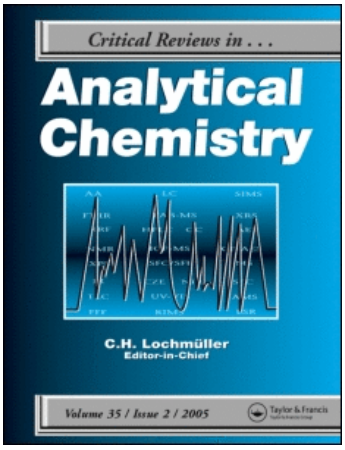

Critical Reviews in Analytical Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713400837

Analytical Applications of Membrane Extraction for Biomedical and Environmental Liquid Sample Preparation

Natalia Jakubowska[a]; Żaneta Polkowska[a]; Jacek Namieśnik[a]; Andrzej Przyjazny[b]
[a] Department of Analytical Chemistry, Chemical Faculty, Gdańsk University of Technology, Gdańsk, Poland [b] Science and Mathematics Department, Kettering University, Flint, Michigan, USA

To cite this Article Jakubowska, Natalia , Polkowska, Żaneta , Namieśnik, Jacek and Przyjazny, Andrzej(2005) 'Analytical Applications of Membrane Extraction for Biomedical and Environmental Liquid Sample Preparation', Critical Reviews in Analytical Chemistry, 35: 3, 217 — 235
To link to this Article: DOI: 10.1080/10408340500304032
URL: http://dx.doi.org/10.1080/10408340500304032

Critical Reviews in Analytical Chemistry, 35:217–235, 2005

ISSN: 1040-8347 print / 1547-6510 online
DOI: 10.1080/10408340500304032

Analytical Applications of Membrane Extraction for Biomedical and Environmental Liquid Sample Preparation

Natalia Jakubowska, Żaneta Polkowska, and Jacek Namieśnik
Department of Analytical Chemistry, Chemical Faculty, Gdańsk University of Technology, Gdańsk, Poland

Andrzej Przyjazny
Science and Mathematics Department, Kettering University, Flint, Michigan, USA

A review of the membrane extraction methods used in determination of various organic compounds in liquid environmental matrices and biological fluids is presented. Theory and principles, possibility of combining membrane extraction methods with methods of final determination, and applications are discussed in detail.

Keywords applications of membrane extraction, biomedical analysis, environmental analysis, final determination techniques, hyphenation and automation, membrane-based sample preparation techniques, membrane extraction, membranes

The trend to determine a possibly broad spectrum of analytes, especially organic compounds in liquid samples characterized by the complex and often variable matrix composition, constitutes the driving force for analytical chemists to search for new methodological and instrumental approaches (1–3). Typical environmental and biological samples usually require special pretreatment prior to analysis by chromatography or related techniques, such as capillary electrophoresis.

The pretreatment involves the transfer (isolation) of analytes from the primary matrix (sample) to the secondary matrix with the simultaneous removal of interferences and increase in concentration of the analytes in the receiving matrix to the value above the detection limit of the instrument (enrichment). The advantages and drawbacks of the most commonly used techniques of isolation and/or enrichment of organic analytes from liquid samples are compiled in Table 1 (4).

Special attention has recently been paid to practical use of so-called solvent-free analyte isolation and/or enrichment techniques, which can be attributed to the widespread acceptance of green analytical chemistry resulting from a general concept of balanced development (5–11). A number of procedures meeting these requirements have been developed, including gas extraction (SHS, DHS, TLHS, PT, CLSA), solid phase extraction (SPE, SPME), supercritical fluid extraction (SFE), and membrane extraction.

Membrane techniques of analyte extraction from liquid samples play a special role among the solvent-free procedures. Recent analytical literature has revealed that these techniques are experiencing the most rapid growth. In this group of extraction techniques, use is made of membrane properties as a thin-layer barrier capable of preferential or selective transfer of mixture components (12). Application of membrane extraction allows for preparation of final determination samples having a very complex matrix using a simple apparatus, which can be readily automated. This review aims at familiarizing analytical chemists who work with liquid samples with the membrane extraction techniques.

MEMBRANES

In the simplest approach, a membrane can be treated as a selective barrier between two phases. The phase, in which mass

This work originated within the framework of activities of the Centre of Excellence in Environmental Analysis and Monitoring, Chemical Faculty, Gdańsk University of Technology, Gdańsk, Poland, as a research project supported by the European Commission under the Fifth Framework Program and contributing to the implementation of the Key Action Sustainable Management and Quality of Water within the Energy, Environment and Sustainable Development (Contract no. EVK1-CT-2002-80010).

Address correspondence to Jacek Namieśnik, Department of Analytical Chemistry, Chemical Faculty, Gdańsk University of Technology, 11/12 G. Narutowicza Street, 80-952, Gdańsk, Poland. E-mail: chemanal@pg. gda.pl

TABLE 1
Advantages and drawbacks of the most commonly used techniques of isolation and/or enrichment of volatile organic compounds from liquid samples (Ref. 4)

Technique		Advantages	Drawbacks
Liquid-liquid extraction (LLE)		• Simplicity • Inexpensive apparatus	• Tediousness • Need to use large volumes of solvents of high purity • Often small enrichment factor of the analyte • Low selectivity of the process • Possibility of formation of emulsions which are difficult to separate • Difficulties with handling large-volume samples
Solid-phase extraction	Solid-phase extraction (SPE)	• Possibility of storage of enriched analytes on the solid sorbent (analytes sorbed on the solid sorbent can be transported and stored) • Reduction of the volume of toxic solvents used • Emulsion formation not a problem • Much larger enrichment factor of the analyte compared to LLE • Ease of automation	• Possibility of low analyte recovery (due either to the matrix-sorbent interactions or to breakthrough of the sorbent bed) • Sometimes poor reproducibility resulting from differences in various batches of the sorbent • Clogging of the sorbent (both in columns and in extraction disks) by particles suspended in a sample
	Solid-phase microextraction (SPME)	• Elimination of solvents • Short time of analysis • Simplicity of operation • Low cost • Ease of automation	• Sensitivity of the PDMS fiber to the presence of suspensions • Low efficiency of the process resulting from the small amount of the stationary phase present on the fiber
Gas extraction	Static headspace analysis	• Simplicity of operation • Ease of automation • Elimination of solvents	• Relatively low sensitivity
	Dynamic headspace analysis	• Low detection limit • Relatively short analysis time • Good precision of determinations • Elimination of solvents from the procedure • Possibility of analysis of samples of large volumes and a complex organic matrix • Ease of automation of the process	• Expensive apparatus • Problems with foaming samples

transfer takes place is called the donor phase while the other phase is called the acceptor phase (13). A general principle of separation of components of liquid mixtures by using membranes is shown schematically in Figure 1 (14). The main factors affecting mass transfer across the membrane are: the type of membrane and the driving force of the extraction process.

Kinds of Membranes

There are a number of criteria used for the classification of membranes. Those most often taken into consideration when characterizing membranes are membrane state, membrane morphology (closely related to their porosity and internal structure), and membrane shape. A diagram illustrating membrane

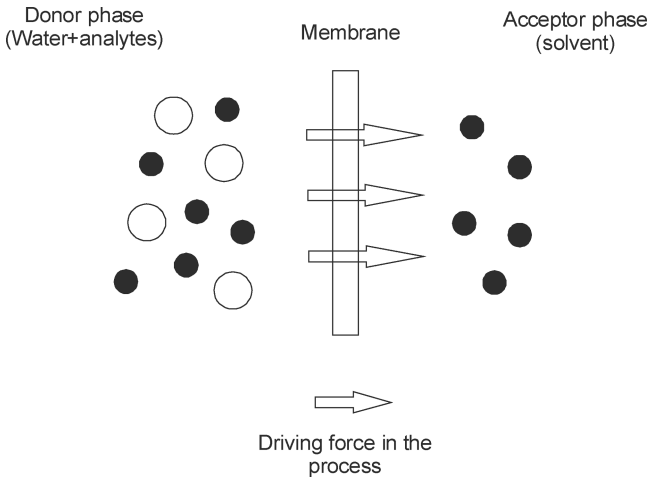

FIG. 1. Schematic representation of the transport through membranes (Ref. 14).

classification according to these criteria is shown in Figure 2. The information on morphology of various types of membranes which could find use in environmental analytical chemistry is compiled in Table 2 (15, 16).

The Driving Force of Mass Transfer Across the Membrane

Separation of components in the membrane process results from the differences in the rate of transfer of chemical compounds across the barrier. It is a nonequilibrium process, in which the flow of a component depends on the driving force (17, 18). Some basic information on the driving forces of the membrane processes is given in Table 3.

MEMBRANE TECHNIQUES

Various analytical techniques make use of both porous and nonporous (semipermeable) membranes. In the case of porous membranes, the separation of components is accomplished as a result of the sieving effect (size-exclusion); that is, the membrane passes molecules with diameters smaller than the membrane pore diameter. Selectivity of such a membrane is thus dependent on its pore diameter. The operation of nonporous membranes is based on the differences in solubility and diffusion coefficients of individual analytes in the membrane material. A porous membrane impregnated with a liquid or a membrane made of a monolithic material, such as silicone rubber, can be used as a nonporous membrane (20). Basic information on the membrane techniques used in analytical practice is provided in Table 4 (17).

Filtration

The general term membrane filtration includes four processes: microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO). The driving force of these processes is the pressure difference across the membrane in a membrane module. Under the pressure gradient applied and due to selective operation of the membrane, some components of a solution penetrate the membrane, while others remain in solution (15, 16).

Individual membrane filtration processes differ with respect to size of molecules retained by the membrane, kind of membrane used, kind of solutions being separated, and magnitude of pressure difference across the membrane (16). The classification of membrane filtration techniques with respect to size of

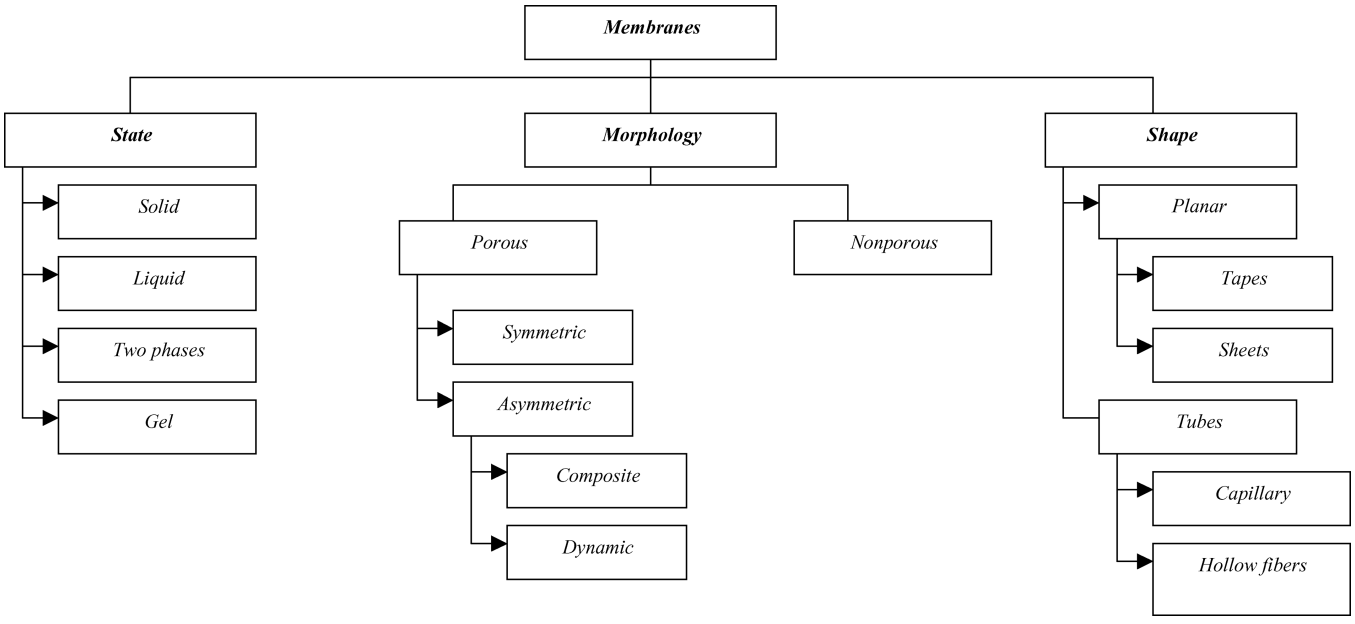

FIG. 2. Classification of membranes with respect to their state, morphology, and shape.

TABLE 2
Information on the morphology of membranes used in membrane processes (Refs. 15 and 16)

Symmetric	Asymmetric
Porous membranes	
• Capillary or irregular pores • Identical porosity in the direction perpendicular to external surfaces • Preparation methods - sintering - radiation with etching - phase inversion	• Increase in porosity in the direction perpendicular to surfaces • Smallest porosity in the surface layer • Separation layer: surface layer • Support layer (reinforcing) - the rest of the membrane • Methods of formation - thermal gelation - vapor adsorption - Loeb-Sourirajan phase inversion • Composite asymmetric membranes - two- or multilayer - different composition of individual layers - formed by coating a layer of selective properties onto a porous protective layer • Dynamic asymmetric membranes - formed dynamically - formed by coating colloids or macromolecular compounds onto a porous bed under pressure - support: filtration foil made from an organic material; plate, tube or molder made from a ceramic, carbon or metal sinter
Nonporous membranes	
• Lack of conventional pores (pores of molecular dimensions) • Continual variations in the number, size, and location of pores as a result of thermal motions of the membrane material molecules	
Solid	**Liquid**
Inorganic membranes • Material: metals, metal alloys, sintered ceramics, glass Organic membranes • Material: natural and synthetic polymers (e.g., cellulose acetate, silicone rubber, polyethylene)	• Thin layer of a liquid with a dissolved mediator • Separates a donor solution from an acceptor solution • Kinds - thick-layer - emulsion - reinforced
Ion-exchange membranes	
• Nonporous, microporous, and porous membranes of symmetric or asymmetric structure • Kinds - cationic (cation exchange): in constant electric field pass cations toward the cathode but exclude anions - anionic (anion exchange): in constant electric field pass anions toward the anode and exclude cations	

molecules being separated and the range of pressures used is shown in Table 5.

The membrane filtration techniques are often discussed in papers dealing with membrane extraction; however, it should be pointed out that they are not strictly membrane extraction techniques (13, 19).

Microfiltration

Microfiltration is the membrane process most closely related to filtration of suspensions in conventional filters. The pore sizes in membranes range from 0.05 μm to 10 μm. This ensures retention of molecules with diameters greater than 0.1 μm. Membranes for microfiltration are prepared from polymers

TABLE 3
Basic information on the driving forces in membrane processes (Refs. 17 and 19)

No.	Driving force of extraction process	Name and mathematic form of the equation used to describe mass transfer	Membrane techniques in which the mass transfer equations are used
1	Concentration gradient	Fick's law of diffusion: $J_m = -DA(dC/dx)$	Dialysis, membrane extraction
2	Pressure difference	Hagen-Poiseuille equation: $J_v = -KA(dP/dx)$	Filtration
3	Potential difference	Ohm's law: $J_c = -RA(dE/dx)$	Electrodialysis

Where D = diffusion coefficient; K = hydrodynamic permeability; R = resistance; A = diffusion surface (membrane surface).

such as cellulose esters, fluorinated and chlorinated polyolefins, polyamides, and polyesters. The technique is used primarily for sterilization of water, wine, fruit juices, and pharmaceutical solutions as well as for purification of various technological liquids in the electronics and biotechnological industries (22–31).

Ultrafiltration

Ultrafiltration is characterized by the use of membranes in which the pore sizes range from 1 to 50 nm. This allows separation of components with molecular masses ranging from 5×10^3 to 1×10^6 amu. At pressure differences of 0.2–1.0 MPa, only the solvent and molecules of those substances whose size is less than the molecular cut-off level can penetrate the membrane. At present, asymmetric and composite membranes are primarily used in ultrafiltration. They are made of cellulose esters, polyolefins, aromatic polymers, and so forth. Ultrafiltration is used for the separation, enrichment, and purification of solutions of high-molecular-weight compounds in the chemical, pharmaceutical, food, and biotechnology industries (32–41).

Nanofiltration

Nanofiltration is a relatively new membrane technique. This technique can be placed between UF and RO, revealing typical characteristics of both UF, such as the sieving effect, and of RO (i.e., separation of substances with molecular sizes smaller than the pore diameter of the membranes used). Nanofiltration makes use primarily of porous, asymmetric membranes with ionic groups on the surface of the pores. The NF technique is employed predominantly for the softening and sterilization of waters with moderate salinity (12, 15, 42–50).

Reverse Osmosis

Reverse osmosis is a membrane process in which the solvent is separated from low-molecular-weight inorganic and organic compounds at a pressure difference of 1–10 MPa. Hence, the molecules being separated have sizes comparable to those of solvent molecules. Thus, the membranes used in RO must have considerably lower porosity (<1 nm) than the membranes used in UF or MF. Asymmetric and composite membranes are presently used in RO. They are mostly made up of cellulose acetate and other cellulose esters as well as polyamides and their copolymers with polyesters. Reverse osmosis finds use in the production of potable water from seawater and brackish water and in purification of industrial water, especially in the electronic and pharmaceutical industries as well as in the final stages of municipal and industrial wastewater treatment (51–61).

TABLE 4
Basic information on types of membrane techniques (Ref. 17)

Technique	Kind of membrane	Principle	Driving force	Mainly combined with
Filtration	Porous	Size-exclusion	Pressure difference	LC
Dialysis	Porous	Size-exclusion	Concentration gradient	LC
Electrodialysis	Porous	Size-exclusion and selective ion transport	Potential difference	CE
Membrane extraction	Nonporous	Difference in partition coefficient	Concentration gradient	LC, GC, CE

TABLE 5
Classification of filtration techniques on the basic of the size of molecules begin separated and the range of pressures applied (Refs. 16 and 21)

Filtration technique	Size of molecules being separated (nm)	Pressure gradient (MPa)
Reverse osmosis	0.1–1.0	>1
Nanofiltration	~1.0	~1
Ultrafiltration	1.0–10.3	0.2–1
Microfiltration	10.3–10.5	<0.2

Dialysis

Dialysis is the process of separation of solutes in liquid samples as a result of a concentration gradient. Separation of components is based on differences in diffusion rates of solutes in the membrane material, which in turn results from the differences in size of molecules (62–70). The material of a porous membrane is used to retain molecules of sizes exceeding the membrane coefficient (dependent on the kind of material), thus preventing them from passing across the membrane due to a steric effect. Smaller molecules freely pass across the membrane, thus leveling off the concentration difference. If osmotic pressure in donor and acceptor phases is different, solute molecules can also cross the membrane to equalize the pressure. For this reason, dialysis is especially effective in the separation of colloidal compounds from low-molecular-weight compounds in the pharmaceutical and biochemical industries, while its applications in environmental analysis have thus far been limited (18).

Electrodialysis

Electrodialysis (ED) is a membrane process in which ionic components of a solution pass across the membrane driven by an external electric field (71–80). The membranes used in this process are ion exchange membranes capable of selective transfer of ions. An electrodialyzer of conventional design is equipped with alternating cation and anion exchange membranes. Anions present in a sample are passed through the anion-permeable membrane and stopped by the cation-permeable membrane. Similarly, cations moving in the opposite direction are passed through the cation-permeable membrane and stopped by the anion-permeable membrane. As a result, the adjacent compartments have alternating high and low concentrations of an ionic solution (81). Consequently, the application of this technique enables enrichment or depletion of electrolyte solutions. Since in ED only ions are transferred directly, it is possible to remove ionic compounds from nonionic products (i.e., their purification). Electrodialysis reversal (EDR) is an automatic self-cleaning version of ED in which the polarity of the DC voltage is reversed two to four times per hour, thus reversing the direction of ion movement across the membrane. Limitations of this technique are small enrichment coefficients, possible pH changes of the feed solution during the extraction, and thermal decomposition of the membrane at a high applied potential. As a result of these drawbacks, ED is of little importance as an analytical technique (18).

Membrane Extraction

The membrane extraction process makes use mainly of nonporous membranes (13). Such a membrane can be in a liquid or a solid phase (polymer impregnated with a liquid), which is placed between two other phases, usually liquid, but sometimes also gaseous (82). On the basis of available literature, it can be concluded that the term *membrane extraction* includes the following apparatus and procedures (13, 17, 18, 82–85): supported liquid membrane extraction (SLM), microporous membrane liquid-liquid extraction (MMLLE), polymeric membrane extraction (PME), and membrane extraction with a sorbent interface (MESI). Basic information on these techniques is provided in Table 6 (18).

Supported Liquid Membrane Extraction

The first use of liquid membranes in analytical techniques dates back to the mid-1980s (84), followed by a number of subsequent applications (82, 83, 91, 105). Supported liquid

TABLE 6
Basic information on the membrance extraction techniques which find use in the analysis of liquid samples (Refs. 18 and 82)

Acronym	Name of technique	Type of membrane	Combination of phases used for donor/membrane/acceptor	Reference no.
SLM	Supported liquid membrane extraction	Nonporous	Aqueous/organic/aqueous	(82, 83, 84, 85)
MMLLE	Microporous membrane liquid-liquid extraction	Nonporous (microporous)	Aqueous/organic/organic Organic/organic/aqueous	(82, 83, 85, 86)
PME MASE	Polymeric membrane extraction, Membrane assisted sorbent extraction	Nonporous	Aqueous/polymer/aqueous Organic/polymer/aqueous Aqueous/polymer/organic	(82, 85)
MESI	Membrane extraction with a sorbent interface	Nonporous	Gaseous/polymer/gaseous Liquid/polymer/gaseous	(82, 85)

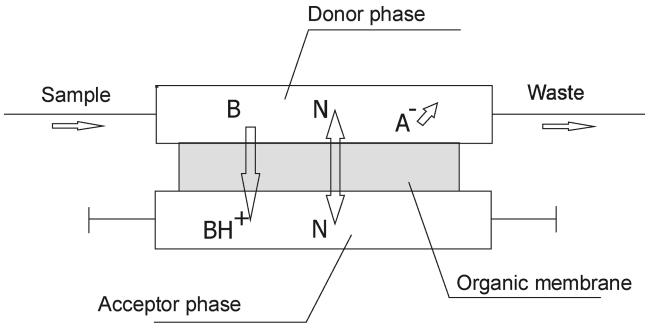

FIG. 3. Schematic representation of extraction process using the supported liquid membrane (SLM) technique (Ref. 91).

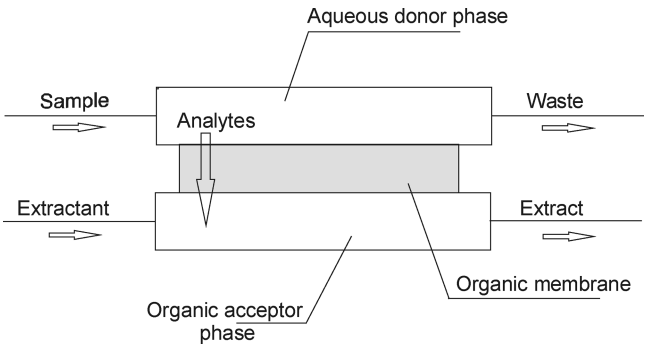

FIG. 4. Schematic diagram of the analyte extraction using the microporous membrane liquid-liquid extraction (MMLLE) technique (Ref. 82).

membrane extraction has been used mainly for the isolation of metal ions from industrial wastewater or organic acids from municipal wastewater (91).

The driving force of the SLM process is the concentration difference of the analyte between the donor and acceptor phase. In order to maintain the concentration gradient between these two phases, solutes must exist in two forms, nonionic in the donor phase **B** (to be extracted into the membrane) and ionic ($\mathbf{BH}^+$) in the acceptor phase, where they should be irreversibly trapped. This is accomplished by adjustment of the pH in both aqueous phases. Following extraction, the acceptor phase is transferred to the analytical instrument (*off-line* or *on-line*) (82, 87–109). The SLM extraction process is shown schematically in Figure 3.

In the SLM technique, an organic solvent is immobilized through capillary forces in the pores of an inert membrane (usually PTFE), which separates the two aqueous phases: donor and acceptor. Liquid membranes are typically made from solvents, such as n-undecane or kerosene, and more polar compounds, such as dihexyl ether and dioctyl phosphate (82). The composition of liquid membranes can be changed by adding modifiers, which can improve the extraction efficiency (82). Due to compatibility requirements for the acceptor phase (aqueous extract), the SLM technique is usually combined with reverse-phase liquid chromatography and ion chromatography. The form of acceptor phase limits the applications of the SLM technique to ionic compounds (e.g., medium-strong and weak acids and bases) (18, 82).

A typical flat membrane module is made up of two blocks of inert material (e.g., polytetrafluoroethylene (PTFE), polyvinyledene fluoride (PVDF), titanium) with a machined groove in each. The blocks are clamped together with an impregnated membrane between them. Thus, flowthrough channels (donor and acceptor) are formed on each side of the membrane. The volume of these channels is typically in the 10- to 1,000-μL range for the flat module, while for the membrane module with hollow fibers the channel volume is on the order of 1.3 μL (83).

Microporous Membrane Liquid-Liquid Extraction

The MMLLE technique is based on the difference in the partition coefficients (K) of the analytes between the organic and the aqueous phase, which means that the driving force in the separation is a concentration gradient across the membrane (82, 96, 108, 110–115). A schematic diagram of the analyte extraction process using the MMLLE technique is shown in Figure 4.

In MMLLE, the acceptor phase is a water-immiscible organic solvent, which also fills the pores of the hydrophobic membrane (83). The technique is used for the extraction of hydrophobic, mostly uncharged, compounds. These compounds are more easily extracted from the aqueous phase to the organic phase. They cannot, however, be back-extracted to the aqueous phase as is the case in the SLM technique. The MMLLE technique can be accomplished using the same kinds of membranes as in SLM (e.g., hydrophobic membranes made of PTFE) (83). The obtained extract is organic and its composition can be determined by using gas chromatography or normal-phase liquid chromatography. Microporous membrane liquid-liquid extraction is complementary to SLM since it allows isolation and enrichment of the compounds which cannot be extracted by SLM extraction. A comparison of fundamental parameters of the two membrane extraction techniques (SLM and MMLLE) is shown in Table 7.

Polymeric Membrane Extraction

Polymeric membrane extraction makes use of monolithic membranes, usually made of silicone rubber (82, 116). This material is characterized by high permeability toward small hydrophobic molecules. The lack of pores in silicone rubber membranes ensures a minimal contact between the two phases, thus increasing applicability of the technique, which can be used for the extraction of aqueous, gaseous, and organic samples. The membrane material assures a long life span of the membrane. The extraction using polymeric membranes is usually accomplished in one of the two modes. The first mode, similar to SLM extraction, is the aqueous phase-polymer-aqueous phase extraction with trapping of the analytes in the acceptor phase. The second mode is the aqueous phase-polymer-organic phase, similar to MMLLE (116).

TABLE 7
Camparison of fundamental parameters of the membrance extraction techniques SLM and MMLLE (Ref. 83)

	SLM	MMLLE
Analytes	Compounds in ionic form (acids and bases weak and of medium strength)	Uncharged hydrophobic compounds
Type of extract	Aqueous	Organic
Enrichment factor	Depends primarily on the degree of trapping	Depends primarily on partition coefficient
Combination with final determination techniques	Ion chromatography, reverse-phase liquid chromatography	Gas chromatography, normal-phase liquid chromatography
Possibility of automation	Apparatus used is similar; therefore, the possibility of automation of both SLM and MMLLE techniques is comparable	

Membrane Assisted Sorbent Extraction. The principle of membrane-assisted sorbent extraction involves the transfer of organic compounds across a polymeric membrane to a small volume of organic solvent (see Figure 5) (117–121). The extraction cell consists of a vial with a membrane insert attached to the metal funnel and fixed with a PTFE ring, the funnel being suspended in the opening of the vial. The vial is filled with an aqueous sample and the membrane bag with an organic solvent (e.g., cyclohexane). The solvent should dissolve the analytes well, it should be immiscible with water, and it should not pass through the membrane into the aqueous sample. The extraction takes place in the vial during stirring at an elevated temperature, resulting in the transfer of analytes into the organic solvent. A sample of organic solvent with the extracted analytes is subjected to gas chromatographic (GC) analysis. A number of modifications of the solvent and membrane material as well as the instrumentation used for the final determination are possible (117, 118, 120, 121).

Membrane Extraction with a Sorbent Interface

The membrane techniques of extraction to the gaseous phase find application to the isolation of analytes from both the liquid and the gaseous phase. The MESI technique is fully compatible with gas chromatography due to its gaseous acceptor phase (82, 122, 123, 124). The extraction is usually carried out using the membrane module made of silicone rubber, into which the analytes are collected and extracted from the surrounding gaseous or liquid sample. A stream of inert gas flowing inside the module transports the extracted analytes to a cryogenic or sorption trap. The analytes retained in the trap are subsequently released by way of thermal desorption and introduced with a stream of carrier gas onto the front of a GC column (122).

Other Membrane Extraction Techniques

The available literature provides information on a number of modifications and variations of the techniques making use of the membrane extraction process at the analyte isolation/enrichment step. One such novel approach utilizes permeation of analytes through thin membranes into the inlet of a mass spectrometer: membrane inlet mass spectrometry *MIMS*). In this case, the extracting membrane is an integral part of a sampling system introducing analytes into the ionization chamber of a mass spectrometer.

Membrane Inlet Mass Spectrometry. This technique is based on using thin membranes as mass spectrometric sampling

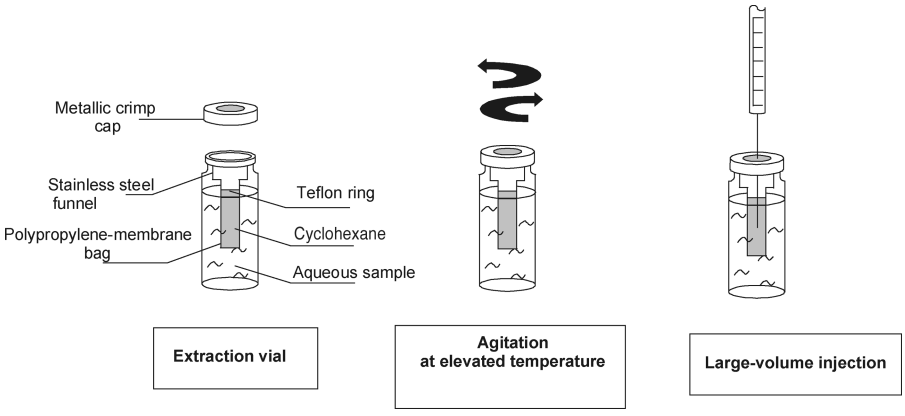

FIG. 5. Schematic representation of the analyte extraction process from aqueous samples using the membrane-assisted sorbent extraction (MASE) technique (Ref. 119).

devices. It allows a direct introduction of specific components of liquid or gaseous samples into the ionization chamber of a mass spectrometer (21, 125–137). The analytes pass across a semipermeable membrane made of silicone rubber in the pervaporation process, consisting of three steps (15, 125):

1. adsorption of analytes on the membrane surface,
2. diffusion of analytes across the membrane due to concentration gradients, and
3. evaporation of analytes in the ionization chamber of the mass spectrometer.

The transfer of individual compounds across the silicone membrane depends primarily on their solubility in the membrane matrix. Using the MIMS technique, trace amounts of volatile organic compounds can be determined directly in aqueous or air samples without interference from acids, bases, metals, ions, suspended matter, or organic matter.

The MIMS technique has a number of important advantages, including short time of analysis (1 to 6 mins), elimination of solvent from the analytical procedure, low cost, simplicity (omission of the sample preparation step), and possibility for its use in monitoring (4).

If volatile organic compounds are present in a sample, they can be identified by their characteristic mass spectrum and quantified by comparing them to Standard Reference Materials (SRMs). A disadvantage of MIMS is the possibility for overlap of spectra of various compounds, which would preclude correct identification of individual analytes.

PARAMETERS AFFECTING THE MEMBRANE EXTRACTION PROCESS

The applicability and efficiency of different membrane extraction techniques in biomedical and environmental analysis are influenced by such parameters as the enrichment factor, selectivity, and membrane memory effect (membrane stability).

Enrichment Factor

One of the most important parameters affecting the membrane extraction process is the concentration enrichment factor (E_e) defined as follows (83):

$$E_e = C_A/C_S \quad [1]$$

where C_A and C_S are the concentrations in the acceptor phase (i.e., the extract) and in the extracted sample, respectively.

The concentration enrichment factor (E_e) is especially influenced by the partition coefficient (K). For small values of the partition coefficient (K), the enrichment factor (E_e) also will be small, resulting from an insufficient extraction and diminished diffusion of the analyte across the membrane. For intermediate K values the transfer of analyte is limited by the transport properties in the flowing donor phase, and in this region the largest enrichment factors (E_e) can be obtained. For very large K values, the enrichment factor (E_e) decreases as a result of the limited transfer of the analyte across the membrane to the acceptor phase (the membrane memory effect) (18).

In MMLLE and PME (i.e., aqueous-organic type of extraction), the maximum value of E_e is equal to the distribution coefficient K between the donor and the acceptor phases. Consequently in those techniques, large distribution coefficients are needed to obtain appreciable enrichment factors. On the other hand in SLM, the concentration enrichment factors are not limited by only the partition coefficient. Instead, the trapping conditions in the acceptor phase are crucial (138). In the case of SLM extraction of a basic compound, the maximum enrichment factor on the acceptor pH and the dissociation constant of the analyte is as follows:

$$\log E_{e(max)} = pK_a - pH_A \quad [2]$$

The enrichment factor obtained can also be described for all membrane extraction techniques by Equation 3, which relates the enrichment factor (E_e) to the extraction efficiency (E) (83):

$$E_e = E \cdot V_S/V_A \quad [3]$$

where V_S is the volume of the extracted sample and V_A is the volume of the extract (in SLM, the volume of the acceptor channel).

It follows from Equation 3 that even if the extraction efficiency E approaches 1, the enrichment factor can never become larger than the volume ratio (V_S/V_A). In SLM, high extraction efficiencies can be obtained by keeping the extract volume small because of trapping. For nontrapping techniques such as MMLLE, it is very difficult to achieve a large extraction efficiency E with a stagnant acceptor phase (unless the partition coefficient is very large) so the acceptor phase must be pumped, leading to larger V_A and consequently a smaller E_e. The relationship between the donor phase flow rate, the extraction efficiency, and the enrichment factor is shown (for SLM) in Figure 6 (83). The extraction efficiency E can be seen to approach unity as the flow rate of the donor phase approaches zero, so that the most efficient extractions are obtained at low donor phase flow rates. However, in analytical practice, it is more relevant to

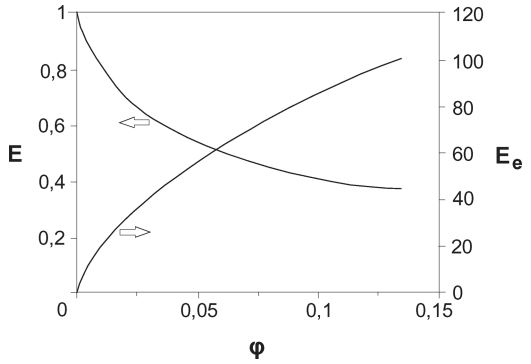

FIG. 6. The relationship between extraction efficiency (E) and enrichment factor (E_e) as functions of the donor phase flow rate (φ) (Ref. 83).

maximize the enrichment factor after a given time than to maximize the extraction efficiency. This leads to larger peak areas (or other instrumental signals) in a subsequent analysis and thus to more time-efficient analysis. An increase in the donor phase flow rate results in an increased sample consumption. Therefore, if the available sample volume is limited, a possibly low flow rate of the donor phase should be used to maximize the extraction efficiency (82).

Selectivity of Membrane Extraction

The term *selectivity* can be interpreted in two ways: first, as the ability to distinguish among molecules according to their size and, secondly, as the differentiation of compounds of the same molecular mass. The selectivity of membranes used in the membrane extraction techniques depends primarily on the membrane material (physical state, morphology, structure, and polarity), on the properties of the donor and acceptor phases (pH value, polarity), and on the properties and concentration of analytes. By selecting proper values of the above parameters, the selectivity of a given membrane module can be adjusted.

Membrane Memory Effect

The membrane memory effect (membrane blocking) takes place during an incomplete transfer of the analytes from the membrane (membrane surface and support surface) to the acceptor phase. This phenomenon limits the analyte transfer and can considerably reduce the fluxes. The memory effect is caused by the deposition of high-molecular-weight compounds on the surface or in the pores of a membrane (15). It also is related to the kind of membrane used (liquid, solid), its structure, and the flow rate of the acceptor and donor phases. In SLM the membrane memory effect is mainly associated with the structure and composition of a liquid membrane, while in MMLLE it results from the flow rates of the donor and acceptor phases. In practice, the effect is studied by the analysis of successive samples of the acceptor phase (139).

COUPLING MEMBRANE EXTRACTION TECHNIQUES TO THE METHODS OF FINAL DETERMINATION OF ANALYTES

The available literature provides information on various methods of coupling membrane extraction techniques to the methods of final determination. They can be classified with respect to the final determination method used (liquid chromatography, gas chromatography, capillary electrophoresis) or the method of interfacing extraction with the final determination technique (*off-line* or *on-line*).

Coupling Membrane Extraction to Liquid Chromatography

The membrane extraction techniques can be successfully coupled with high-performance liquid chromatography (HPLC) both *on-line* and *off-line*. An example of *on-line* interfacing of membrane extraction with HPLC is shown schematically in Figure 7 (19).

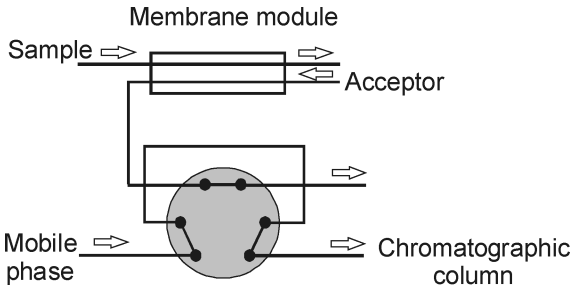

FIG. 7. Schematic diagram of the membrane extraction module connected on-line to a liquid chromatograph (Ref. 19).

During the transfer of analyte molecules across the membrane material, the acceptor phase remains stagnant. After the extraction, the acceptor phase is pumped into the sample loop of the injection valve of a liquid chromatograph (19). The membrane unit is typically a planar membrane, but it also is possible to use hollow-fiber membranes. Supported liquid membrane extraction has been mainly used in *on-line* combination with HPLC. A schematic diagram of such an interface is depicted in Figure 8 (92). Typically in this design, the sequence for the valve and pumps can be arranged so that one sample is extracted during the time period when the previous sample is chromatographed, thus increasing the sample throughput. In *off-line* interfacing of membrane extraction with liquid chromatography, solid polymeric membranes (79) and supported liquid membranes (97) are used.

Interfacing Membrane Extraction with Gas Chromatography

The membrane extraction techniques can be coupled to GC both *on-line* and *off-line*. The MMLLE technique has been used in *on-line* combinations with GC. This is due to a relatively hydrophobic nature of the analytes and the organic acceptor phase which is compatible with GC. The organic acceptor phase can be introduced directly into the GC column using large volume injection (86) or by means of the so-called extraction syringe (Personal Chemistry Co., Uppsala, Sweden) (140). In the latter case, the MMLLE extraction process is carried out automatically on a microscale (the extract volume is in the order of a few microliters) in the membrane module placed inside a syringe. The sample to be extracted (donor phase) is pumped around the fiber containing the organic acceptor phase in the lumen of the fiber and the analytes are partitioned into the organic solvent. The extracting syringe is placed directly on top of a gas chromatograph for automated injection of the extract onto the GC column by means of a pneumatic piston. A diagram of the extraction syringe is shown in Figure 9 (20, 140).

In the case of *off-line* systems, a common combination of membrane extraction with GC involves membrane-assisted

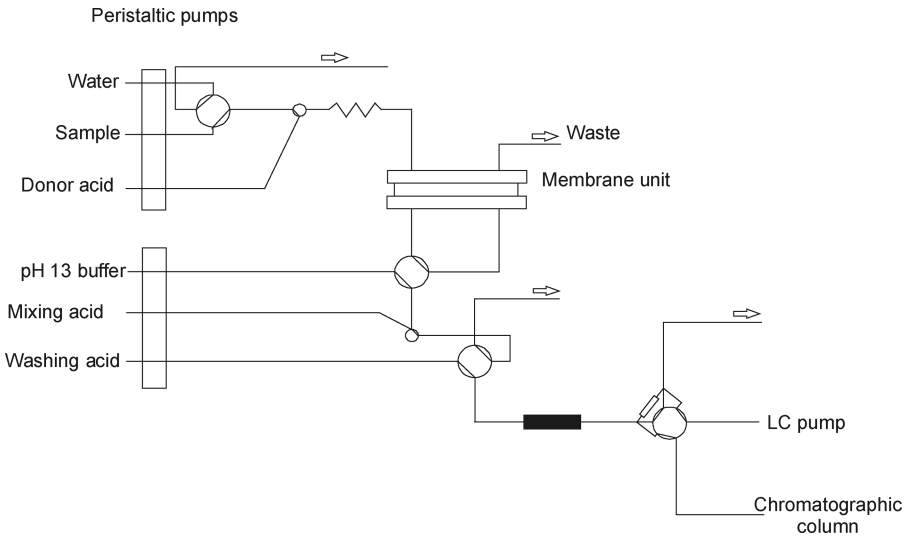

FIG. 8. Schematic diagram of the apparatus for the supported liquid membrane extraction connected on-line to a liquid chromatograph (Ref. 92).

solvent extraction (117–121). The *in-line* combination of MESI with GC has also been described in the literature. A typical set-up is shown in Figure 10. Such an apparatus has found use for the monitoring of volatile and semivolatile organic compounds in environmental liquid and gaseous samples (122).

Coupling Membrane Extraction to Capillary Electrophoresis

Capillary electrophoresis (CE) is a relatively new analytical technique and it has been used, among other applications, for the determination of pharmaceuticals in biological materials (103, 141, 142). In practice, the most common combination used is an *off-line* interface of SLM with CE (88, 126). Only a few examples of direct connection of membrane extraction *on-line* with CE have been reported (141).

The membrane extraction-CE interfacing (see Table 5) is not as popular as the combination of membrane extraction with GC or liquid chromatography because in CE the sample volume has to be very small, typically in the nanoliter region. This can be partly overcome by means of various so-called stacking procedures, by which several microliters are introduced and the analytes are accumulated in the front of the separation capillary. Another problem is the high voltage applied to the electrodes, which can pose a hazard during the analysis [85].

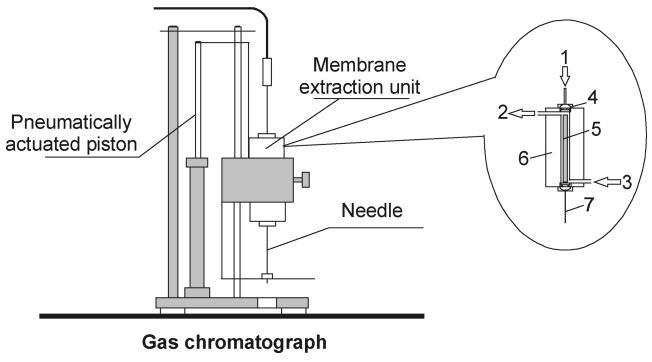

FIG. 9. Schematic diagram of the extraction syringe (ESy technique): 1, solvent (acceptor phase) inlet; 2, sample outlet; 3, donor phase inlet; 4, nut; 5, hollow fiber; 6, thermostat (Kel-F block); 7, needle.

APPLICABILITY OF MEMBRANE EXTRACTION TECHNIQUES

Applications of membrane extraction techniques to the determination of a wide variety of analytes in samples of biological fluids and liquid environmental samples can be found in the literature.

Biomedical Analysis—Determination of Organic Compounds in Biological Material

Membrane extraction techniques combined with various methods of final determination have been applied to the determination of various compounds, mainly drugs, in biological fluids, such as blood, plasma, and urine. In these cases, the most important factors are selectivity and the possibility of automation. Since the sample volumes of biological material are usually small, obtaining high enrichment factors during analysis becomes essential (94). Selected applications of membrane extraction techniques to the determination of organic compounds in complex biological matrices are compiled in Table 8.

Environmental Analysis—Determination of Organic Compounds in Liquid Environmental Samples

Reliable determination of pollutants and natural compounds in liquid environmental samples is based on two important requirements. First, the enrichment factor for the trace components has to be large and, second, the selectivity of the procedure also

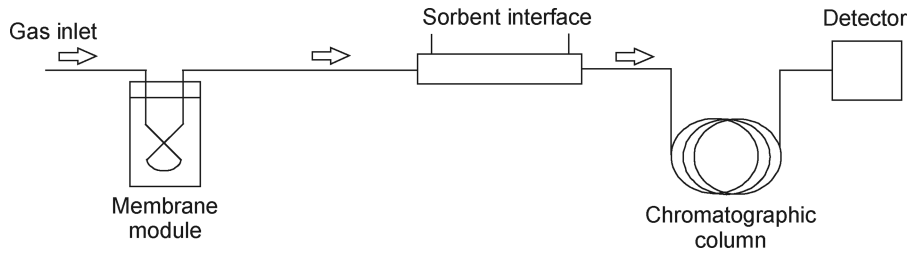

FIG. 10. Schematic diagram of the apparatus for the membrane extraction with a sorbent interface (MESI) technique connected in-line with a gas chromatograph.

has to be high to preclude interference by some natural compounds such as humic acids (91). The use of membrane extraction techniques in the analysis of liquid environmental samples is listed in Table 9.

ADVANTAGES AND DRAWBACKS OF MEMBRANE EXTRACTION TECHNIQUES

Membrane extraction techniques have numerous advantages. Among them is the substantial reduction or complete elimination of organic solvents. In MESI and PME with the aqueous acceptor phase organic solvents are not used at all, whereas SLM makes use of a small volume of high-boiling organic liquid. In MMLLE and PME with the organic acceptor phase, very small volumes of a conventional organic solvent (not exceeding 1 mL) are sufficient.

The most serious drawbacks of membrane extraction techniques result from the sensitivity of the membrane to solid contaminants, which extend analysis time by clogging the membranes. This disadvantage can be avoided by using an automated extraction apparatus with the membrane regeneration device. The analysis time can also be shortened by interfacing the membrane extraction modules with the instrumentation for final determination. In this case the operations of the sample preparation system and the analytical instrument can be synchronized, so one

TABLE 8
Applications of membrane extraction techniques in the procedures for determination of organic compounds in biological samples

Type of biological matrix	Type of membrane extraction	Analyte	Final determination technique	Reference no.
Urine	SLM	Antidepressants (opipramol, amitriptylin, noxiptylin, diethazin)	HPLC/UV[a]	(143)
		Diprivan (propofol)	HPLC with electrochemical detection	(144)
		Ropivacaine metabolites	HPLC	(145)
Urine, blood	LLLME[b] (LPME3)	Amphetamine (methamphetamine)	CE	(146)
	LLME[c]	Diazepam and its metabolites		(147)
Blood	SLM	Phenols	LC/UV (HPLC + biosensor)	(148)
		Dibenzepin, reboxetin, fluvoxamin Amperozide	HPLC/UV	(88, 96)
		Bambuterol	CE	(103, 105)
	MMLLE	Organophosphorus esters	GC/MS	(149)
	MMLLE	Anesthetics (prilocaine, lidocaine, mesocaine, mepivacaine, ropivacaine, bupivacaine, pentycaine)	GC/NPD[d]	(86)
Milk	SLM	Macrolide antibiotics	HPLC/DAD[e]/MS	(99)

[a]UV absorption detector.
[b]Liquid-liquid-liquid membrane extraction.
[c]Liquid-liquid membrane extraction.
[d]Nitrogen-phosphorus detector.
[e]Diode-array detector.

TABLE 9
Application of membrane extraction techniques in liquid environmental samples

Sample type	Type of membrane extraction	Analyte	Final determination technique	Reference no.
Aqueous samples	SLM	Sulfonylurea herbicides	HPLC/DAD	(150)
			HPLC/UV	(151)
		Triazine herbicides	HPLC/UV	(97, 152)
			HPLC	(98)
		Herbicides	CE/UV	(90)
		Cephalosporin antibiotics	HPLC/UV	(154, 155)
		Aniline and its derivatives	HPLC /UV/DAD	(100)
		Chlorophenols	HPLC/DAD	(93)
		Pesticides	LC, electrochemical detection	(92)
		Aromatic aminophosphates	UV-VIS[a]	(106)
		Amino acids	CE/UV	(153, 156)
		Organotin compounds	GC/FID[b]	(157)
	SLM MMLLE	Fungicides and their polar metabolites	HPLC/UV	(107, 108)
	MMLLE	Vinclozolin	HPLC/UV	(158)
		Cationic surfactants	HPLC/UV	(114)
		Alkylphenols: 4-nonylphenol, 4-tert-octylphenol	HPLC/FLD[c]	(112)
		Pesticides, PAHs	GC/FID	(113)
		Organotin compounds	GC/MS	(110)
	LLMME	Aromatic amines	HPLC/UV	(159)
	PME	Phenol, aniline, nitrobenzene	HPLC/UV	(160)
	PME—MASE	Triazines, other SVOC (2,4-dichloroaniline, simazine, prometon, atrazine, phenanthrene, ametryn, prometryn, tert-butylene)	LVI[d]/GC/MS	(117)
		Polychlorinated biphenyls (PCBs)		(119)
		Organochlorine compounds	LVI/GC/ECD[e]	(118)
	MIMS	Methanol	MS	(126)
		Methylpyrrolidine, tetramethylethylenediamine, 3-bromopyridine, 2-chloro-5-trifluoromethylaniline		(127)
		Phenol, 4-chlorophenol, 2,4-dichlorophenol, 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol, pentachlorophenol, phenanthrene, phenoxyacetic acid		(122)
		Chloromethane, chloroethane, benzene, toluene, bromomethane, chloroform,		(129)
		Benzene, toluene, acetone, methanol, ethanol		(136)
		MTBE, benzene, toluene		(131)
		Benzene, toluene, tetrahydrofuran, phenol, 1-butanol, 1-octanol, chlorobenzene, chloroform, 1,2-chloropropane		(135)
		Toluene, trans-1,2-dichloroethene		(137)
		Terpenes		(134)

[a] UV-Vis absorption detector.
[b] Flame ionization detector.
[c] Fluorimetric detector.
[e] Large-volume injection technique.
[e] Electron capture detector.

TABLE 10
Advantages and disadvantages of membrane techniques used in environmental analysis (Refs. 17 and 82)

Advantages	Disadvantages
Possibility of analysis of samples with very complex matrices	Time-consuming
High selectivity	Low efficiency
Possibility of use for both matrix removal and enrichment of microtrace components	Sensitivity to solid contaminants, which easily clog membrane pores, thus resulting in longer analysis time (problem of membrane stability)
Reduction of use or complete elimination of organic solvents	
Simplicity of the apparatus	
Ease of automation	

sample is extracted during the chromatographic run of the previous sample (82). The fundamental advantages and drawbacks of membrane techniques are compiled in Table 10.

SUMMARY

The need for the determination of organic compounds in liquid samples, characterized by complex and variable matrix composition, requires a continuing search for new analytical procedures. The significance of sample preparation methods based on membrane extraction techniques is expected to increase in the near future. One of the obvious advantages is the large reduction of solvent use compared with alternative extraction techniques. Other advantages include large enrichment factors and high selectivity (161). Due to possibilities for full automation and interfacing with chromatographic and electrophoretic methods, membrane extraction techniques have found wide applicability in biomedical and environmental analysis.

NOMENCLATURE

CE	Capillary electrophoresis
CLSA	Closed loop stripping analysis
DAD	Diode array detector
DHS	Dynamic headspace
ECD	Electron capture detector
ED	Electrodialysis
EDR	Electrodialysis reversal
FID	Flame ionization detector
FLD	Fluorescence detection
GC	Gas chromatography
HPLC	High performance liquid chromatography
LLE	Liquid-liquid extraction
LLLME	Liquid-phase microextraction, three-phase system
LLME	Liquid-phase microextraction, two-phase system
LVI	Large volume injection
MASE	Membrane assisted sorbent extraction
MESI	Membrane extraction with sorbent interface
MF	Microfiltration
MIMS	Membrane inlet mass spectrometry
MMLLE	Microporous membrane liquid-liquid extraction
MS	Mass spectrometry
NPD	Nitrogen/phosphorus detector
RO	Reverse osmosis
PME	Polymeric membrane extraction
PT	Purge and trap
PTFE	Polytetrafluoroethylene
PVDF	Polyvinylidene fluoride
SHS	Static headspace
SFE	Supercritical fluid extraction
SLM	Supported liquid membrane
SPE	Solid-phase extraction
SPME	Solid-phase microextraction
TLHS	Thin-layer headspace
UF	Ultrafiltration
UV	Ultraviolet detector
UV-Vis	Ultraviolet-visible detector

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