Characterisation of polymers and particles by asymmetrical flow field-flow fractionation

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CHAPTER 2
Hollow-fiber membranes in analytical chemistry

INTRODUCTION

Hollow-fiber 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-fiber 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 of Mulder, which contains a detailed overview of the developments in the preparation of membranes and their use in purification.\(^1\) McKinney has provided a useful review of the preparation of organic hollow-fiber membranes.\(^2\) Tsapatsis has reviewed the preparation of inorganic membranes, which are of great interest for applications that require (strong) organic solvents.\(^3\) To the analytical chemist, there is an obvious analogy between the properties of hollow-fiber membranes and open-tubular columns for chromatography. Both areas may benefit from such a comparison, presented in Table 1.

<table>
<thead>
<tr>
<th>Type of membrane selectivity</th>
<th>Chromatographic equivalent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferential interaction and adsorption from a</td>
<td>• Gas chromatography with solid or polymeric stationary phases (GC)</td>
</tr>
<tr>
<td>• gas.</td>
<td>• Normal-phase and reversed phase liquid chromatography (LC)</td>
</tr>
<tr>
<td>• liquid</td>
<td>• Supercritical-fluid chromatography (SFC)</td>
</tr>
<tr>
<td>• or supercritical fluid</td>
<td>• Molar-sieve columns (GC) and Size-exclusion chromatography (SEC)</td>
</tr>
<tr>
<td>• Size selectivity (sieving effect)</td>
<td>• Ion-exchange chromatography and Ion-exclusion chromatography</td>
</tr>
<tr>
<td>• Charge selectivity</td>
<td>• Affinity chromatography</td>
</tr>
<tr>
<td>• Affinity membranes</td>
<td></td>
</tr>
</tbody>
</table>
Types of membranes

Basically, three types of membranes are distinguished:

- Porous membranes
- Non-porous membranes
- Liquid membranes.

All three types can be used in the hollow-fiber geometry. Porous membranes allow the passage of relatively large molecules. Depending on the size of the pores, one speaks of micro-filtration (pore size > 100 nm), ultra-filtration (< 100 nm), or nanofiltration (molecular weight cut-off > ca. 1000 Da). Non-porous 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 et al.4

Hollow-fiber membranes are often the preferred geometry, offering distinct advantages over flat or tubular (diameter larger than 5 mm) membranes, for a number of reasons:

- High surface-to-volume ratio
- Conceptual simplicity
- Easy incorporation in flow streams
- Broad availability.

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

Membranes are used in very 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 semi-permeable 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-fiber-membrane interfaces. HF5 can be placed amongst these techniques. 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 a large amount of sample to be purified within a period of time. Two extensive reviews have been dedicated to this important field.5,6
Extractions. The intrinsic ability of hollow-fiber 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.7

Chiral Separations. The field of preparative chiral separations using hollow-fiber 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-fiber supported liquid membrane can be used to separate two phases, with a chiral selector present in one of these.8 Alternatively, a chiral selector can be chemically bonded to the membrane surface, prepared in a manner similar to the membranes used for affinity chromatography.

Isoelectric Focusing. In 1998, Korlach published an original article on pH-regulated Electro-Retention Chromatography (ERC).9 This technique is quite similar to (electrical) FFF. A voltage is applied across the diameter of a hollow-fiber membrane. Subsequently, a pH gradient is applied in a fluid reservoir which surrounds the fiber. This gradient gradually diffuses into the hollow-fiber membrane. At some point (when the pH crosses the iso-electric point or pI value), the charge on the analyte reverses and the ions will start to migrate to the middle of the fiber, from where they will be rapidly eluted due to the higher axial flow velocity. The bottleneck in the development of this technique, which is mainly applied for the separation of proteins, is adsorption of the analytes on the membrane.

Semi-permeable membranes allow us to manipulate processes that take place at the interface between two (miscible or non-miscible) 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 fibers 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 fibers 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 (non-polar) 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). In case fibers are used for sampling or sample clean-up in analytical chemistry, adsorption effects are often undesirable.
PREPARATION OF HOLLOW-FIBER MEMBRANES

The art of hollow-fiber-membrane preparation has taken a high flight in recent years. Nowadays, hollow-fiber 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-fiber membranes is given below.

The various processes for preparing fibers 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-fiber membranes, including all practical applications within analytical chemistry, the most sensible approach to the technology is to obtain suitable fibers from a commercial source.

Preparing fibers

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 fiber dimension, thickness, etc. On exiting the spinneret, the fiber 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 fiber, but it may also be used to deposit a membrane. Many different polymers can be processed this way and the porosity of the resulting micro-filtration membrane is affected by a large number of parameters. A summary is provided in Table 2. In case of porous fibers, the type of material used is usually of little relevance for 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, cost, etc. A typical example of a hollow-fiber membrane is shown in Figure 1.

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 form a special class of membrane films. They are prepared simply by immersing a microporous hollow fiber in a liquid. The liquid membrane, supported by the hollow fiber, separates two phases; by adding a selective carrier to the membrane (carrier mediated transport), an increased selectivity can be obtained.
**Figure 1.** Typical SEM picture of an asymmetrical composite hollow-fiber membrane, reprinted with permission from reference 10.

**Table 2.** Summary of variables affecting the fiber properties.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition of casting solution</td>
<td>Suspension of polymer in non-solvent “dry spinning”</td>
<td>Great effect on fiber porosity (and other properties)</td>
</tr>
<tr>
<td></td>
<td>Melted polymer (melt spinning”)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polymer solution (“wet spinning”)</td>
<td></td>
</tr>
<tr>
<td>Spinning parameters</td>
<td>Extrusion rate (mass flux of solution)</td>
<td>Determines fiber dimensions (internal and external diameters)</td>
</tr>
<tr>
<td></td>
<td>Tearing rate (speed of drawing the fiber)</td>
<td>Significant effect on fiber porosity</td>
</tr>
<tr>
<td></td>
<td>Bore-fluid rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distance between spinneret and coagulation solution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Composition of coagulation bath</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temperature at the various stages</td>
<td></td>
</tr>
<tr>
<td>Fiber treatments</td>
<td>Washing</td>
<td>Removes contaminations</td>
</tr>
<tr>
<td></td>
<td>Chemical modifications</td>
<td>Determines selectivity</td>
</tr>
</tbody>
</table>
Film-deposition techniques

In order to create a film of a polymeric material on the inside of the fiber, the complete fiber 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 fiber. 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 non-viscous liquid is pumped through the column containing the (viscous) film of polymer solution. The newly introduced liquid must 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 fiber. 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.

In situ polymerization

Using the processes of static or dynamic coating described previously, 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.

Another way is to deposit a polymeric layer on the wall from a polymer solution filling the entire fiber. In this case, the residual solvent needs to be evaporated slowly and carefully after the polymerization to avoid cracks in the film on 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 has been developed in the early 80's by the group of Burggraaf.\cite{11} A sol of nm-sized γ-alumina particles is deposited on the wall of the fiber from an aqueous solution containing a few percents of polyvinyl alcohol. The deposited sol-gel can be converted to a defect-free membrane by sintering.

Okubo pointed out that for the preparation of membranes inside a narrow-bore ceramic hollow fiber (1.4 mm inner and 2.0 mm outer diameter) dynamic coating procedures are required.\cite{12} By forcing the sol-gel through the hollow fiber, a stable and thick defect-free layer can be obtained. Reducing the diameter of hollow-fiber 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 the membrane pores. A great 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. This, however, may result in a less defined product.

Polymers can be attached to the surface ("grafted") through reactive functional groups, or through a pre-deposition radiation. 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 alter the properties of the membrane. Highly inert, non-polar polymeric membranes, such as polyethylene or polytetrafluoroethylene (Teflon®), can be modified to yield highly polar, ionic interfaces.
APPLICATIONS IN ANALYTICAL CHEMISTRY

As said, in most applications of hollow-fiber membranes in analytical science, commercially available fibers are used. In only a limited number of cases, (i.e. liquid membranes and affinity membranes) analytical scientists have reverted to in-house preparation. A non-exhaustive list of major suppliers of hollow-fiber 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 call them fibers.

In Table 4 we present a selection of recently developed applications of hollow-fiber membranes in analytical chemistry, with emphasis on the types of fibers used and their preparation or commercial availability. Here, we concentrate on the use of hollow-fiber 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 or filtration units to standard high-pressure 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.13

In ion chromatography, hollow-fiber 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-fiber membrane between an HPLC column and a detector for continuously exchanging buffer ions.14

Table 3 Some major suppliers of hollow-fiber membranes. *Supplier of (tubular) ceramic membranes.

<table>
<thead>
<tr>
<th>Producer</th>
<th>Location</th>
<th>Web address (sept '99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dow-Corning</td>
<td>Midland, MI, USA</td>
<td><a href="http://www.dowcorning.com">www.dowcorning.com</a></td>
</tr>
<tr>
<td>Hoechst Celgard</td>
<td>Wiesbaden, Germany</td>
<td><a href="http://www.celgard.de">www.celgard.de</a></td>
</tr>
<tr>
<td>MinnTech</td>
<td>Minneapolis, MN, USA</td>
<td><a href="http://www.mintech.com">www.mintech.com</a></td>
</tr>
<tr>
<td>Millipore</td>
<td>Bedford, MA, USA</td>
<td><a href="http://www.millipore.com">www.millipore.com</a></td>
</tr>
<tr>
<td>Sepracor</td>
<td>Marlborough, MA, USA</td>
<td><a href="http://www.sepracor.com">www.sepracor.com</a></td>
</tr>
<tr>
<td>A/G Technology</td>
<td>Needham, MA, USA</td>
<td><a href="http://www.agtech.com">www.agtech.com</a></td>
</tr>
<tr>
<td>Tech-Sep*</td>
<td>Lyon, France</td>
<td>----</td>
</tr>
<tr>
<td>US Filter / Schumacher*</td>
<td>Asheville, NC, USA</td>
<td>schumacher-usa.com</td>
</tr>
</tbody>
</table>
Table 4. A selection of applications of hollow-fiber membranes in analytical chemistry, connecting specific applications (techniques and analytes) with types and sources of membranes, and useful reviews (*). Abbreviations: Liquid chromatography (LC); Capillary Electrophoresis (CE); Capillary Isoelectric Focusing (cIEF).

<table>
<thead>
<tr>
<th>Method</th>
<th>Compound</th>
<th>Membrane type</th>
<th>Manufacturer</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas-phase</td>
<td>GC (MESI)</td>
<td>Volatile Organic</td>
<td>Silicone</td>
<td>Dow-Corning</td>
</tr>
<tr>
<td>extraction</td>
<td>MIMS</td>
<td>Carbohydrates</td>
<td>Silicone</td>
<td>Dow-Corning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Volatile Organic</td>
<td>Silicone</td>
<td>Dow-Corning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbohydrates</td>
<td>Silicone</td>
<td>Dow-Corning</td>
</tr>
<tr>
<td>Liquid-phase</td>
<td>µ-LC</td>
<td>Bambuterol</td>
<td>0.03μm polypropylene</td>
<td>Hoechst Celanese</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>Bambuterol</td>
<td>0.2μm polypropylene</td>
<td>AKZO Nobel</td>
</tr>
<tr>
<td>Pre-column</td>
<td>CE</td>
<td>Organochlorides</td>
<td>Celgard X-10</td>
<td>AKZO Nobel</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>Proteins</td>
<td>Cuprophan, 10 kDa</td>
<td>Hoechst Celanese</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>Methamphetamine</td>
<td>Polypropene, 0.2 μm</td>
<td>AKZO Nobel</td>
</tr>
<tr>
<td>cIEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-column</td>
<td>Reaction</td>
<td>Barbiturates</td>
<td>AFS-2</td>
<td>Dionex</td>
</tr>
<tr>
<td></td>
<td>Ion exchange</td>
<td>Bromate</td>
<td>Nafion</td>
<td>Dupont</td>
</tr>
<tr>
<td></td>
<td>Buffer exchange</td>
<td>Small Anions</td>
<td>Nafion</td>
<td>Dupont</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polyethylene glycol, Proteins</td>
<td>Cuprophan C1</td>
<td>Akzo Nobel</td>
</tr>
<tr>
<td></td>
<td>Dialysis-electrospray-MS</td>
<td>Proteins</td>
<td>Regenerated cellulose, 13 kDa</td>
<td>Spectrum Medical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Instruments</td>
</tr>
</tbody>
</table>

Following Davis et al., the group of Haginaka has developed a hollow-fiber-membrane-based post-column reactor. By immersing the fiber 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 fiber 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-fiber 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 (MS), we speak of membrane-inlet MS or MIMS. When the membrane serves as the inlet for a gas chromatograph (GC) 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-disk 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 its 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 MS vacuum system.

The membrane tubes used for MS are usually 1 or 2 mm in diameter. Using narrower tubes or fibers will not lead to lower detection limits, as the response of an MS 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-fiber 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 equally valid for gaseous samples. The concept is very attractive to introduce components into the MS 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.

A picture of the principle of MESI is presented in Figure 2. 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 head-space 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 on-line coupling of hollow-fiber membranes to modern miniaturized separation techniques, where the intrinsic small volumes of hollow-fiber membranes come fully to their right. The hollow-fiber 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 Thordarson et al., is shown in Figure 3. The fiber is positioned in a small channel (d<1 mm), that serves as the donor compartment. From the receptor compartment, the lumen of the fiber, 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 employed for the analysis of drugs in a matrix of blood plasma.
Figure 2. Principle of the MESI set-up. Copied with permission from the Web page http://sciborg.uwaterloo.ca/chemistry/pawliszyn/.

Figure 3. A liquid-membrane device for sample preparation. A, hollow fiber (reaching through a hole drilled through the whole block); B, fused silica capillaries inserted in the ends of the fiber; C, O-rings for fixing the fiber and capillaries; D, connectors for the donor channel. Reprinted with permission from reference 32.
REFERENCES


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