

Membrane Extraction for Sample Preparation

Guest Authors

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Sample preparation techniques based upon liquid membrane extraction offer a high degree of selectivity and enrichment power and use small amounts of organic solvents. They also provide convenient possibilities for direct and automated interfacing with chromatography systems and other analytical instruments.

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Sample Prep Perspectives Editor

Membrane extraction is a family of techniques that can be applied to many extraction problems. These techniques require very little solvent and provide remarkable cleanup efficiency. Figures 1 and 2 show examples of membrane extraction with biological and environmental samples (1,2). Membrane extraction also can provide very high concentration enrichment factors of hundreds or more. Systems based upon membrane extraction can be automated readily and connected on-line to chromatography systems and other instruments. Both inorganic and organic analytes can be extracted in a wide polarity range.

The application of membrane extraction as a sample preparation tool in analytical chemistry was pioneered by G. Audunsson, who was then at the department of analytical chemistry at Lund University (Lund, Sweden) (3). We further developed this work and applied it to various samples. Several review papers that provide background information and applications have been published (4–8).

The Scope of Membrane Extraction

Membrane systems: *Supported liquid membrane extraction* is the most versatile membrane extraction technique for analytical sample preparation. In this three-phase extraction technique, analytes are extracted from an aqueous sample into another aqueous phase through an organic liquid. The organic phase is held between the aqueous phases by a porous, hydrophobic supporting membrane. Capillary forces in the pores hold the organic liquid. Thus, two different equilibria are involved, which makes the system chemically analogous to extraction and back-extraction in classic liquid–liquid extraction. The back-extraction step considerably increases the selectivity of the extraction. Supported liquid membrane extraction is applicable to analytes of high or moderate polarity with $\log K_{ow}$ (octanol–

water partition coefficient) in the range -1 to $+3$ (9).

Another type of membrane extraction is based upon a two-phase system, with one aqueous phase and one organic phase; thus, it is equivalent to a single-step liquid–liquid extraction. A microporous hydrophobic membrane separates the two phases, and the organic phase also fills the pores of the membrane to provide a direct contact through a liquid–liquid interface without mixing the phases. This principle is called *microporous membrane liquid–liquid extraction* (7,8,10,11). Aqueous and organic phases also can be separated by a thin, inert polymeric membrane made from silicone rubber or polyethylene. This technique, *polymeric membrane extraction*, provides a more mechanically stable system but at the expense of extraction speed. These systems can be very similar chemically to supported liquid membrane systems, in which the polymeric membrane constitutes an organic phase between two aqueous liquids or to microporous membrane liquid–liquid extraction in which one of the liquid phases is organic.

Membranes in sample preparation have several other uses in addition to extraction. These uses include dialysis, ultrafiltration, and other types of filtration. In these techniques, no chemical separation principles are involved, only size discrimination without enrichment.

In this “Sample Prep Perspectives” column, we will direct our attention mainly to supported liquid membrane extraction, because its systems generally provide the best versatility and cleanup efficiency. Also, supported liquid membrane extraction provides unique possibilities for extracting polar, ionizable, and even permanently charged compounds, including metal ions, which are more difficult to extract with other techniques.

Supported liquid membrane principles: Figure 3 shows a typical supported liquid membrane extraction system setup for

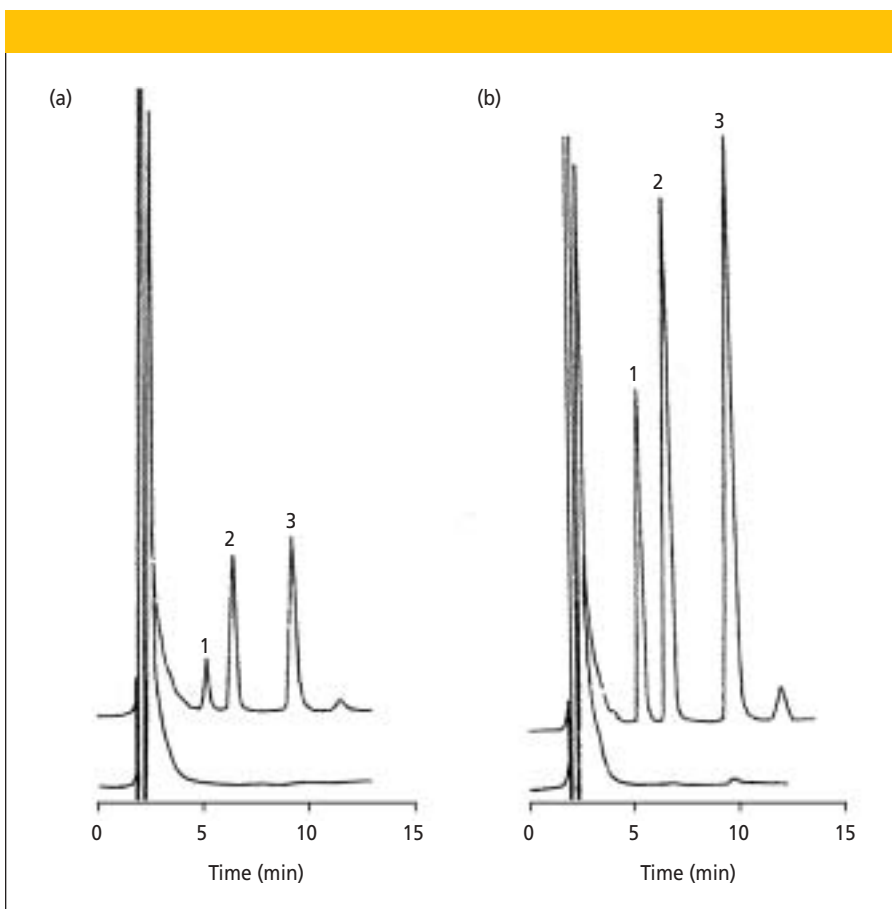


Figure 1: Chromatograms of (a) amperozide and its metabolite and homologue with the subsequent blank after enrichment from blood plasma and (b) after enrichment from an aqueous buffer solution. Peaks: 1 = amperozide (4 $\mu\text{g/mL}$), 2 = metabolite (4 $\mu\text{g/mL}$), 3 = homologue (8 $\mu\text{g/mL}$). (Reprinted from Lindegård et al. [1], copyright 1994 American Chemical Society.)

extracting basic compounds such as amines. The pH of the sample can be adjusted to a sufficiently high value, at which the amines are uncharged and therefore capable of being extracted into the organic membrane phase. The sample is pumped through the donor channel, and the amines (B) will partition into the membrane. The acceptor channel on the other side of the membrane is filled with a stagnant acidic buffer, in which an amine molecule that has diffused through the organic membrane is immediately protonated (BH^+). Because it is protonated, it is prevented from reentering the membrane and is trapped in the acceptor phase. The resultant driving force continually transports amine molecules from the donor to the acceptor phase.

Obviously, strongly acidic compounds (HA) that are charged in the alkaline donor phase are excluded completely from the membrane. The same holds true for permanently charged compounds. Neutral compounds (N) can be extracted, but they will not be enriched because they are not

trapped in the acceptor. In summary, under the conditions mentioned, the supported liquid membrane extraction will be highly selective for small, basic molecules.

Acidic compounds can be extracted in a similar way by reversing the pH conditions. Several chemical principles suitable for extraction of other compounds such as metals and permanently charged compounds are described elsewhere (7,8).

Factors influencing mass transfer:

Readers should consult the literature for detailed treatments of the mass transfer in supported liquid membrane extraction (12). We will discuss only a few basic principles in this "Sample Prep Perspectives" column.

The rate of extraction — that is, the flux of analyte molecules from donor to acceptor — is proportional to the concentration difference (ΔC) of the diffusing species (uncharged analyte molecules) through the membrane. Thus

$$\Delta C = \alpha_D C_D - \alpha_A C_A \quad [1]$$

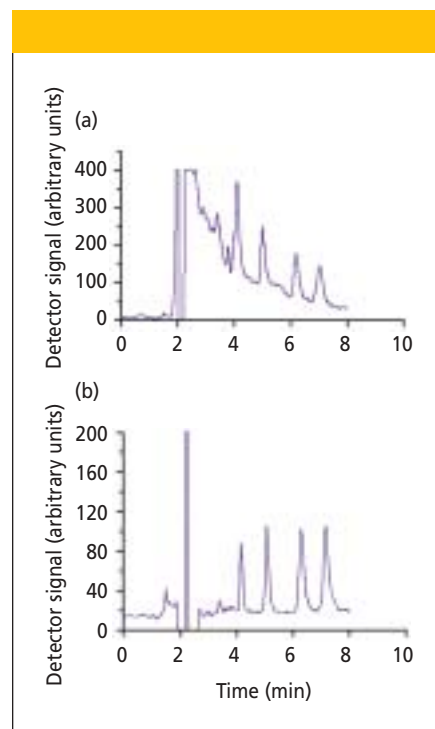


Figure 2: LC-UV chromatograms of methoxy-s-triazine herbicides. Shown are (a) SPE extraction of spiked river water (1.0 $\mu\text{g/L}$ of each analyte) and (b) supported liquid membrane extraction of spiked river water (0.5 $\mu\text{g/L}$ of each analyte). Peaks: 1 = simetone, 2 = atratone, 3 = secbumetone, 4 = terbumetone. (Reprinted from Megersa et al. [2] with permission from Elsevier Science B.V.)

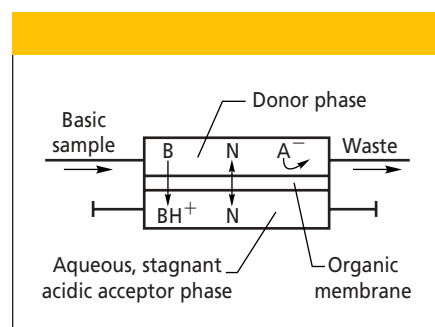


Figure 3: Schematic description of the supported liquid membrane principle. For details see the text.

where C_D and C_A are the concentrations in the donor (sample) and acceptor phase, respectively, and α_D and α_A are the fractions of the analytes that are in uncharged form in the actual phase. Equation 1 is somewhat simplified regarding the effects of different ionic strengths in the aqueous phases. Typically, extraction conditions are selected so the value of α_D is close to 1 and α_A is a very small value. C_A is zero in the beginning of the extraction and increases

during the operation, usually to values greater than those of C_D , which is equal to the total concentration in the extracted sample (C_S).

Extraction usually is evaluated in terms of extraction efficiency (E), which is the fraction of analyte that is collected in the acceptor

$$E = n_A/n_S \quad [2]$$

where n_S and n_A are the number of moles input from the sample during the extraction and those collected in the acceptor, respectively. This parameter is similar to, but not identical to, recovery as observed in solid-phase extraction (SPE).

Detailed equations for extraction efficiency as a function of flow rate and other physical parameters can be found elsewhere (12). An important fact is that the organic-aqueous partition coefficient K does not influence the extraction efficiency as much as could be anticipated (for example, from comparisons with liquid-liquid extraction). As a general rule, supported liquid membrane systems work best if K is approximately 10–10,000. Too-low values lead to insufficient extraction into the membrane, and too-high values lead to insufficient transfer of analyte molecules

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from the membrane into the acceptor (9). The latter condition, called *memory effect*, not only causes a decrease in the recovery but also leads to undesirable carryover effects in sequential extractions in automated systems. On a practical basis, memory effects can be studied by extracting a blank sample directly after a real sample. In some cases, memory effects demand a scheme for washing the membrane system between each sample before negligible carryover can be demonstrated.

The most efficient extractions are obtained at low donor flow rates, because a low flow rate increases the residence time

of an analyte molecule in the donor channel. However, in practice, it often is more relevant to maximize the concentration enrichment rather than the extraction efficiency. Maximizing the concentration enrichment will provide larger instrumental signals (peak areas) for a given extraction time and thus provide a more time-efficient analysis. In most cases in which quantitative determinations are made, E should be 20–80%. Provided that E is constant under the selected conditions and as determined in the calibration, a deviation from 100% does not influence the accuracy. This situation can be compared with other techniques such as atomic-absorption spectroscopy (AA), in which the nebulization efficiency is about 10%; dialysis, in which often only a small percentage of analyte is transferred; and mass spectrometry (MS), in which the ionization efficiency can be less than 1%, depending upon the ionization technique.

The concentration enrichment factor (E_c) is related to the extraction efficiency as

$$E_c = C_A/C_S = E(V_S/V_A) \quad [3]$$

where V_S and V_A are the volumes of the extracted sample and the acceptor channel, respectively. When the donor flow rate is increased, an increasing amount of analyte is input to the system, which is offset by a decrease in E . This change usually results in an increase of the enrichment factor with donor flow rate for a given time.

Trapping: If α_A is kept small, the second term in equation 1 is negligible. Then the flux, and consequently E , will be constant during the course of the extraction. This constant flux leads to linear extraction, in which the enrichment factor increases with the extracted sample volume. Also, the concentration in the acceptor is proportional to the concentration of analyte in the sample, which is a preferred situation.

Usually, the α_A value can be calculated easily: for a monoprotic basic analyte, as in Figure 3, simple dissociation considerations lead to

$$\alpha_A = \frac{[B]}{([BH^+] + [B])} = \frac{K_a}{([H^+] + K_a)} \quad [4]$$

where K_a is the dissociation constant of the corresponding ammonium ion. It turns out that a sufficiently low value of α_A in practice is 0.0005, which leads to the general rule that the acceptor pH should be at least 3.3 units below the pK_a to obtain sufficient trapping of bases (12). This process

is referred to as *complete trapping*. It also is possible to work with incomplete trapping, but the enrichment factors will be smaller and more dependent upon the conditions. The relationships between different degrees of trapping and extraction properties are well known (13).

The conditions in the donor phase are somewhat less important compared with those of the acceptor. In principle, the analyte should be in its extractable form; that is, $\alpha_D \approx 1$. However, if α_D is somewhat less than 1, the extraction efficiency is not crucially influenced. In practice, analysts observe no major influence upon the extraction efficiency, even if $\alpha_D \approx 0.1$. This outcome is due to the fast kinetics (protonation) that usually are involved and lead to a fast shift in the equilibria in the donor phase.

Quantitative Analysis

For quantitative analysis, calibration preferably is made in natural matrices. Straight-line curves typically are obtained when extracting samples of equal volumes spiked with different concentrations of analytes. Additionally, if the trapping is complete, the extraction is linear when plotted against time or volume, so the concentration found in the extract increases proportionally with the extracted sample volume. It is equivalent to say that the extraction efficiency is constant with the sample volume. Thus, it is possible to increase the enrichment factors and decrease the detection limits by increasing the extracted volume. In some cases, it is possible to reach very high enrichment factors and low detection limits. In environmental applications involving the extraction of organic or inorganic pollutants, analysts routinely obtain limits of detection in the parts-per-trillion range.

Instrumentation

Membrane extraction in flow systems:

Membrane extraction for sample preparation can be performed in a flow system format that permits more-or-less automated on-line operation. Off-line systems also can be used, as described below.

For flow systems, the membrane extraction units or contactors are made of two blocks of inert material with a machined groove in each. The blocks are clamped together with a membrane between them. Thus, flowthrough channels (donor and acceptor) are formed on each side of the membrane. The volume of these channels typically is in the 10–1000 μ L range. Fig-

ure 4 shows examples of different designs. In principle, these membrane units are applicable to all versions of membrane extraction for analytical sample preparation or sampling. Membrane units can be purchased from suppliers of flow-injection analysis equipment such as Global FIA (Gig Harbor, Washington). They also can be prepared in-house or obtained from the Lund University workshop through the guest authors of this column.

Membrane units based upon a hollow fiber membrane have been used in technical applications and occasionally for analytical applications in flowthrough formats, which permit very small channel volumes, but the handling of the hollow fibers tends to be somewhat difficult.

Membrane-extraction flow systems can be constructed in several ways. Figure 5 illustrates some examples. The simplest design is built around a peristaltic pump and a membrane unit with channel volumes of approximately 1 mL (Figure 5a). This system can be used for reasonably large sample volumes of 100 mL or more. In this simple setup, the acceptor phase is removed manually by a syringe after each extraction. This type of setup is suitable for simple experiments and out-of-laboratory applications (14,15).

To increase automation, workers can arrange a direct transfer of the acceptor phase to a high performance liquid chro-

matograph by a precolumn (see Figure 5b). The precolumn is necessary to enable the injection of as much as possible of the extracted analyte, which will be contained in a 1–2 mL volume. This type of system can be automated with pneumatically or electrically actuated valves controlled by computer systems (16,17).

To avoid using a precolumn, chemists can use a heart-cutting technique so only a part of the extract can be accommodated in the injection loop for direct injection into the high performance liquid chromatography (HPLC) column. This technique requires smaller extraction units, smaller samples, and more precise timing and pumping.

For small samples of 1 mL or less, the precision of peristaltic pumps is insufficient, so analysts should apply membrane extraction equipment based upon robotic liquid handlers with syringe pumps, as shown in Figure 5c (1,18). A robotic needle connected to a syringe pump pipettes buffer to adjust the pH of the sample vials, picks up an aliquot, and pumps it through a donor channel with an approximate volume of 10 μ L. The entire extract then is transferred from the acceptor channel to an injection loop connected to the HPLC system. Thus, the entire extract from the 1-mL sample goes to a single chromatographic injection. During the chromato-

graphic separation of one extract, the next sample is extracted, the cycle time of the system is determined by the chromatogram time, and the extraction time does not add to the total analysis time.

Microporous membrane liquid–liquid extraction, which provides an extract in an organic solvent, is best interfaced with gas chromatography (GC). An automated instrument provides on-line analysis of environmental water samples that contain hydrophobic compounds in trace amounts (19). This technology currently is under development as the E-Sy instrument (Personal Chemistry, AB, Uppsala, Sweden).

Off-line equipment: The literature has some examples of off-line membrane extraction devices (20–22). With this approach, several individual extraction units can be handled in a parallel, off-line manner, either manually or with auto-samplers. Both three-phase and two-phase systems have been described.

Rasmussen and co-workers (20) presented liquid membrane extraction in a porous hollow fiber under the name liquid-phase microextraction. In this technique, the fiber is impregnated with an organic phase to create both supported liquid membrane and microporous membrane liquid–liquid extraction systems, depending upon the nature of the acceptor phase, inside the fiber. The fiber is

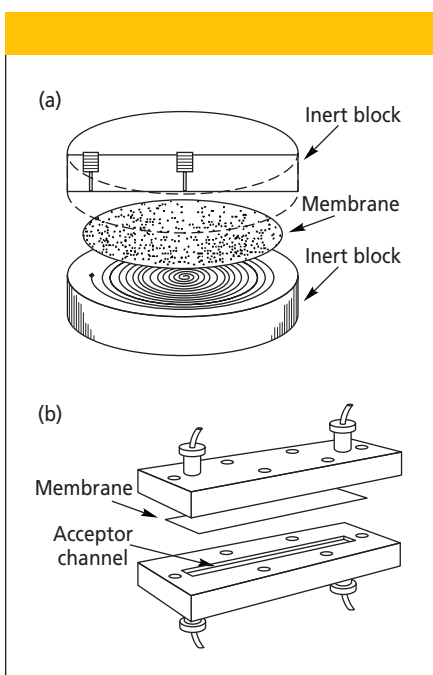


Figure 4: Membrane units for liquid membrane extraction. Shown are flat membrane modules with (a) 1-mL and (b) 10- μ L channel volumes.

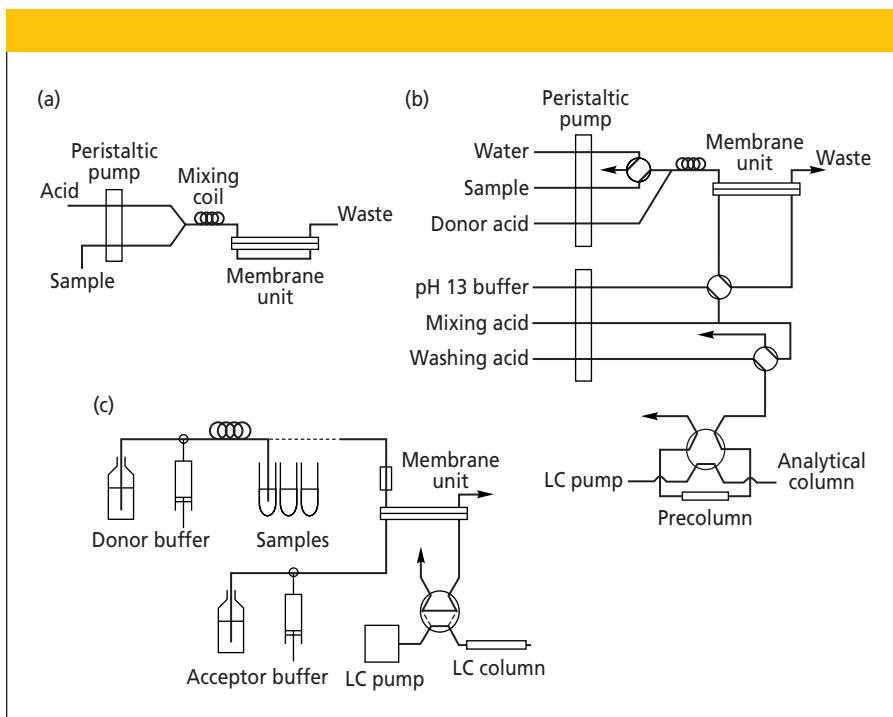


Figure 5: Apparatuses for liquid membrane extraction. Shown are (a) a manual off-line instrument based on a peristaltic pump (14), (b) an instrument with an on-line connection to HPLC for environmental studies (16), and (c) an experimental setup for supported liquid membrane–HPLC determination of biomolecules in blood plasma or urine (1).

arranged under the cover of an auto-sampler vial using two hypodermic needles to create a disposable extraction unit. Similar devices have been described by Lee and colleagues (21), Andrews and co-workers (22), and others.

Applications

Membrane extraction has been applied to several analytes and matrices. A number of applications have been published for bioanalysis as well as environmental, food, and industrial analysis. In the review papers mentioned above, especially in references 7 and 8, these applications are listed in detail. Table I lists some examples (2,10,11,14–18,20,22–53).

In bioanalysis, membrane techniques have been applied to the determination of drugs but also to other compounds in biological fluids such as blood plasma and

urine. For these applications, selectivity is crucial and so is the possibility of automation. Figure 2 illustrates an example. Similar high degrees of selectivity have been demonstrated with enrichment factors of 30–70 times for other applications in flow systems. Researchers have applied off-line approaches to the extraction of sulfonylurea and several other drugs in blood plasma and other biological matrices.

Pollutants and natural compounds have been determined in natural waters and other environmental matrices. In these applications, various types of membrane extraction provide high enrichment factors for determining compounds in low concentrations. The selectivity to discriminate against other naturally occurring interferences, especially humic compounds, also is important (see Figure 2). Compounds that have been extracted successfully from nat-

ural waters with supported liquid membrane extraction include phenoxy acids, sulfonylurea herbicides, phenolic compounds, triazine herbicides, aniline derivatives, metal ions, and surfactants. Microporous membrane liquid–liquid extraction permits the extraction of nonionizable compounds such as toluene, chlorobenzenes, and naphthalene.

In food analysis, vitamin E was determined in butter, and various pesticides were determined in eggs (47). Triazine herbicides were extracted from cooking oils by a microporous membrane liquid–liquid extraction approach (50). In an extension of the supported liquid membrane extraction principle to solid or semisolid samples, analysts were able to extract and quantify nicotine in snuff (54).

Researchers have presented some industrial membrane extraction applications,

Table I: Selected applications of membrane extraction

Analytes	Matrices	Membrane Extraction Technique	Analytical Technique	References
Basic drugs	Blood plasma	Supported liquid	HPLC	23
	Blood plasma	Supported liquid	CE*	24–26
	Blood plasma, urine	Liquid-phase microextraction	HPLC, GC, CE	20,22,27
	Urine	Supported liquid	HPLC	18,28,29
	Blood plasma	Microporous membrane liquid–liquid	GC	10
Organophosphate esters	Blood plasma	Microporous membrane liquid–liquid	GC–MS	30
Lead	Urine	Supported liquid	AA	31
Phenoxy acids	Natural water	Supported liquid	HPLC	14,32
Sulfonylurea herbicides	Natural water	Supported liquid	HPLC	16
Phenolic compounds	Natural water	Supported liquid	HPLC	17
	Nutrient solutions	Supported liquid	HPLC	15
Carboxylic acids	Soil, liquid	Supported liquid	IC†	33
Triazine herbicides	Natural water	Supported liquid	HPLC	2,34,35
	Natural water	Microporous membrane liquid–liquid	Flow-injection analysis	36
Anilines	Natural water	Supported liquid	HPLC	37
Metals	Natural water	Supported liquid	AA	38–40
Anionic surfactants	Natural water	Supported liquid	HPLC	41
Cationic surfactants	Natural water	Microporous membrane liquid–liquid	HPLC	42
Fungicides	Natural water	Supported liquid, microporous membrane liquid–liquid	HPLC	43,44
Semivolatile organic compounds	Water	Polymeric	HPLC	45,46
Pesticides	Eggs	Polymeric	HPLC	47
	Wine	Microporous membrane liquid–liquid	GC	11
Biogenic amines	Wine	Supported liquid	HPLC	48
Vitamin E	Butter	Polymeric	HPLC	49
Triazine herbicides	Cooking oil	Microporous membrane liquid–liquid	Flow-injection analysis, HPLC	50
Phenols	Mineral oil	Polymeric	HPLC	51,52
	Pyrolysis oil	Microporous membrane liquid–liquid	LC–LC	53

*CE = capillary electrophoresis.

†IC = ion chromatography.

usually in the polymeric membrane or microporous membrane liquid-liquid versions, mainly related to determination of phenols in fuels, oils, and gasoline.

Future of Membrane Extraction

One of the most obvious advantages of membrane extraction is the large reduction of solvent use compared with alternative extraction techniques. For example, U.S. Environmental Protection Agency (EPA) Method 3535 is a generic SPE procedure that requires 85 mL of organic solvent to extract 1 L of water. The corresponding liquid-liquid extraction method (EPA Method 3510) is applicable to many more analytes and requires 180 mL of organic solvent.

These solvents often are chlorinated (for example, methylene chloride), and they are expected to be banned from general use in the near future and already are in several countries. Membrane-based methods use considerably less solvent. Supported liquid membrane methods use only as much as 300 μ L in the membrane, which usually is replaced once a week or more frequently. Microporous membrane liquid-liquid extraction methods might use less than 1 mL per sample.

Because membrane extraction provides unsurpassed cleanup, large enrichment factors, and possibilities for full automation, we expect these techniques to be of increased interest in the near future. Currently, several companies are making attempts to commercialize membrane extraction techniques and to extend their scope of application. We welcome further suggestions to these ends.

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