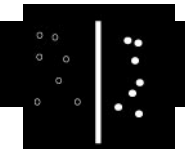
MEMBRANE PREPARATION



Hollow-Fibre Membranes

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Introduction

Hollow-fibre membranes are an attractive alternative to conventional flat membranes in a growing number of important applications. Arguably, they have proliferated most in the biomedical and biochemical fields, thanks to their simple geometry and small dimensions in combination with their inherently high surface-to-volume ratio. Dialysis is the technique in which hollow-fibre membranes are most commonly employed.

There exist a number of extensive reviews on the technology, application and fabrication of membranes. A true classic is the book by Mulder, which contains a detailed overview of developments in the preparation of membranes and their use in purification. McKinney has provided a useful review of the preparation of organic hollow-fibre membranes. Tsapatsis has reviewed the preparation of inorganic membranes.

We have a particular interest in hollow fibres for polymer separations, with hollow-fibre flow field–flow fractionation (HF_5) as the analytical principle. Inorganic fibres are of great interest for polymers that require (strong) organic solvents. This article is biased due to this specific interest, our limited personal experience with different types of fibres and their preparation, and by our background as analytical chemists. The latter also provides us with an original perspective. To us there is an obvious analogy between the preparation of hollow-fibre membranes and open-tubular columns for chromatography. Both areas may benefit from such a comparison, presented in **Table 1**.

Types of Membranes

Basically, three types of membranes are distinguished:

- porous membranes;
- nonporous membranes; and
- liquid membranes.

All three types can be used in the hollow-fibre geometry. Porous membranes allow the passage of relatively large molecules. Depending on the size of the pores, one speaks of microfiltration (pore size > 100 nm), ultrafiltration (pore size < 100 nm), or nanofiltration (molecular weight cut-off $>$ ca. 1000 Da). Nonporous membranes are permeable to very small molecules (gases). Liquid membranes are of interest because of the selectivity and flexibility they provide. A broad review of liquid membranes has been provided by Sastre and co-workers.

Hollow-fibre membranes are often the preferred geometry, offering distinct advantages over flat or tubular (diameter larger than 1 mm) membranes, for a number of reasons:

- high surface-to-volume ratio;
- conceptual simplicity;
- easy incorporation in flow streams;
- broad availability.

In preparing hollow-fibre membranes, we must try and capitalize on these advantages. For example, if the surface-to-volume ratio is a key parameter, then narrow-bore fibres are most interesting.

Membranes are used in many different ways in analytical chemistry. Most of their applications are in the areas of sampling and sample preparation, thanks to the fundamental ability of semipermeable

Table 1 Analogy between the properties of membranes and chromatographic columns

Type of membrane selectivity	*Chromatographic equivalent(s)*
Preferential interaction and adsorption from a gas, liquid or supercritical fluid	Gas chromatography with solid or polymeric stationary phases (GC) Normal-phase and reversed-phase liquid chromatography (LC) Supercritical-fluid chromatography (SFC)
Size selectivity (sieving effect)	Molar sieve columns (GC) Size exclusion chromatography (LC)
Charge selectivity	Ion exchange chromatography Ion exclusion chromatography
Affinity membranes	Affinity chromatography

membranes to differentiate between different materials (viz. matrix and analytes). This selectivity of the membrane can be based on molecular size, affinity, charge, or a combination of these properties. There are only a limited number of situations in which the actual analysis relies on the application of hollow-fibre membrane interfaces. These include the following:

- *Affinity chromatography*. Porous membranes combine a large surface area with a high permeability. By bonding specific groups to the surface, targeted species can be bound very strongly to the membrane. After the entire sample has been passed through the membrane, the analyte(s) can be removed. Affinity chromatography is of particular interest in the biochemical and biomedical areas. Since the membranes have a high permeability, the danger of degradation of vulnerable proteins is reduced. Moreover, the high fluxes possible allow more mass to be purified within the same period of time. Two extensive reviews (Roper and Josic) have been dedicated to this important field.
- *Extractions*. The intrinsic ability of hollow-fibre membranes to separate two distinct phases has found multiple applications in the field of extractions. Recently, Gabelman and Hwang published an extensive review on the subject of membrane contactors, i.e. membranes used to separate two immiscible phases.
- *Chiral separations*. The field of preparative chiral separations using hollow-fibre membranes is too interesting to remain unmentioned. In particular, in the pharmaceutical industry there is a great demand for the separation of racemic mixtures on a preparative scale. For example, a hollow-fibre supported liquid membrane can be used to separate two phases, with a chiral selector present in one of these. Alternatively, a chiral selector can be chemically bonded to the membrane surface, prepared in a manner similar to the membrane used for affinity chromatography.
- *Hollow-fibre flow field–flow fractionation* (HF_5). A technique in which the simplicity of hollow-fibre membranes is very advantageous is flow field–flow fractionation (flow FFF). The concept of flow FFF was brilliantly conceived by Giddings. In flow FFF, macromolecules or particles are injected into a channel with a porous wall and displaced by a flow perpendicular to its direction of movement. Based on the difference in average velocity lines that are occupied by particles with different diffusion characteristics (related to particle size or molecular mass), a fractionation is obtained. Ideally (i.e. for spherical particles), the retention time is directly related to the diffusion coefficient of the analyte.

  HF_5 was introduced by Carlshaf and Jönsson in 1988 as an instrumentally simple and cost-effective alternative to flow FFF channels with a flat configuration. However, during the 1990s only a limited number of papers have been dedicated to this promising technique. Flow FFF poses very high demands on the quality of the hollow-fibre membrane and, especially, on the fibre-to-fibre repeatability. This is definitely the most important reason for slow progress on the subject. Recently, Lee *et al.* showed an impressive fractionation of latex particles (**Figure 1**). For this type of fractionation their HF_5 system performed at least as good as alternative techniques, such as the more-established flat-channel flow FFF.
- *Isoelectric focusing*. In 1998, Korlach published an original article on pH-regulated electro-retention chromatography (ERC). This technique is quite similar to (electrical) FFF. A voltage is applied

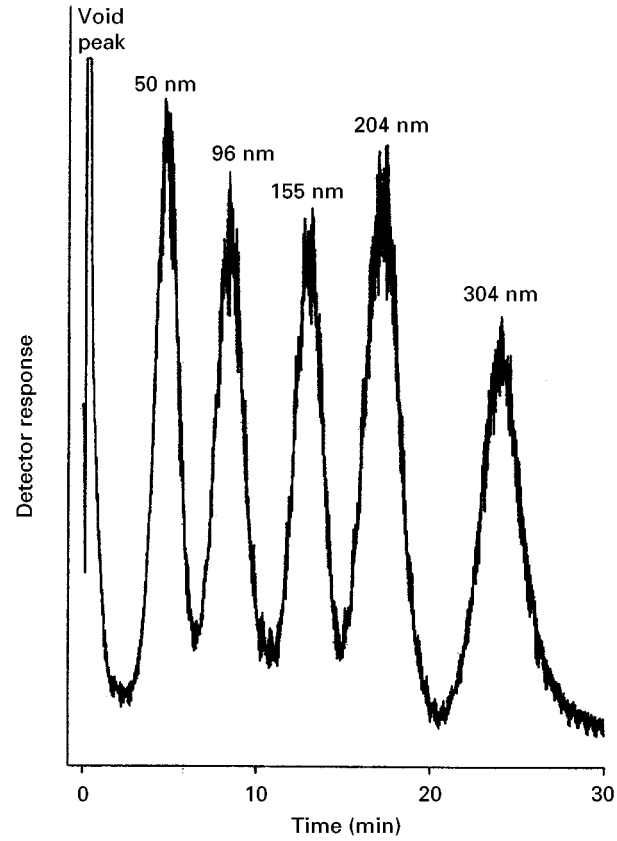

Figure 1 Hollow-fibre flow FFF fractogram showing the separation of polystyrene latex beads. (Reprinted with permission from Lee WJ, Min BR and Moon MH (1999) Improvement in particle separation by hollow fiber flow field-flow fractionation and the potential use in obtaining particle size distribution. *Analytical Chemistry* 81: 3446–3452.)

across the diameter of a hollow-fibre membrane. Subsequently, a pH gradient is applied in a fluid reservoir which surrounds the fibre. The gradient gradually diffuses into the hollow-fibre membrane. At some point (when the pH crosses the isoelectric point or p*I* value), the charge on the analyte reverses and the ions will start to migrate to the middle of the fibre, from where they will be rapidly eluted owing to the higher axial flow velocity. The bottleneck in the development of this technique, which is mainly applied to the separation of proteins, is adsorption of the analytes on the membrane.

Semipermeable membranes allow us to manipulate processes that take place at the interface between two (miscible or nonmiscible) phases. They can be used in the gas phase for sampling purposes (e.g. membrane-assisted headspace injection in GC, membrane inlet mass spectrometry, MIMS) or in the liquid phase for sample preparation (e.g. dialysis) or sample concentration. Membranes used for gas sampling usually consist of simple fibres made of polymeric materials, such as polysiloxanes. More sophisticated separations, such as affinity chromatography, require more sophisticated membranes with dedicated selectivities. Also when in contact with liquid phases, most of the fibres used in analytical chemistry are based on organic (polymeric) materials.

The most important characteristic of a membrane is its separation selectivity. Differences in permeability for different materials can be based on a sieving effect (size selectivity) or on the chemical structure of the membrane. Hydrophobic membranes are more permeable to (nonpolar) organic molecules, while hydrophilic membranes are more permeable to water. Membranes will also show adsorption effects. Certain materials (analytes or matrix components) may be preferentially contained in and on the membrane. In some cases this is a desired effect (affinity membranes are the obvious example). Where fibres are used for sampling or sample clean-up in analytical chemistry, adsorption effects are often undesirable.

Preparation of Hollow-Fibre Membranes

The art of hollow-fibre-membrane preparation has taken a high flight in recent years. Nowadays, hollow-fibre membranes are attainable in a fantastic variety of membrane and support materials, pore sizes, diameters, thicknesses, etc. An overview of the techniques involved in the preparation of hollow-fibre membranes is given below.

The various processes for preparing fibres tend to be rather complex, and certainly are laborious and time-consuming. The most difficult step is the optimization of the process, viz. ensuring repeatable (in-house) and ultimately reproducible (transferable) results. Hence, for small-scale applications of hollow-fibre membranes, including all practical applications within analytical chemistry, the most sensible approach to the technology is to obtain suitable fibres from a commercial source.

Preparing Fibres

Most commonly, polymer tubing is prepared by a process referred to as spinning. This can be seen as an extrusion process. A viscous polymer solution (or melted polymer) is pressed through a small hole, while a fluid (bore liquid) is pumped through the centre. This construction is known as a spinneret. It allows precise control of the fibre dimension, thickness, etc. On exiting the spinneret, the fibre is drawn through a coagulation bath, after which additional treatment steps may take place.

The coagulation bath may merely be used to solidify the polymer and stabilize the fibre, but it may also be used to deposit a membrane (see next section). Many different polymers can be processed this way and the porosity of the resulting microfiltration membrane is affected by a large number of parameters. A summary is provided in **Table 2**. In the case of porous fibres, the type of material used is usually of little relevance to the properties of the membrane. The latter are almost totally determined by the parameters of the pores (size distribution, shape) and the membrane thickness. The material is selected based on other criteria, such as compatibility with the materials (fluids) encountered in the application, mechanical strength and cost. A typical example of a hollow-fibre membrane is shown in **Figure 2**.

Membrane Films

Polymeric membrane films are usually formed by transferring a polymer from the liquid phase (solution, melt or suspension) to the solid phase. Such a process is known as *phase inversion*. Alternatively, membranes can be formed by *in situ* polymerization. Several processes will be considered below in some detail.

Liquid membranes from a special class of membrane films. They are prepared simply by immersing a microporous hollow fibre in a liquid. The liquid membrane, supported by the hollow fibre, separates two phases; by adding a selective carrier to the membrane (carrier-mediated transport), an increased selectivity can be obtained.

Table 2 Summary of variables affecting fibre properties

Variable	*Values*	*Effects*
Consumption of casting solution	Suspension of polymer in non-solvent ('dry spinning') Melted polymer ('melt spinning') Polymer solution ('wet spinning')	Great effect on fibre porosity (and other properties)
Spinning parameters	Extrusion rate (mass flux of solution) Tearing rate (speed of drawing the fibre) Bore fluid rate Distance between spinneret and coagulation solution Composition of coagulation bath Temperature at the various stages	Determines fibre dimensions (internal and external diameters) Significant effect on fibre porosity
Fibre treatments	Washing Chemical modifications	Removes contamination Determines selectivity

Film deposition techniques In order to create a film of a polymeric material on the inside of the fibre, the complete fibre can be filled with a solution of a polymer. Upon evaporation of the solvent, a film will be formed (*static coating*). The critical step is the evaporation of the solvent. This must take place slowly and regularly, in order to obtain a membrane with constant properties throughout the fibre. After a film has been deposited, it may be stabilized by heat treatment or by *in situ* cross-linking.

Instead of an evaporation step, a solvent displacement step may be introduced. In this case, a nonviscous liquid is pumped through the column containing the (viscous) film of polymer solution. The newly introduced liquid may either be a solvent or a non-solvent for the polymer, but it must dissolve the initial solvent. The solvent is then either extracted from the film, or replaced by a non-solvent. In either case, phase inversion will occur and a solid polymeric layer is obtained.

A second method for depositing a film is to press a plug of a polymer solution or a liquid polymer through the fibre. Behind this plug, a polymeric film will be left on the wall (*dynamic coating*).

Important parameters determining the properties of the membrane include the solution thermodynamics of the specific polymer–solvent combination, the concentration of the polymer in the solution, the temperatures at various stages of the process, the rate of solvent evaporation (or the rate of replacement of the solvent by a non-solvent) and the presence of additives in the solution.

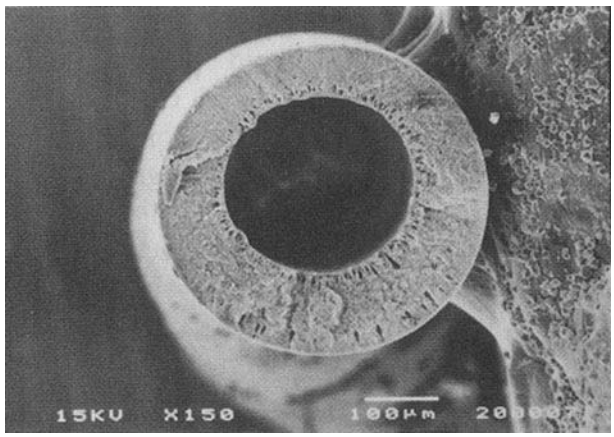

Figure 2 Typical scanning electron micrograph of an asymmetrical composite hollow-fibre membrane. (Reprinted with permission from Chung TS, Teoh SK and Hu X (1999) Formation of ultra-thin high-performance polyethersulfone hollow-fiber membranes. *Journal of Membrane Science* 133: 161–175.)

***In situ* polymerization** Using the processes of static or dynamic coating described above, it is also possible to deposit a film of a solution containing monomers or polymer precursors (pre-polymers). This has the considerable advantage of a low solution viscosity, allowing the formation of relatively thick films without the need to apply high pressures. The residual solvent needs to be evaporated slowly and carefully after the polymerization to avoid cracks in the film or radial differences in film thickness.

Sol–gel deposition A promising class of membranes is that of the inorganic membranes, which are resistant to a wide variety of solvents, including potent organic solvents such as tetrahydrofuran or hexafluoro-isopropanol. The most common technique of preparation is sol–gel deposition on a ceramic support. This procedure was developed in the early 1980s by Burggraaf's group. A sol of nanometre-sized γ-alumina particles is deposited on the wall of the fibre from an aqueous solution containing a small percentage of polyvinyl alcohol. The deposited sol

can be converted to a defect-free membrane by sintering.

Okubo pointed out in 1991 that for the preparation of membranes inside a narrow-bore ceramic hollow fibre (1.4 mm inner and 2.0 mm outer diameter) dynamic coating procedures (see Film Deposition Techniques, above) are required. By forcing the sol through the hollow fibre, a stable and thick defect-free layer can be obtained. Reducing the diameter of hollow-fibre membranes is important, as it results in an increase of the surface-to-volume ratio, so that very small volumes can be separated or purified. Many applications in medicine, biology and analytical chemistry stand to benefit.

Chemical Modification of Membranes

Polymers or reactive groups can be chemically bonded to suitable groups on the solid surface inside membrane pores. A large number of surface modification reagents are readily available and specific functional groups, to create the desired membrane selectivity, can be readily attached to such molecules. The process of chemically modifying membrane surfaces may also involve several reaction steps, which, however, may result in a less well-defined product.

Polymers can be attached to the surface ('grafted') through reactive functional groups, or through a pre-deposition radiation treatment. This process allows the creation of a great variety of selective membranes, which can be tailored for specific separations. These tailor-made phases allow affinity-type separations to be performed, in which extremely selective interactions are realized between the membrane surface and a selected analyte. Such interactions can be very strong, but desorption is possible by an appropriate change of conditions (displacing solvent or buffer).

Polymeric films can also be modified by introducing ionic groups, which drastically alters the properties of the membrane. Highly inert, nonpolar polymeric membranes, such as polyethylene or polytetrafluoroethylene (Teflon®), can be modified to yield highly polar, ionic interfaces.

Hollow Fibres in Analytical Chemistry

As stated earlier, in most applications of hollow-fibre membranes in analytical science commercially available fibres are used. In only a limited number of cases (i.e. liquid membranes and affinity membranes) have analytical scientists reverted to in-house preparation. A nonexhaustive list of major suppliers of hollow-fibre membranes is provided in **Table 3**. Also, two suppliers of ceramic tubular membranes are listed in this table. Ceramic tubular membranes are not yet commercially available in diameters small enough ($d < 1$ mm) to be called fibres.

In **Table 4** we present a selection of recently developed applications of hollow-fibre membranes in analytical chemistry, with emphasis on the types of fibres used and their preparation or commercial availability. Here, we concentrate on the use of hollow-fibre membranes directly coupled with analytical techniques. The case in which the membrane solely determines the separation process has been covered above. Omitted from this table are instruments featuring on-line couplings of either dialysis of filtration units to standard high performance liquid chromatography (HPLC) instruments. These techniques are already well established and commercially available. A very useful review on the state of the art in the on-line coupling of dialysis to HPLC and capillary electrophoresis (CE) has been provided by van de Merbel.

In ion chromatography, hollow-fibre membranes can be used either before the analytical separation column (pre-column) for sample preparation, or post-column to suppress the conductivity of the effluent (mobile phase) prior to conductivity detection. In an interesting article, Kaufmann described the insertion of a hollow-fibre membrane between an HPLC

Table 3 Some major suppliers of hollow-fibre membranes

Producer	*Location*	*Web address (April 2000)*
Dow-Corning	Midland, MI, USA	www.dowcorning.com
Hoechst Celgard	Wiesbaden, Germany	www.celgard.de
Minn Tech	Minneapolis, MN, USA	www.minntech.com
Millipore	Bedford, MA, USA	www.millipore.com
Sepracor	Marlborough, MA, USA	www.sepracor.com
A/G Technology	Needham, MA, USA	www.agtech.com
Tech-Sep[a]	Lyon, France	–
US Filter/Schumacher[a]	Asheville, NC, USA	schumacher-usa.com

[a]Supplier of (tubular) ceramic membranes.

Table 4 A selection of applications of hollow-fibre membranes in analytical chemistry, connecting specific applications (techniques and analytes) with types and sources of membranes, and useful reviews*

	Method	*Compound*	*Author*	*Membrane type*	*Manufacturer*
Gas phase extractions	GC (MESI)	Volatile organic	Mitra (1996)	Silicon	Dow-Corning
		carbohydrates	Yang (1994)	Silicon	Dow-Corning
	MIMS	Volatile organic	Ketola (1998)	Silicon	Dow-Corning
		carbohydrates	Cisper (1995)	Silicon	Dow-Corning
			Srnivisan (1997)*		
			Degn (1992)*		
Liquid phase pre-column	μ-LC	Bambuterol	Thordarsson (1996)	Polypropylene, 0.03 μm	Hoechst, Celanese
	CE	Bambuterol	Palmarsdottir (1997)	Polypropylene, 0.2 μm	AKZO Nobel
	CE	Organochlorides	Bao (1998)	Celgard X-10	AKZO Nobel
	CE	Proteins	Zhang (1997)	Cupruphan, 10 kDa	Hoechst Celanese
	CE	Methamphetamine	Pedersen (1999)	Polypropene, 0.2 μm	AKZO Nobel
	clEF		Wu (1999)*		
Post-column	Reaction	Barbiturates	Haginaka (1987)	AFS-2	Dionex
		Bromate	Inoue (1997)	Nafion	Dupont
	Ion exchange	Small anions	Hanaoka (1982)	Nafion	Dupont
	Buffer exchange	Polyethylene glycol, proteins	Kaufmann (1993)	Cuprophan C1	Akzo Nobel
	Dialysis–electro-spray MS	Proteins	Lutz (1999)	Regenerated cellulose, 13 kDa	Spectrum Medical Instruments

Abbreviations: LC, liquid chromatography; CE, capillary electrophoresis; clEF, capillary isoelectric focusing.

column and a detector for continuously exchanging buffer ions.

Following Davis, Haginaka's group has developed a hollow-fibre membrane-based post-column reactor. By immersing the fibre in, for example, an alkaline solution, the pH of the eluent can be altered to enable the detection of penicillins, amino acids, barbiturates, etc. However, since the process is diffusion-limited, a long fibre is usually required, leading to additional band broadening. Nonetheless, this is an elegant method to change the pH without the need to introduce an additional reagent stream and a post-column mixing coil.

Two important applications of hollow-fibre membranes are as sample preparation devices to extract specific analytes from a gaseous matrix. When the extracted components are directly fed into the ion source of a mass spectrometer, we speak of membrane-inlet mass sepectometry or MIMS. When the membrane serves as the inlet for a gas chromatograph various acronyms are used, of which MESI (membrane extraction with a sorbent interface) is the most common. The main objective of using membranes in these cases is to prevent large amounts of water (vapour) from entering the analytical instrument.

The membrane in MIMS can be used in different configurations. One of these involves a flat-disc membrane at the tip of a tubular probe, which is inserted or immersed in the sample or sample stream. In most cases, however, a tubular membrane is used. Polysiloxane tubes (of surgical quality) are the most popular. The sample can either flow through this tube or be on the outside. In the first case, the membrane tube will be inside the mass spectrometer. In the second case, the membrane forms the interface between the mass spectrometer and the outside (chemical) world. A purge gas may pass through the inside of the tube, or it may just be connected to the mass spectrometer vacuum system.

The membrane tubes used for mass spectrometry are usually 1–2 mm in diameter. Using narrower tubes or fibres will not lead to lower detection limits, as the response of a mass spectrometric system increases with the amount (mass) of sample introduced per unit time. In principle, the mass flow of sample is proportional to the tube diameter, so that larger tube diameters are more favourable in this respect. A very large area can also be obtained by using flat, folded membranes. The use of hollow-fibre membranes for MIMS has the advantage that very small samples or sample streams suffice. An efficient parameter by which to affect the sensitivity of the system is the thickness of the membrane (tube wall). The selectivity of the system may be influenced by varying the tube materials. MIMS is most commonly applied to liquid samples, although the concept is

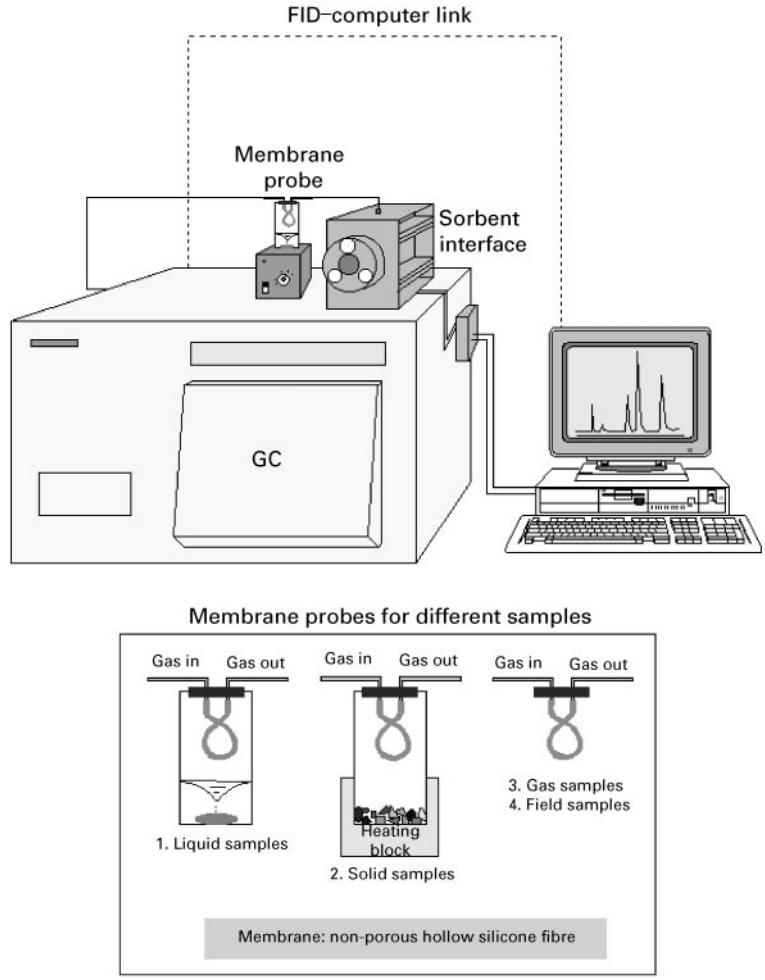

Figure 3 Principle of the MESI set-up. (With permission from the Web page 〈http://sciborg.uwaterloo.ca/chemistry/pawliszyn/〉.)

equally valid for gaseous samples. The concept is very attractive for introducing components into the mass spectrometer from aqueous samples, such as those encountered in biotechnology (e.g. measuring the amounts of gases in fermentation broths) or in waste management, but can also be a practical tool in the laboratory. There are at this time relatively few known applications of MIMS for process monitoring, although this is one of the most promising areas.

The principle of MESI is illustrated in **Figure 3**. Analytes, following selective passage through the membrane, are trapped onto a sorbent interface. After a sufficient amount of the analytes has been accumulated, these components are desorbed. In GC this can be done by rapidly increasing the temperature (thermal desorption). Finally, the analytes are separated on the GC column. Most commonly, the membrane probe is used to sample a gaseous phase, either a gaseous sample or sample stream, or the headspace of a liquid or solid sample. However, there is no fundamental reason why a liquid (e.g. aqueous) phase cannot be sampled directly. The technique can elegantly be used for the field analysis of air.

An interesting trend is the online coupling of hollow-fibre membranes to modern miniaturized separation techniques, where the intrinsic small volumes of hollow-fibre membranes come fully to their right. The hollow-fibre membrane introduces selectivity between analytes and matrix components (sample preparation), and can be used to concentrate the analytes prior to analysis. A liquid membrane device for sample preparation, developed by Mathiasson and Jönsson in 1996, is shown in **Figure 4**. The fibre is positioned in a small channel ($d < 1$ mm) that serves as the donor compartment. From the receptor compartment, i.e. the lumen of the fibre, small volumes can be manipulated towards the attached separation devices through narrow-bore capillaries. The device has been coupled to both μ-LC and CE, and has been

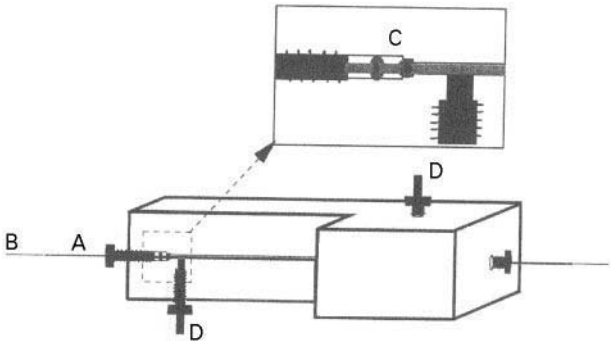

Figure 4 A liquid membrane device for sample preparation. A, hollow fibre (reaching through a hole drilled through the whole block); B, fused silica capillaries inserted in the ends of the fibre; C, O-rings for fixing the fibre and capillaries; D, connectors for the donor channel. (Reprinted with permission from Thordarson E, Palmarsdottir S, Mathiasson L and Jonsson JA (1996) Sample preparation using a miniaturized supported liquid membrane device connected on-line to packed capillary liquid chromatography. *Analytical Chemistry* 68: 2559–2563.)

employed for the analysis of drugs in a matrix of blood plasma.

See also: **III/Membrane Preparation:** Interfacial Composite Membranes; Phase Inversion Membranes.

Further Reading

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Interfacial Composite Membranes

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Introduction

The development of asymmetric cellulose acetate membranes in the 1960s was a breakthrough in membrane technology. These membranes consisted of a thin surface skin layer on a microporous support. The skin layer performed the separation required and because it was very thin fluxes were high. The microporous support provides the mechanical strength required. Following these developments Rozell *et al*. in 1967 described the preparation of the first interfacial (IFC) composite membranes. These membranes have since become the standard for reverse osmosis (RO) and nanofiltration (NF) applications.

IFC membranes have the same asymmetric status of the first-generation cellulose acetate membranes but are made by a very different procedure, shown schematically in **Figure 1**. In a first step a microporous polysulfone support membrane is impregnated with an aqueous solution containing a multifunctional amine. The impregnated membrane is then contacted with a hexane solution containing a multifunctional acid chloride. Because the two solutions are immiscible the reactants can only combine at the membrane interface and so a thin polymer film layer forms at the surface. This layer performs the separation required.

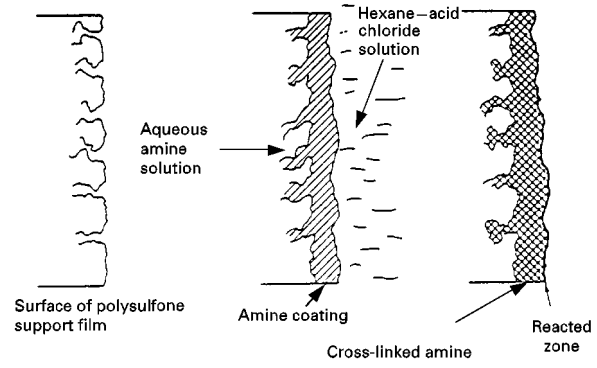

Figure 1 Schematic of the interfacial polymerization procedure. (From Cadotte JE and Petersen RJ (1981) Thin-film composite reverse osmosis membranes: origin, development and recent advances. In Turbak AF (ed.) *ACS Symposium Series 153*, Washington, DC, pp. 305–326.