Analytical and Bioanalytical Chemistry (2019) 411:1687–1693
https://doi.org/10.1007/s00216-018-1512-x

TRENDS

Electromembrane extraction—looking into the future

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Received: 22 September 2018 / Revised: 7 November 2018 / Accepted: 22 November 2018 / Published online: 18 December 2018
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Abstract

Analytical microextraction techniques, including solid-phase microextraction (SPME) Arthur & Pawliszyn (Anal Chem 62:2145–2148, 1990), stir bar sorptive extraction (SBSE), Baltussen et al. (J Microcol 11:737–747, 1999), single-drop microextraction (SDME) Jeannot & Cantwell (Anal Chem 68:2236–2240, 1996), hollow-fiber liquid-phase microextraction (HF-LPME) Pedersen-Bjergaard & Rasmussen (Anal Chem 71:2650–2656, 1999), dispersive liquid-liquid microextraction (DLLME) Berijani et al (J Chromatogr A. 1123:1–9, 2006), and electromembrane extraction (EME) Pedersen-Bjergaard & Rasmussen (J Chromatogr A 1109:183–190, 2006) have gained considerable interest in recent years. The latter technique, EME, differs from the others by the fact that mass transfer and extraction is facilitated by electrokinetic migration. Thus, basic or acidic analytes are extracted in their ionized form from aqueous sample, through an organic supported liquid membrane (SLM) and into an aqueous acceptor solution under the influence of an electrical potential. EME provides pre-concentration and sample clean-up, and can be performed in 96-well format using only a few microliter organic solvent per sample (green chemistry). Extraction selectivity is controlled by the direction and magnitude of the electrical field, by the chemical composition of the SLM, and by pH in the acceptor solution and sample. This trends article discusses briefly the principle, performance, and current status of EME, and from this future directions and perspectives are identified. Unlike traditional extraction methods, EME involves electrokinetic transfer of charged analyte molecules across an organic phase (SLM) immiscible with water. This process is still not fully characterized from a fundamental point of view, and more research in this area is expected in the near future. From author's point of view, such research at the interface between electrophoresis and partition will be highly important for future implementation of EME.

Keywords Sample preparation · Microextraction · Electromembrane extraction · EME

Introduction

Electromembrane extraction (EME) is an analytical microextraction technique which evolved from hollow-fiber liquid-phase microextraction (HF-LPME) [1]. EME was introduced in 2006 [2], and up to date, about 275 scientific papers have been published related to the subject (Scopus, September 15, 2018). The principle of EME is presented in Fig. 1. Basic or acidic analytes are extracted in their ionized form from an aqueous sample, through an organic supported liquid membrane (SLM), and into an aqueous acceptor solution. The driving force for mass transfer is a dc electrical potential sustained across the SLM by an external power supply. For extraction of basic analytes, pH conditions in the sample and acceptor solution are neutral or acidic to support analyte protonation, and the cathode (negative electrode) is located in the acceptor solution. By such, mass transfer of basic analyte molecules is achieved by electrokinetic migration. For extraction of acidic analytes, pH conditions are neutral or alkaline, and the direction of the electrical potential is reversed. Samples for EME are aqueous, such as biological fluids (blood, urine, saliva) and environmental waters.

The first EME experiments

The first experiments with EME were conducted in author's laboratory together with Knut Rasmussen in year 2005. At

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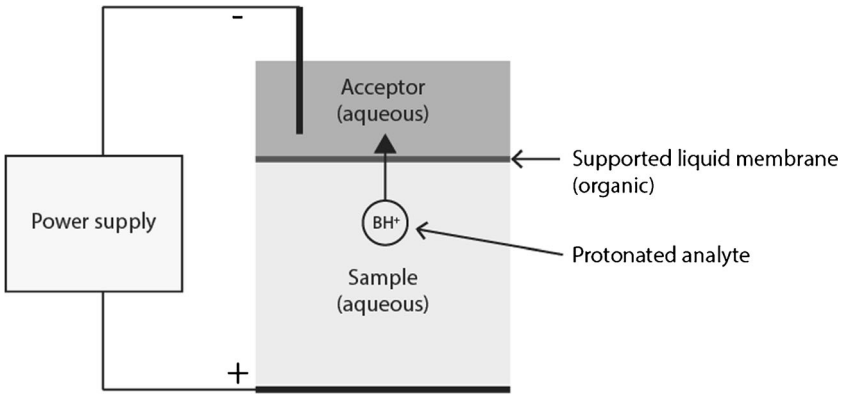

Fig. 1 Principle for electromembrane extraction (EME). Illustration shows a single well in a 96-well plate. With illustrated direction of the electrical potential, the system is tuned for basic analytes

that time, we were not sure that EME was feasible due to our understanding that organic molecules in their charged state have very poor partition from aqueous phase and into a lipophilic organic phase. However, we considered the electrical potential across the aqueous/organic interface as favorable for partition, and therefore, we conducted the initial experiments with some optimism. Unfortunately, the first series of experiments with selected lipophilic basic drugs as model analytes were not successful, because we used typical HF-LPME solvents such as n-dihexyl ether and dodecyl acetate as SLM. Fortunately, after several days without success, we randomly tested 2-nitrophenyl octyl ether (NPOE) as SLM, and we discovered that EME worked very efficiently with this particular solvent. These experiments served as starting point for our first EME publication [2]. Although we have tested a large number of organic solvents since 2005, we have not found any solvents more efficient than NPOE for lipophilic basic analytes!

A typical application

Experimental conditions for a typical EME application in 96-well configuration are illustrated in Fig. 2. In this case, benzodiazepines were extracted from human plasma samples, and the final measurements were by liquid chromatography-tandem mass spectrometry (LC-MS/MS) [3]. This set-up enabled 96 samples to be extracted in parallel during 15 min. Samples were pipetted into the wells of a laboratory built 96-well plate in stainless steel (sample plate). The anode (positive electrode) was connected directly to the sample plate, and was common to all samples extracted simultaneously. Each sample comprised 50 μL of human plasma, and this was diluted with 40 μL 20 mM formic acid and 10 μL internal standard solution. Addition of formic acid ensured acidification of the sample, which in turn increased analyte protonation and electrokinetic transfer. A commercial 96-well filter plate with polyvinylidene fluoride (PVDF) filters was used for holding the SLMs and acceptor solutions. Each SLM comprised 3 μL NPOE, and was created by pipetting NPOE directly onto the filter. Due to capillary forces, NPOE distributed across the entire pore volume of the filter and was immobilized immediately. Above the SLM, 100 μL of 250 mM trifluoroacetic acid (TFA) was pipetted as the acceptor solution. Normally, we use 20 mM HCOOH as acceptor solution for basic analytes, but benzodiazepines are extremely weak bases, and to keep these substances protonated in the acceptor solution, we used 250 mM TFA in this particular case. After loading the samples, SLMs and acceptor solutions, the sample plate and the filter plate were clamped, and a 96-well lid plate with electrodes (laboratory built) was placed on top of the filter plate. The sample and lid plates were connected to an external power

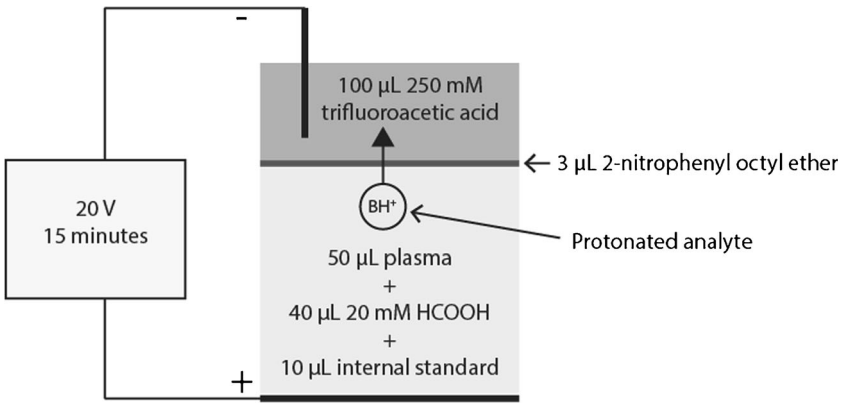

Fig. 2 Experimental conditions for EME of benzodiazepines from human plasma

supply, and the entire assembly was placed on an agitation platform. EME was initiated by simultaneous on-set of voltage (20 V) and agitation, and the duration was 15 min. After EME, acceptor solutions were collected and transferred to autosampler for direct injection in LC-MS/MS.

Performance data and extraction kinetics are illustrated in Fig. 3. This figure illustrates that the system came to equilibrium after 5–10 min. In this time frame, up to 96 samples were extracted simultaneously, and the acceptor solutions were directly injectable in LC-MS/MS. Thus, no evaporations/reconstitutions were required. Recoveries ranged between 80 and 95%. Although the setup was considered a microextraction system, exhaustive (or near-exhaustive) extraction was accomplished under the selected experimental conditions. Individual calibration curves for each analyte were obtained from spiked human plasma samples, and in this way, quantitation was performed with correction for analyte-to-analyte differences in extraction recovery. Due to the direction of the electrical field and due to the lipophilic nature of the SLM, matrix compounds in plasma were prevented from entering the acceptor solution, and therefore, EME provided very efficient sample clean-up. And finally, the total consumption of organic solvent required for 96 samples was less than 300 μL. We therefore consider EME as a green chemistry technique for sample preparation. Validation data for determination of benzodiazepines in human plasma by EME and LC-MS/MS were in compliance with international guideline requirements, and in terms of performance, throughput, costs, and consumption of chemicals and reagents, EME appeared attractive as compared with existing approaches for benzodiazepines [4].

Current state of EME and the understanding of mass transfer

As mentioned above, about 275 articles have currently been published related to EME. It is not the purpose of the current article to review this literature comprehensively. However, several reviews have been published recently, and detailed overview of the literature are found there [5–9]. Original research papers have been devoted to fundamental understanding of EME, development of technical devices/formats, and applications. Technical formats have included development of micro-chip systems [10] and 96-well technology [11], and applications have among others been reported for extraction of heavy metals [12], inorganic anions [13], basic drugs [14], acidic drugs [15], amino acids [16], and peptides [17]. Thus, EME has been used for:

- cationic and anionic substances
- hydrophilic and lipophilic substances
- inorganic, organic, and biological substances
- substances in molecular size range from less than 50 Da and up to 2 kDa (currently)

This illustrates that EME potentially has a very broad application window as long as the compounds can carry positive or negative charge. EME is compatible with a broad range of samples, including biological fluids such as human whole blood, plasma, urine, and saliva. Exploring EME for new applications may be justified by some of the following advantages:

- efficient sample clean-up
- selectivity easily tunable by changes in the electrical field
- aqueous extracts directly compatible with LC and LC-MS/MS
- can be performed in 96-well configuration
- consumption of organic solvent is limited to a few microliter per sample

Fundamentally, EME can be considered as electrophoresis across an oil membrane (SLM). Due to the phase transfer in and out of the oil membrane, EME also involves partition. A complete and exact model for mass transfer has not been developed yet. However, a somewhat simplified model for the time-dependent concentration of analyte in the acceptor solution ($C_A(t)$) is given by the mass transfer equation in Table 1 [18]. The different parameters in the equation are defined in the same table. The volume parameters V_D, V_m, and V_A are all defined by the physical dimensions of the EME system and can be considered constant. Based on this, the mass transfer equation predicts that the concentration of analyte in the acceptor solution is proportional to the original analyte concentration in the sample (C_D^0). This is important in order to obtain linear calibration curves.

The mass transfer equation also defines time, voltage, and agitation as principal operational parameters. The dependence of time is illustrated in Fig. 3 (experimental data), and typically EME enters equilibrium after 5–15 min, and there is no

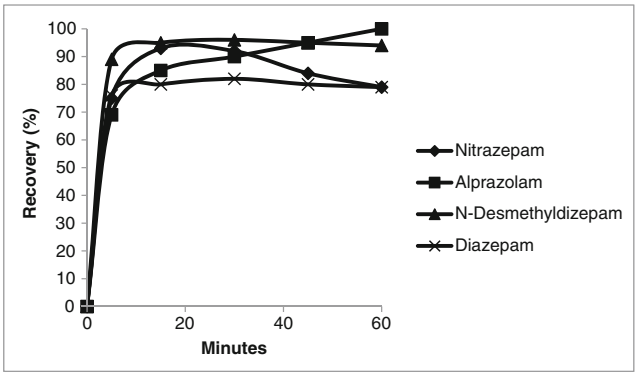

Fig. 3 Extraction of benzodiazepines as function of time (adapted from [3])

Table 1 Mass transfer equation for EME

$$C_A(t) = \frac{V_D \cdot C_D^0 - C_D^0 \cdot \exp\left(-\frac{A_f \cdot P^{D\to A}}{V_D} t\right)\left(V_D + \exp\left(\frac{zF}{RT}\left(\Delta_o^w\varphi - \Delta_o^w\varphi^0\right)\cdot V_m\right)\right)}{V_A}$$

Constants	
R	Gas constant
F	Faradays constant
Constant parameters defined by geometry	
V_D	Sample volume
V_m	SLM volume
V_A	Acceptor solution volume
A_f	SLM surface area
Sample dependent parameters	
C_D^0	Initial analyte concentration in sample
Operational and analyte dependent parameters	
$\Delta_o^w\varphi$	Galvani potential difference across SLM
t	Time
T	Absolute temperature
z	Analyte charge
$P^{D\to A}$	SLM permeability coefficient for analyte
$\Delta_o^w\varphi^0$	Analyte distribution parameter

further gain in recovery from this point forward. Recoveries increase with increasing voltage up to a certain point, and above this mass transfer no longer increases with increasing voltage. The optimal voltage is highly dependent on experimental conditions, and has to be optimized experimentally. Agitation is not a parameter in the mass transfer equation, but the equation is developed under the assumption that mass transfer in the bulk sample is not a limiting factor. In practical terms, agitation at 600–1000 rpm is used.

Analyte partition into the SLM is basically controlled by the partition term $\Delta_o^w\varphi^0$, and migration across the SLM is controlled by the permeability term $P^{D\to A}$. For efficient EME, the chemical composition of the SLM should be favorable both in terms of partition and permeability. Therefore, selection of the SLM solvent is highly critical and often the first step in EME method development.

Partition and permeability: we need more fundamental understanding

A substantial number of research papers have reported on different SLM compositions. To a large extent, pure organic solvents (immiscible with water) have been used as SLM up to date. For polar analytes, however, carriers have been added to the solvent. The solvents and carriers have mainly been conventional organic chemicals, but also more specialized materials have been used including ionic liquids [19], carbon nanotubes [20], and silver particles [21]. Commercially available, low price and low toxicity solvents and carriers are preferable, and the discussion below is focused on such materials.

As mentioned above, the first successful EME experiments in 2005 were accomplished using 2-nitrophenyl octyl ether (NPOE). Since 2005, NPOE has been used as a very efficient SLM solvent in a large number of applications related to lipophilic basic drugs (log $P > 1.5$). For such substances, NPOE is excellent both in terms of partition and permeability. In addition, NPOE is non-volatile and has extremely low water solubility. The former characteristic is important to avoid evaporative losses of the SLM during operation, and the latter is mandatory to avoid leakage of the SLM to the sample and acceptor solution. Several alternatives to NPOE have been found, such as ethyl nitrobenzene, diallyl phthalate, and dodecanenitrile [22], but still NPOE is preferred. Although research has not identified a SLM solvent superior to NPOE, it has clarified the physiochemical properties of successful SLM solvents for lipophilic basic drugs. In common, these all have strong hydrogen bond basicity, and this indicate that hydrogen bond interactions are of vital importance for the partition of protonated lipophilic basic drugs into the SLM. Protonated drug molecules are hydrogen bond donors and SLM solvent molecules serve as hydrogen bond acceptors. More generally, the required properties for a successful SLM solvent for lipophilic basic drugs can be summarized to:

- $3 < \log P < 5.5$
- Boiling point > 200 °C
- High hydrogen bond basicity
- High polarity/polarizability
- No hydrogen bond acidity

While SLM solvents for lipophilic basic drugs have been studied in details, less has been reported for hydrophilic basic drugs (log $P < 1.5$) and acidic drugs. Hydrophilic basic drugs are poorly extracted with pure NPOE, but dissolution of ionic carriers such as di(2-ethylhexyl) phosphate (DEHP) in the SLM solvent can improve mass transfer [22]. In such cases, ionic interactions are heavily involved at the sample/SLM interface. The same type of SLMs has also been used for net positively charged peptides extracted under acidic conditions [17]. Unfortunately, ionic carriers tend to increase the current in the EME system, and in such cases EME has to be conducted at lower voltage to avoid excessive current. Recently, pure solvents have been proposed for EME of hydrophilic basic drugs such as tributyl phosphate [23]. With these solvents, ionic carriers are not required. This is highly interesting for the future, but knowledge is currently limited.

Lipophilic acidic drugs have primarily been extracted with 1-octanol as SLM solvent. The effectiveness of 1-octanol is explained by high hydrogen bond acidity. Deprotonated drugs are hydrogen bond acceptors and SLM solvent molecules serve as hydrogen bond donors. The water solubility for 1-octanol is higher than for NPOE, and the SLM is therefore less stable. Alternatively, 1-nonanol can be used to improve stability, but even this SLM solvent is less stable than NPOE. To further improve stability, alcohols have been mixed with

NPOE without reducing extraction efficacy [24]. Hydrophilic acidic compounds have been studied to very little extent [15].

Although we have several SLMs for acidic drugs and hydrophilic basic drugs, EME will benefit from development of additional SLMs that are more optimal, especially in terms of stability and current. Not only should the SLMs work, but we also need to understand why they work in terms of molecular interactions and physiochemical properties. In parallel, alternative SLMs should be developed for peptides. EME of peptides has been reported, among others based on their isoelectric point, and this is a very interesting direction for the future [17]. Thus, EME may be developed into a flexible low-cost approach for selective extraction of peptides, and may be implemented in small-size and single-use devices for on-site measurements. In addition, with substantial knowledge on EME of peptides, the technology may be extended to proteins. Development of new SLMs will increase the versatility of EME, and give the technique a better scientific anchor. I expect such research in the near future, and I expect that we will learn from this in such a way that new directions will open up for EME. To justify and motivate the latter statement, the following section gives a flavor of recent progress, where new SLMs have been developed with outstanding performance.

Motivation for more SLM research: a few recent (and conceptual) cases

Basically, with NPOE as SLM, small inorganic ions remain in the sample during EME. However, in one research paper by Kuban and co-workers, such ions were selectively extracted by addition of the macrocyclic compound bambus [2] uril (BU6) to the SLM solvent (nitrobenzene) [13]. BU6 facilitated strong host-guest interactions with selected inorganic anions only, and strongly affected EME. Mass transfer was directly related to association constants between BU6 and the inorganic anions, and very high selectivity was achieved for EME of iodide, bromide, and perchlorate. Major inorganic anions such as chloride, nitrate, sulfate and carbonate were efficiently discriminated. Conceptually, this work is highly interesting, and addition of analyte specific complexation reagent to the SLM may be an important future direction for EME, to develop systems of very high specificity.

As discussed above, EME of hydrophilic basic substances is a challenge due to poor partition into the SLM. However, in a research paper from Schappler, Rudaz, and co-workers, hydrophilic basic endogenous metabolites were extracted from human plasma with nitrophenyl pentyl ether (NPPE) as SLM [25]. A total number of 45 metabolites were included in the work, with log *P* values in the range from − 5.7 to 1.5. While NPOE was not very efficient for the polar analytes, NPPE was found to be more efficient. NPPE has a shorted alkyl chain and a lower log P value than NPOE. In combination with acetic acid as the background electrolyte, the highly polar metabolites were extracted with recoveries in the range from 20 to 100%. Acetic acid as background electrolyte improved the efficiency of the system as compared to formic acid, and the author of this article has similar experience with trifluoroacetic acid (unpublished data). Although not proved yet, there are indications that certain organic background electrolytes can improve mass transfer, probably through ion-pairing. This should be investigated in more details in the future, and may give EME a very important role because existing extraction techniques are inefficient for highly polar analytes.

EME of peptides is still in very early phase. In research from the authors' laboratory, extraction of selected peptides was investigated with two different SLM solvents, namely 2-octanone and 1-nonanol, using di(2-ethylhexyl) phosphate (DEHP) and tridecyl phosphate (TDP) as carriers [26]. In spite of similarity between the two solvents and between the two carriers, peptide recoveries were highly dependent both on the solvent and the carrier. This was unexpected, and the mechanisms behind those observations were not discussed due to the limited number of experiments. However, the experiments indicate that strong selectivity can be obtained by proper selection of SLM solvent and carrier. This should be investigated systematically in the future, and may open new possibilities that we are not aware of today.

To finalize this discussion, it should be emphasized that selectivity is also affected by the magnitude of the electrical potential [27] and by pH in the acceptor solution [28]. Thus, by reducing the potential applied across the SLM, the EME system becomes more selective and fever compounds penetrate the SLM. This is related to the fact that $\Delta_o^w\varphi^0$ values are compound dependent. Due to local pH effects at the SLM interfaces, mass transfer is highly sensitive to the pH value of the acceptor solution. For basic analytes, the EME system become more selective as pH in the acceptor solution is increased. Therefore, selectivity obtained by the chemical properties of the SLM can be combined with selectivity obtained by the applied voltage and by pH in the acceptor solution.

Outlook

From a fundamental point of view, I consider EME as preparative electrophoresis across an oil membrane, and I have a strong feeling that this principle will be used for separation in the future. Although the principle has general applicability,

future applications will definitely be those where established methodologies are not appropriate. From my current understanding, I think EME is competitive in the following directions:

1) For extraction of very polar organic acids, bases, and small biomolecules—prior to analysis by chromatography and mass spectrometry
2) As sample clean-up interface between biological samples and lab-on-a-chip systems
3) As sample clean-up interface between biological samples and Smartphones, and other handheld devices
4) For depletion of surfactants, salts, and other high-abundance constituents
5) For applications outside analytical chemistry

Applications outside analytical chemistry are currently very few, but EME was recently used to regenerate template substance after synthesis of molecularly imprinted polymers [29]. Within analytical chemistry, EME development in directions 1, 2, and 3 can be exemplified by papers published in 2018. Recent work by Schappler, Rudaz, and co-workers on hydrophilic basic endogenous metabolites indicate potential of EME for highly polar analytes (1) [17]. Such substances are difficult by most existing extraction methods due to poor partition. However, in EME partition is not only affected by the chemical composition of the SLM, but is also controlled by the electrical potential. Development of new SLMs and more fundamental understanding will hopefully establish EME as a routine technique for extraction of very polar species. In this direction, compound-to-compound variation of extraction recoveries should be avoided in order to simplify calibration. Commercially available equipment is close to market, and is another important requirement to approach routine applications.

Recent work by Kutter and co-workers has demonstrated EME in the lab-on-chip format, where basic drug substances were extracted from 70 μL biological fluid and into 6 nL acceptor solution [30]. EME in micro-chip systems has also been demonstrated by other research groups [10, 31], and enrichment factors up to 400–500 have been reported from small volumes of biological fluid. Lab-on-chip technologies have been explored for several decades, but their general implementation has been somewhat limited. Part of this may be due to their limited compatibility with complex real samples, such as biological fluids. Therefore, implementation of EME on lab-on-chip systems may be very attractive.

The combination of EME with smartphone detection was demonstrated by Yamini, Seidi, and co-workers [32]. Phenazopyridine (model analyte) was extracted from human urine samples in an EME micro-chip. After EME, the acceptor solution was transferred to a small cation exchanger, where the analyte was retained. This changed the color of the sorbent, and a digital picture of the sorbent was taken. The analyte was quantified based on RGB analysis of the digital pictures using the smartphone. This research is in an early phase, but with development of highly selective EME systems, and with expected smartphone development, such measurements may be important in future analytical chemistry. With such systems, measurements are no longer performed by analytical chemists in laboratory facilities, but rather on-site by persons with no training in analytical chemistry.

Compliance with ethical standards

Conflict of interest The author declares that there are no conflicts of interest.

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