry [5, 6], the concentration and fractionation of value-added products from agro-industrial wastes [7] and the purification of thermally sensitive compounds as active pharmaceutical ingredients (APIs) and catalysts [8]. Among the numerous examples, important ultrafiltration (UF) and nanofiltration (NF) implementations can be cited in the recovery of polysaccharides and polyphenols from winery effluents [9, 10], or the fractionation of olive mill wastewaters [11, 12], where almost all polyphenols were recovered in the permeate solution from nanofiltration and subsequently concentrated by osmotic distillation. The recovery of valuable compounds found as subproducts in diluted effluents through membrane separation and concentration makes them attractive for use in the food, cosmetic and pharmaceutical industry.

1.1 Membranes used for separation of biologically active compounds

Widely used membranes are asymmetric polymeric membranes, especially in solvent-resistant applications. In general, they are inexpensive for fabrication and easy to scale-up, but their typical drawbacks concern membrane compaction and fouling, as well as thermal and chemical stability. Detailed reviews on the polymeric materials used for membrane preparation could be found in [2, 3]. Their basic configuration of dense selective layer supported by microporous structure, which can be of the same material (the integral type) or from a different one (the thin-film composite type), is the focus of numerous investigations including new membrane materials or membrane modifications. Examples can be found among the most commonly used polymers such as polyimide (PI) [13, 14], polyamide (PA) [15], polyacrylonitrile (PAN) [16], polyphenylsulfone (PPSU) [17, 18], polyether sulphone (PES) [19] and polypyrrole (PPy) [20], as well as in new directions like polyarylene sulfide sulfone (PASS) [21] or crosslinked polybenzimidazole membranes (PBIs) [22]. Enhancement of the membrane performance is searched through improving the permeance of the membrane after crosslinking [14], modulating the hydrophobic–hydrophilic behaviour of the membrane in the search of high rejection and reasonable

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flux in aqueous media [19], as well as membranes for use in organic media with enlarged ability to withstand harsh chemical environment [22]. In order to obtain higher membrane selectivity, able to serve specific separation needs, new membrane technologies involving molecular imprinting are used [23, 24] which overcome the limitations of the conventional size-exclusion membranes. In the same time, higher flux and preserved rejection values are observed with the molecularly imprinted membranes. Concerning the separation and purification capability in organic solvent medium, MMMs and metal−organic frameworks (MOFs) membranes have a great potential for implementation.

The MMMs are composite organic–inorganic membranes which can be designed to possess good chemical and mechanical stability, as well as rejection and flux and to overcome drawbacks such as flux decline due to compaction of polymeric membranes or their aging [4]. This is achieved by incorporating inorganic nanoparticles into the membrane matrix, which can be visualized as discrete particles in a continuous polymer phase. The connection between these two can be through covalent bonds, van der Waals forces or hydrogen bonds. Various metal oxide nanoparticles – TiO_2, ZnO, Fe_2O_3, Al_2O_3, silica-containing (SiO_2) or carbon fillers – are used. In the area of solvent-resistant nanofiltration, examples can be cited for embedding nanoparticles, containing Cu in PPSU-based membranes [25], Ti in crosslinked PI membranes [26], Zn in PA network [27], as well as zeolites in polydimethylsiloxane [28] or UZM-5 zeolite in PA [15], inorganic organosiloxane in PI [29], etc.

In all these cases, improved membrane compaction resistance was reported, which results in enhanced fluxes and better or unchanged rejection performance as compared to commercially available solvent-resistant polymeric nanomembranes [29] (e.g. Duramem™ 300, Evonik Membrane Technology Ltd Milton Keynes, UK), as well as in better chemical and thermomechanical properties.

Concerning flux decline and rejection with MMM, further development is searched for improving the adhesion between the polymer and the inorganic filler, thus avoiding a possible nonselective void formation. The latter is achieved by using MOFs, i. e. porous crystalline material, containing metal ions/clusters and organic linkers, which posses better affinity towards polymer chains. This structure possesses flexibility and mechanical strength characteristic of the polymer membranes, but incorporates the separation potential of MOFs. Investigations with potential application in organic solvent nanofiltration are directed to MOF–thin-film composite (TFC) membranes, as well as to integrally skinned asymmetric membranes, examples being given in [30, 31]. The TFC membrane structure – ultrathin selective layer and highly porous support – suppose smaller resistance to solvent flux, which is an advantage to integrally-skinned asymmetric membranes. Concerning the membrane morphology, an even MOF distribution throughout the membrane and across the membrane surface is achieved [32], and further possibilities are searched in the use of MOFs with different pore sizes in view of the molecular weight cut-offs. Successful applications of the MMMs are found in:

- In olive oil wastewater treatment [33], the hydrophobicity of the polyethersulfone membrane is modified by the concentration of functionalized multiwall carbon nanotube (F-MWCNT) in the membrane structure, improved antifouling properties were obtained, resulting in reduced flux decline and high rejections through Chemical Oxygen Demand (COD) and total phenols in the olive oil wastewater;
- API purification, employing PI-based membranes incorporating anorganic–inorganic hybrid network (3-aminopropyl trimethoxysilane
- APTMS as crosslinking agent and organosilicone precursor). A review of organic solvent membrane application in the pharmaceutical industry for solvent recovery and API purification is given in [34] including peptide and oligonucleotide production, removal of excess reagents and removal of APIs from organic solvents.

1.2 Concentration and purification of bioactive compounds from natural extracts

An area of special interest to this chapter is the application of membrane separations in organic solvents coupled with solid–liquid extraction for production of high-value products from natural plant extracts [35]. The latter are multicomponent with complex chemical structure of the individual compounds depending on the number of aromatic rings, hydroxyl, carboxylic groups, etc., and are characterized by a large molecular weight (MW) distribution and different molecular polarity. Examples are the phenolic compounds and their numerous non-flavonoid and flavonoid representatives, whose MW typically ranges between 100 and over 600 Da. Additional intermolecular solute or solute–solvent interactions can result in bigger molecular structures, which determine the wider use of ultrafiltration and nanofiltration membranes. Examples for such applications and analysis of the separation behaviour depending on the pore sizes of the membrane are reviewed in [36] in order to distinguish the effects of molecular sieving mechanism, polarity and solute–solvent interactions. The authors discuss the possibilities to achieve better flexibility of the membrane or membrane sequence (UF-NF) for particular separations taking into account the biological activity, for instance the removal of "heavier" phenolic

classes without affecting the overall antioxidant properties of the permeate. Examples are given concerning successful UF separations of low and high MW: anthocyanins from winery sludge extract; proanthocyanidins from grape seeds extract; pectin from phenols in olive mill wastewater; hydroxycinnamic acids and flavanones from blood orange juice etc. [36].

The multicomponent character and unique bioactive properties of the natural extracts from different plants, sometimes with large MW distribution profile and very different solubility, make them a challenge for membrane separation on a molecular level exploring the potential of organic solvent nanofiltration (OSN).

Table Table 1 summarizes recently reported investigations, representative for the application of polymeric membranes in separating/concentrating biologically active compounds from natural extracts. The interest in combining membrane filtration with solid-phase extraction is to improve the amount of BACs extracted from plant materials provided that membranes with high rejections and reasonable permeate fluxes are selected. By *concentrating* the extracts new potential applications areas are offered for these natural extracts as preservatives and functional ingredients for food, cosmetic, nutraceutical and medical uses. Examples are the concentrated through NF rosemary extract [37]; the almost 100 % retention of anthocyanins in roselle extract using a sequence of UF and NF membranes [38]; the concentration of water–ethanolic extracts from propolis with over 95 % rejections towards flavones, flavonols, flavanones, dihydroflavonols as well as total phenolic substances [39–41]. On the other hand, the possibility for *fractionating* the extracts, thus obtaining fractions enriched in target BACs, is another promising perspective, though it is more difficult for realization. The reason is the complex mechanism involved in pressure-driven membrane separations on a molecular level, where the molecular sieving mechanism is not enough to explain the permeance of the solutes, but also component solubility, as well as membrane hydrophobicity, polarity resistance and solute–solvent interactions have to be taken into account. An example could be the phenolic compounds as solute and the hydroethanolic solvent interacting with the nonpolar and polar sides within their molecules [36] which leads to improved solubility and preservation of the antioxidant properties of the latter. Positive examples for fractionation of BACs from multicomponent solutions originating from natural sources are also reported in the literature using membranes with different molecular weight cut-off (MWCO) [12, 42–45].

Table 1: Summary of applications of polymeric membranes to separate/concentrate biologically active compounds from natural extracts. Table Table 1.I. Aqueous extracts

Extracted material	Mem-brane Proc.	Membrane material (Manufacturer)	MWCO	Filtration module	Composition	Ref.
Grape seeds	UF	Fluoropolymer : FSM0, 15PP (Alfa Laval) Polyethersulphone (PES): UP150 (Nadir) Polyvinylidene difluoride (PVDF): UV050 (Nadir)	150 kDa 50 kDa	Dead-end stirred cell	Total polyphenols (as gallic acid equivalent)	[53]
Jamun seed *Syzygium cumini* (L.)	UF⇒ NF	Polyethersulphone (PES): UF supplied by M/s Alfa Laval Pvt. Ltd., India NF supplied by M/s. Permionics Membranes Pvt. Ltd., India	100 kDa 250 Da	Flat sheet, cross-flow Dead-end stirred cell	Total polyphenols (as gallic acid equivalent); total flavonoids (as quercetin equivalent)	[54]

Roselle extract	UF	Composite polyamide: GE, Thin film: GH, GK (GE Osmonics); Polyethersulphone: UP005, UP020, UP150; UH030, UH050 (Microdyn-Nadir)	1–150 kDa	Flat sheet, cross-flow	Anthocyanins: delphinidin 3-xylo-syl-glucoside (delphinidin 3-sambu-bioside or hibiscin); cyanidin 3-xylosyl-glucoside (cyanidin 3-sambubio-side or ossyp-icyanin);	[38]
	NF	Polyamide thin-film composite: NF90 (Dow); NF200, NF270 (FILMTEC); Crosslinked polyamide composite: UTC60 (TORAY); Composite: MPF36, MPF34 (Koch); Polyamide polysulfone, thin-film: DL, DK (GE Osmonics); Polyethersulphone: NP010, NP030 (Microdyn Nadir);	150–400 Da			
Bark residues from mate tree	NF	Polyvinylidene difluoride (PVDF) thin-film membrane: Desal HL2521TF (Osmonics, USA)	150–300 Da	Spiral module	Gallic, chlorogenic (5-caffeoyl quinic), 3,4-dihydroxyben zoic, 4,5-dicaffeoyl quinic acid; epigallocate-chin gallate	[55, 56]
Soybeans	NF	Polyvinylidene difluoride (PVDF) (GE Osmonics, USA)	150–300	Spiral module	Malonyl and β-glucosides (genistin, daidzin, glycitin), aglycones (daidzein genistein, glycitein)	[57]

Castanea sativa leaves	UF	Modified polyethersulfone (Omega Membranes, Minisette, Pall Filtron)	5 and 10 kDa	Flat sheet, cross-flow incl. batch redilution of the retentate	Flavonoids (quercetin and cirsiliol), phenolic acids (gallic, proto-catechuic and vanillic acids) and lignans (medioresinol)	[58, 59]
Olive-extracted oleuropein	NF	Aromatic polyamide on polysulfone support (PA/PS): DK Osmonics Desal, USA; DL Osmonics Desal, USA; Polyethylene glycine (PEG): G10 Osmonics Desal, USA; G5 Osmonics Desal, USA; Silicone on polysulfone support (SB/PS): MPF34 KOCH, USA ; MPF36 KOCH, USA; MPF44 KOCH, USA Polyvinyl alcohol (PVA): NTR7250 Nitto Denko Co, JP Sulfonated polyether sulfone (SPES): NTR7410 Nitto Denko Co., JP ; NTR7430 Nitto Denko Co., JP ; NTR7450 Nitto Denko Co., JP;	150, 300 Da 1–2.5 kDa 200, 1000, 250 Da 300–400 17.5 kDa, 2 kDa, 700–800 Da	Dead-end stirred cell	Oleuropein	[60]

Table Table 1.II. Organic solvents

Extracted material	Solvent	Process	Membrane material	MWCO	filtration module	Composition	Ref.

Pequi (*Caryocar brasiliense* Camb.)	EtOH–H_2O (95:5 v/v) H2O	NF	Polyamide (PA): NF 90, Filmtec, Dow Chemical Company, Sao Paulo, SP, Brazil)	200–300 Da	Dead-end stirred cell	Polyphenols, carotenoids	[61]
Cotinus coggygria	MeOH; EtOH(azeotr.); EtOH/H_2O (50/50); H_2O	NF	Crosslinked polyimide (Duramem, Evonik, UK)	200–900 Da	Dead-end flat sheet tangential	Polyphenols and flavonoids: gallic acid, catechin, quercetin, rutin	[62]
Persimmon	MeOH	UF	Polysulfone (Tianjin, Tianfang, China)	10 kDa	Hollow fiber	Polyphenols, including condensed tannin	[63]
Sage-Salvia officinalis L. (*Labiaceae* family)	EtOH–H_2O 50 % v/v	UF	Polysulfone (PSF) and polyacrylonitrile (PAN)-based membrane (prepared)	Not specified	Flat sheet tangential	Carnosic acid, carnosol and rosmarinic acid	[64]
Viscum album L. (*Loranthaceae*),	H_2O	UF	Polysulfone (PSF) and polyacrylonitrile (PAN) membrane	Not specified	Flat sheet tangential	Phenolic acids, flavonoids, carotenoids	[64]
Grape marc	EtOH–H_2O 0–100 %	NF	Advanced polyamide, (HAR SpA, Milan, Italy)	470 Da det. exp. with PEG of diff. MW	Spiral wound	Total phenols Catechin Quercetin Epicatechin Rutin	[65]
Grape seeds	MeOH-H_2O	NF⇒MF⇒UF NF⇒UF⇒MF⇒UF (incl. diafil.)	AFC40: Polyamide (PA) ES404: Polyethersulphone (PES) ; PU608: Polysulphone (PS); PU120: Polysulphone (PS); FP200: Polyvinilidene fluoride (PVDF)	4 kDa 8 kDa 20 kDa 200 kDa	Monotubular	Oligomeric proanthocyanidins; polyphenolic acids: cinnamic (coumaric, caffeic, ferulic, chlorogenic, neochlorogenic); flavonoids: flavan-3-ol (catechin, epicatechin, their polymers or esters with galactic acid or glucose)	[42]

Propolis,	EtOH–H_2O H_20; EtOH–H_2O	NF	NF90: Polyamide/polysulphone (Osmonics, USA) Crosslinked polyimide (Duramem, Evonik, UK)	180–300 Da 200–900 Da	Spiral wound filtration Dead-end filtration	Phenolic compounds and flavonoids – flavones, flavonols, flavanones, dihydro-flavonols (e.g. pinocem-brin, pinoban-ksin, caffeic acid, quercetin, pinoban-ksin-methilether, p_coumaric acid, crysin)	[39–41, 43]
Sideritis	EtOH	NF	Crosslinked polyimide : Duramem (Evonik, UK): polyimide : StarmemTM 240:	300–500 Da	Dead-end flat sheet, tangential	Chlorogennic acid, lavan-dulifolio-side,verbascoside, leucosepti-side, 7 flavonoid gluosides	[48–50]
St John's wort *(Hypericum perforatum L.)*	EtOH (96 %)	NF	Crosslinked polyimide Duramem (Evonik, UK polyimide: Starmem™ 240	500 Da 400 Da	Dead-end stirred cell	Quercetin; catechin ; hyperoside (quercetin 3-o-galactoside); hyperforin; hypericin; quercitrin (quercetin 3-o-rhamnoside); Iso-quercitrin (quercetin 3-o-glucoside);	[47, 50]
Lemon balm	EtOH–H_2O	NF	Crosslinked polyimide: Duramem (Evonik, UK	200 Da	Dead-end stirred cell	Rosmarinic acid	[47]
Rosemary	EtOH	NF	Crosslinked polyimide: Duramem (Evonik, UK	200–500	Flat sheet, tangential	Rosmarinic acid	[37]

Cocoa seeds	EtOH	NF, RO	Commercial NF and RO membranes: NF: DL, HL (GEOsmonics), NF-90 (Film-tec-Dow). RO: SG (GE-Osmonics), BW-30 (Filmtec-Dow)	Retention charact. provided by manufactures 96–99.5 %	Dead end	Polyphenols (mono to decamers)	[66]
Thymus capitatus	Hexane, Acetonitrile, Methanol	NF UF	Polysulphone and polyamide (NF-DK; Desal 5 DK, Osmonics) ;		Dead end	Carnosic and rosmarinic acids	[67]
Artichoke (*Cynara scolymus* L.) wastes	EtOH–H_2O	NF	NF270: Polyamide thin-film composite; GE Osmonics: Polyamide; GE Osmonics: Cross-linked aromatic polyamide;	200–400 Da 200 Da 150–300 Da	Flat sheet tangential filtration	Phenolic acids : cynarin (1,5-dicaffeoylquinic acid) and chlorogenic acid (5-caffeoylquinic acid) flavonoid derivatives: Luteolin-7-glucoside, Apigenin-7-glucoside, flavones	[68]
Green tea Polyphenon-60	EtOH–H_2O 10–80 %	NF	Polysulphone/polydimethylsiloxane (PSF/PDMS) Desalination Systems, USA, G-5, G-10, G-20 and G-50 membranes; HC-50 and HR98PP, DOW Denmark A/S, Denmark; MPF-60, Abcor Tokyo, Japan and 960PP, DDS Filtration, Denmark.	Polychromatic characteristic only	Dead end stirred cell	Polyphenols: catechins	[69]

Eucalyptus globulus bark	EtOH–H_2O 80/20 (v/v)	UF	Polyamide composite: GE 1, GE Osmonic Polyethersulfone PLEAIDE: P5, Orelis Env. Polyvinylidenefluoride: JW 30, GE Osmonic Polysulfone: EW 60.	1 kDa 5 kDa 30 kDa 60 kDa	Flat sheet tangential	Polyphenols	[70]
Tobacco leaves and waste	EtOH	NF	Duramem™ (Evonik, UK): Crosslinked polyimide Starmem™ 240: polyimide	300 Da 400 Da	Dead-end stirred cell	Chlorogenic acid and its isomers neochlorogenicacid (5-o-caffeoylquinic acid) and 4-o-caffeoylquinic acid; Rutin (quercetin-3-o-rutinoside) Kaempferol-3-rutinoside	[50, 71]

1.3 Recovery of extraction solvents

Successful concentration of the solutes supposes high membrane rejections and possibility for *recovery and direct solvent reuse*. In this case, membrane separation replaces fully or to some extent distillation/evaporation processes, showing improved environmental, safety and economical aspects. Applications of solvent recovery by OSN are reported in the pharmaceutical and the oil industry [46]. Examples are the commercial polymeric OSN membranes (Starmem 122 and Duramem 150), successfully tested for treating pharmaceutical/solvent mixtures [1]; separation of oil from different solvents [2]; solvent recovery from ethanolic extract of rosemary, lemon balm [37, 47] (Duramem 200) and Sideritis (Duramem 300) [48–50] where the reuse of the permeate as solvent proved equal and even better extraction capability and considerably reduced the required solvent volume. This solvent recovery as compared to the traditional distillation process has also the advantage of being a greener alternative for separation of solvents, requesting mild conditions and providing reduced volumes of toxic solvent effluents to the environment and lower energy consumption (the effect being stronger for solvents with higher boiling point). Further development of tighter membranes for removal of small solutes by OSN is pointed out as important in view of solvent purification in fine chemistry processing, in order to explore the potential of OSN as sustainable and competitive to other purification technologies [46].

The use of natural and renewable sources of BACs combined with membrane separation techniques that can be viewed as environmentally friendly makes the whole process to be classified as a green one. In the scope of a green technology also, the production of the polymer membranes has to be taken into account. The latter has been in the focus of recent publications of leading groups in the field of membrane technology and especially in organic media applications – the OSN separation process [46, 51, 52]. The idea is to reduce the discharge of hazardous chemicals as waste by replacing toxic solvents with environmentally friendly ones without worsening the membrane performance. Investigations are made with solvent-resistant PI membranes [51] as well as polyether ether ketone (PEEK) membranes [52] and performed on bench and industrial scales. Concerning the membrane performance, the authors pointed out the need of research and optimization work in scaling-up.

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