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Organic solvents in electromembrane extraction: recent insights

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Abstract: Electromembrane extraction (EME) was invented in 2006 as a miniaturized sample preparation technique for the separation of ionized species from aqueous samples. This concept has been investigated in different areas of analytical chemistry by different research groups worldwide since the introduction. Under the influence of an electrical field, EME is based on electrokinetic migration of the analytes through a supported liquid membrane (SLM), which is an organic solvent immobilized in the pores of the polymeric membrane, and into the acceptor solution. Up to date, close to 150 research articles with focus on EME have been published. The current review summarizes the performance of EME with different organic solvents and discusses several criteria for efficient solvents in EME. In addition, the authors highlight their personal perspective about the most promising organic solvents for EME and have indicated that more fundamental work is required to investigate and discover new organic solvents for EME.

Keywords: electromembrane extraction; Kamlet-Taft solvent parameters; organic solvent; supported liquid membrane.

Introduction

Prior to analysis of biological and environmental samples by chromatography and mass spectrometry, sample preparation is usually required. The purpose of the sample preparation is to make the samples compatible with the analytical instruments. During sample preparation, the complexity of the sample is reduced by removal of major sample matrix components. This is important to avoid contamination of the instruments and to avoid interferences during analyte detection. Finally, analytes are often pre-concentrated during sample preparation to enable trace level detection.

Sample preparation is traditionally performed by liquid-liquid extraction (LLE) or solid-phase extraction (SPE). Over the last two decades, however, substantial efforts have been reported to develop different microextraction techniques as alternatives to LLE and SPE, including solid-phase microextraction (SPME) (Arthur and Pawliszyn 1990), stir bar sorptive extraction (SBSE) (Baltussen et al. 1999), single drop microextraction (SDME) (Jeannot and Cantwell 1996), hollow-fiber liquid-phase microextraction (HF-LPME) (Pedersen-Bjergaard and Rasmussen 1999), dispersive liquid-liquid microextraction (DLLME) (Rezaee et al. 2006), solidified floating organic drop microextraction (SFODME) (Dadfarnia et al. 2008), parallel artificial liquid membrane extraction (PALME) (Gjelstad et al. 2013), and electromembrane extraction (EME) (Pedersen-Bjergaard and Rasmussen 2006). Microextraction techniques are interesting for several reasons. First, the consumption of hazardous organic solvents is strongly reduced or even eliminated by using microextraction techniques. This represents a major saving, and laboratory personnel are no longer exposed to vapors of harmful compounds. Second, using microextraction techniques, sample evaporation and reconstitution are avoided. This represents a major improvement in terms of work-flow simplicity, duration, risk for analyte loss, and risk for sample contamination. Third, several microextraction techniques are readily automated, and this is an important issue in modern high-throughput laboratories. Finally, the extraction efficiency can be tuned with several microextraction techniques. Thus, both exhaustive extraction and soft extraction may be accomplished. Soft extraction is highly interesting in cases where equilibria between target analytes and the sample matrix are not to be disturbed.

EME is one of the recently developed microextraction techniques (Pedersen-Bjergaard and Rasmussen 2006). In EME, target analytes are extracted in their ionic form from

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an aqueous sample solution through a water-immiscible organic solvent immobilized as a thin liquid membrane (supported liquid membrane, SLM) in the pores of a polymeric membrane and into an aqueous acceptor solution. The driving force for the extraction is an electrical field sustained across the SLM. Currently, approximately 150 research papers have been published on EME, covering fundamental aspects about mass transfer, technical configurations, and potential future applications. Also, several reviews on EME have been published in recent years (Lee et al. 2008, Gjelstad 2010, Majors 2010, Gjelstad and Pedersen-Bjergaard 2011, Petersen et al. 2011a,b, Basheer et al. 2012, Gjelstad and Pedersen-Bjergaard 2013, Krishna Marothu et al. 2013, Gjelstad and Pedersen-Bjergaard 2014, Rezazadeh et al. 2014a,b,c, Soltani and Jouyban 2014, Carasek and Merib 2015, Gjelstad et al. 2015, Huang et al. 2015a,b,c,d,e,f, Seip et al. 2015, Ocaña-González et al. 2016). In the current review, which is not an exhaustive review on EME, we focus especially on the different organic solvents that have been used as the SLM in EME before 2016. This is highly important because the chemical composition of the SLM plays a major role for the analyte mass transfer and the selectivity in EME. Overview and understanding of this are highly important for future development and optimization of EME and for the long-term propagation of the EME principle into routine analytical laboratories.

EME principle

A typical set-up of EME is illustrated in Figure 1. The EME equipment comprises a sample solution located in a sample reservoir (typically a glass vial), an SLM located in the pores in the wall of a porous hollow fiber, an acceptor solution located in the lumen of the hollow fiber, two electrodes (anode and cathode) connected to an external power supply, and an agitation system to agitate the entire set-up. During EME, the target analyte is extracted in the fully ionized state through the SLM and into the acceptor solution under the influence of the electrical field. After EME has been completed, the acceptor solution is collected and principally can be analyzed by any analytical techniques, typically by high-performance liquid chromatography (HPLC-UV) or liquid chromatography-mass spectrometry (LC-MS).

The pH value in the sample is adjusted (if necessary) to ensure full ionization of the target analytes. This is important to ensure efficient electrokinetic migration in the system. The SLM volume is typically 10–15 µl of

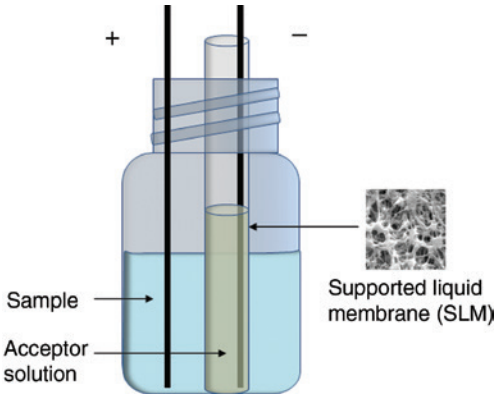

Figure 1: Schematic illustration of electromembrane extraction (EME) with hollow fiber membrane.

2-nitrophenyl octyl ether (NPOE) or another water-immiscible organic solvent immobilized in the pores in the wall of the porous hollow fiber. The SLM is easily immobilized by dipping the dry and porous hollow fiber in the solvent for a few seconds, and the SLM is immediately immobilized by capillary forces. One electrode is inserted in the sample solution, while the second electrode is situated in the acceptor solution. For extraction of cationic species, the cathode (–) is located in the acceptor solution, whereas the direction of the electrical field is reversed for extraction of anionic species. Thus, the selectivity of the EME system can be determined by the direction of the electrical field. In addition, research has demonstrated that the selectivity in EME also is dependent on the magnitude of the electrical field, and this can easily be tuned by the external power supply (Domínguez et al. 2012). Finally, the selectivity and the efficiency of the EME system are highly dependent on the chemical properties of the SLM. The latter will be reviewed and discussed in detail below.

In addition, EME can be performed in a variety of technical configurations and formats. Thus, in 2009, drop-to-drop EME was designed to extract basic drugs from a drop of stagnant sample (10 µl) into a drop of stagnant acceptor phase (10 µl) with an SLM of NPOE using a porous polymeric polypropylene flat membrane (Petersen et al. 2009). Based on this research, on-chip EME was developed to extract basic drugs from dynamic samples into stagnant (Petersen et al. 2010) or dynamic (Petersen et al. 2011a,b, Petersen et al. 2012) acceptor solutions. Recently, three-hollow fiber EME was designed for exhaustive extraction of hydrophobic basic drugs using larger acceptor solution volume (Eibak et al. 2012a,b). However, using the three-hollow fiber arrangement in EME was more complex than using a single hollow fiber in operation. Therefore, an exhaustive EME device was

developed using a sheet of thin flat porous membrane, which enables much larger capacity of acceptor solution volume (up to 600 µl has been tested) (Huang et al. 2014). With this new and improved technical EME set-up, exhaustive EME of basic drugs (Huang et al. 2014), acidic drugs (Huang et al. 2015a,b,c,d,e,f), and peptides (Huang et al. 2015a,b,c,d,e,f) has been achieved. Dual EME (Seidi et al. 2012, Arjomandi-Behzad et al. 2013, Tabani et al. 2013a,b,c, Ara et al. 2015) and all-in-one EME (Koruni et al. 2014) were tailor-made for simultaneous EME of cations and anions or ions with different polarities. Parallel EME (Eibak et al. 2014a,b) was proposed to improve the throughput of sample pretreatment using 96-well technology (Eibak et al. 2014a,b). EME has also been coupled with other sample preparation techniques such as ultrasound-assisted emulsification microextraction (Guo and Lee 2012), dispersive liquid-liquid microextraction (Seidi et al. 2013), solid phase microextraction (Rezazadeh et al. 2013a,b, Rezazadeh et al. 2014a,b,c, Abedi and Ebrahimzadeh 2015, Fakhari et al. 2015a,b, Rezazadeh et al. 2015a,b), and liquid-phase microextraction (Huang et al. 2015a,b,c,d,e,f).

With the advantages mentioned above and sufficient sample clean-up capability (Figure 2), EME has been used for the extraction of basic drugs (Fotouhi et al. 2011, Seidi et al. 2011a,b, Šlampová et al. 2012, Hasheminasab et al. 2013, Fakhari et al. 2014, Kubáň and Boček 2014a,b, Liu et al. 2014, Sun et al. 2014), acidic drugs (Balchen et al. 2007, Payan et al. 2011, Hasheminasab et al. 2013, Fakhari et al. 2015a,b), amino acids (Strieglerová et al. 2011a,b, Rezazadeh et al. 2013a,b, Rezazadeh et al. 2014a,b,c, Rezazadeh et al. 2015a,b), small peptides (Balchen et al. 2008, Balchen et al. 2009, Balchen et al. 2012), organic pollutants (Alhooshani et al. 2011, Suh et al. 2015a,b, Zhang et al. 2015a,b), and inorganic cations (Basheer et al. 2008, Kubáň et al. 2011, Hosseiny Davarani et al. 2015) and anions (Hu et al. 2011, Nojavan et al. 2014) from biological fluids and environmental samples with different matrix components, respectively. However, EME is still facing some challenges such as pH shift and high system-current generated during EME and limited recoveries for polar species as discussed in previous reviews (Majors 2010, Gjelstad and Pedersen-Bjergaard 2011, Petersen et al. 2011a,b, Seip et al. 2012, Gjelstad and Pedersen-Bjergaard 2013, Gjelstad and Pedersen-Bjergaard 2014, Rezazadeh et al. 2014a,b,c, Carasek and Merib 2015, Gjelstad et al. 2015, Huang et al. 2015a,b,c,d,e,f, Seip et al. 2015, Ocaña-González et al. 2016). From the authors' point of view, discovery or development of new, stable, and efficient SLMs for EME is the most important element for future propagation of the concept.

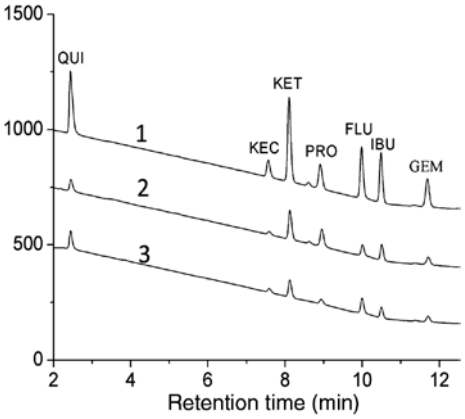

Figure 2: Sample clean-up capability of EME: chromatograms of the acceptor solutions after 20-min EME from 40 times diluted plasma (1) and after 10-min EME from 6 times diluted plasma (2), and the standard solution (3) (STD, 5 µg/ml). Reprinted from Ref. Huang et al. 2015f, with permission © 2015 Elsevier B.V.

Organic solvents in EME

From a theoretical point of view and based on the steady-state model, the analyte flux (J_i) in EME is proportional to the diffusion coefficient of the analyte (D_i) in the SLM (Gjelstad et al. 2007a,b, Huang et al. 2015a,b,c,d,e,f). This can be expressed using the following equations:

$$J_i = \frac{-D_i}{h_m}\left(1+\frac{\nu}{\ln\chi}\right)\left\{\frac{\chi-1}{\chi-\exp(-\nu)}\left(c_{ih}-c_{i0}\exp(-\nu)\right)\right\} \quad (1)$$

$$D_i = kT/6\pi\eta R \quad (2)$$

Here, c_{ih} and c_{i0} are the analyte concentrations at the SLM/sample interface and the acceptor solution/SLM interface; h_m is the thickness of the SLM;ν is the driving force; χ is the ion balance; T is the absolute temperature (K); k is the Boltzmann constant; η is the viscosity of the organic solvent; and R is the radius of the analyte.

Thus, J_i is inversely proportional to the viscosity of the organic solvent (Equation 3), which means that organic solvents of low viscocity are beneficial in terms of analyte flux (J_i).

$$J_i \propto 1/\eta \quad (3)$$

Based on the transient model (Seip et al. 2013a,b, Huang et al. 2015a,b,c,d,e,f), the amount of analyte transferred to the acceptor solution depends on the SLM permeability coefficient from the sample to the acceptor solution ($P_i^{D\to A}$), the distribution coefficient of the analyte between the organic solvent and the aqueous phases (K_d^*), and also

the volume of the organic solvent (V_m), as shown in Equation (4). The two former parameters indicate that the affinity of the analyte for the organic solvent affect the EME efficiency.

$$C_{A_i}(t) = \frac{V_D C^0_{D_i} - C^0_{D_i} \cdot \exp\left(-\frac{A_f \cdot P_i^{D\to A}}{V_D} \cdot t\right)(V_D + K^*_d \cdot V_m)}{V_A}, \quad (4)$$

where V_D, V_A, and V_m are the volume of the sample, the acceptor solution, and the SLM; $C^0_{D_i}$ and $C_{A_i}(t)$ are the analyte concentrations in the sample (at t=0) and in the acceptor solution (at time t); and A_f is the contact surface area of the SLM.

From the two mass transfer models discussed above, the EME efficiency is strongly dependent on the properties of the organic solvent. A low viscosity organic solvent is preferable, and high affinity and strong molecular interactions between the organic solvent and the analyte are required for efficient EME.

The stability of an EME system must be addressed for a successful operation. As reported, the system-current across the SLM in an EME system depends strongly on the applied voltage, the resistance of the immobilized organic solvent (SLM), and the two aqueous phases (Moazami et al. 2014). As the two aqueous phases normally display high conductivity, the system-current in EME under a fixed voltage mainly depends on the resistance of the SLM. This is strongly related to the properties of the organic solvent and the amount of solvent in use. Solvents with low water solubility and low volatility are preferred. In addition, because the support of the SLM used in EME is hydrophobic in nature (normally polypropylene), the solvents should possess suitable surface tension in order to be easily and well spread on the hydrophobic material.

In summary, ideal organic solvents in EME should fulfil several criteria, such as a certain hydrophobicity to spread well in the membrane support, strong ability for hydrogen binding interactions or dipole-dipole interactions to facilitate the transfer of analytes from the sample into the SLM, low viscosity to maintain a fast mass transfer of the analytes from the SLM into the acceptor solution, low water solubility and high boiling point to minimize the loss of the SLM, and to maintain the stability of the SLM during EME (Kubáň et al. 2010, Nojavan and Fakhari 2010, Kiplagat et al. 2011, Seidi et al. 2011a,b, Balchen et al. 2012, Davarani et al. 2013a,b, Ramos-Payán et al. 2013, Rezazadeh et al. 2013a,b, Seidi et al. 2013, Tabani et al. 2013a,b,c, Liu et al. 2014, Nojavan et al. 2014, Sanagi et al. 2014, Šlampová et al. 2014a,b, Fakhari et al. 2015a,b, Fotouhi et al. 2015, Suh et al. 2015a,b, Sun et al. 2015). After a comprehensive literature survey, we here give a summary of the organic solvents used up to date in EME, including the following groups: (1) nitroaromatic and other ethers; (2) benzenes; (3) alcohols; (4) ketones and aldehydes; (5) other solvents including alkylated phosphates, nitriles, esters, amines, carboxylic acids, and ionic liquids. In addition, the additives used in EME to facilitate the extraction are reviewed as well.

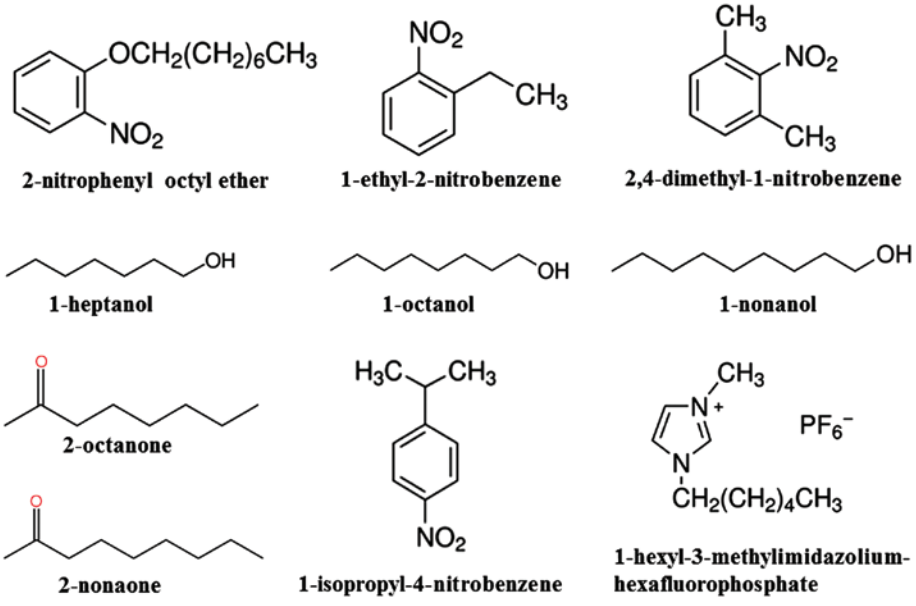

Figure 3: Structures for the representatives of organic solvents in EME.

Nitroaromatic ethers and other ethers

Different ethers have been tested as the SLM in EME, including NPOE (Figure 3), 2-nitrophenyl pentyl ether (NPPE), 2-nitrophenyl phenyl ether, 2-nitrodiphenyl ether, dodecyl-2-nitrophenyl ether, benzyl 2-nitrophenyl ether, phenyl methyl ether (anisole), ethyl phenyl ether (phenetole), di-hexyl ether (DHE) (Balchen et al. 2007, Basheer et al. 2008, Seidi et al. 2011a,b, Seip et al. 2014a,b).

Among all the organic solvents tested, NPOE has been the most popular and the most efficient solvent in EME for basic drugs (Gjelstad 2010, Majors 2010, Petersen et al. 2011a,b, Gjelstad and Pedersen-Bjergaard 2013, Gjelstad and Pedersen-Bjergaard 2014, Gjelstad et al. 2015, Huang et al. 2015a,b,c,d,e,f, Seip et al. 2015). NPOE was selected as the optimal SLM for the first demonstration of the EME concept (Pedersen-Bjergaard and Rasmussen 2006). In this case, five non-polar basic drugs (pethidine, nortriptyline, methadone, haloperidol, and loperamide) were used as model analytes, and the EME recoveries were in the range of 70–79% after EME for 5 min using a voltage of 300 V. After this first successful application in EME, NPOE has been used frequently for EME of non-polar basic drugs (Gjelstad et al. 2007a,b, Petersen et al. 2009, Nojavan and Fakhari 2010, Petersen et al. 2010, Eskandari et al. 2011, Petersen et al. 2011a,b, Seidi et al. 2011a,b, Domínguez et al. 2012, Eibak et al. 2012a,b, Fakhari et al. 2012, Gjelstad et al. 2012, Petersen et al. 2012, Eibak et al. 2012a,b, Kubáň and Boček 2012, Nojavan et al. 2012, Ahmar et al. 2013, Arjomandi-Behzad et al. 2013, Nojavan et al. 2013, Payán et al. 2013, Seidi et al. 2013, Seip et al. 2013a,b, Tabani et al. 2013a,b,c, Dugstad et al. 2014, Eibak et al. 2014a,b, Fakhari et al. 2014, Huang et al. 2014, Kubáň and Boček 2014a,b, Rezazadeh et al. 2014a,b,c, Sanagi et al. 2014, Seip et al. 2014a,b, Tabani et al. 2014, Abdossalami Asl et al. 2015, Asl et al. 2015a,b, Bazregar et al. 2015, Fakhari et al. 2015a,b, Fuchs et al. 2015, Hasheminasab and Fakhari 2015). The success of NPOE for EME of non-polar basic drugs is due to several facts. First, the hydrophobic property of the solvent results in rapid and highly stable immobilization within the porous membrane support. Second, NPOE has extremely low water solubility (6×10^{-3} g/l) and relatively high boiling point (351°C), and therefore, the SLM is not prone to dissolution into the sample or to evaporation. Third, and highly important, NPOE has high Kamlet Taft values for dipolarity-polarizability (π^*) and hydrogen bonding basicity (β). Thus, NPOE effectively interact with positively charged (protonated) drug substances through dipole-dipole interactions and hydrogen bonding interactions. In the latter aspect, NPOE serve as a strong hydrogen bonding acceptor.

Besides NPOE, the closely related solvent NPPE has been studied for EME of non-polar basic drugs (Middelthon-Bruer et al. 2008, Petersen et al. 2009, Eibak et al. 2010, Petersen et al. 2010, Petersen et al. 2011a,b, Rezazadeh et al. 2011, Seidi et al. 2011a,b, Jamt et al. 2012, Rezazadeh et al. 2012, Arjomandi-Behzad et al. 2014, Seip et al. 2014a,b, Ara et al. 2015, Yamini et al. 2015). However, in most cases, NPPE was inferior to NPOE. Thus, only in one case (Middelthon-Bruer et al. 2008), NPPE was selected as the optimal SLM to extract singly charged basic drugs with log P>2 using 50 V, and the recoveries were in the range of 30–81% after 5 min of EME. DHE, which has been used successfully for liquid-phase microextraction (LPME) of acidic drugs (Boström et al. 2014, Huang et al. 2015a,b,c,d,e,f), has been tested several times in EME for acidic and basic drugs. In all cases, however, DHE has been inefficient as SLM (Pedersen-Bjergaard and Rasmussen 2006, Balchen et al. 2007, Payan et al. 2011, Seidiet al. 2011a,b, Hasheminasab and Fakhari 2013, Hasheminasab et al. 2013, Ramos-Payán et al. 2013, Rezazadeh et al. 2013a,b, Asl et al. 2015a,b, Fakhari et al. 2015a,b, Hasheminasab and Fakhari 2015, Hidalgo et al. 2015). This is due to the relatively lower β and π^* values of DHE as compared to NPOE, reducing both dipole-dipole and hydrogen bonding interactions with the analytes.

Alcohols

Aliphatic alcohols including 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, 1-nonanol, 1-decanol, 1-undecanol, 1-dodecanol, 2-undecanol,iso-amyl alcohol, 2-ethylhexanol, 2-octyl-1-dodecanol, and 2-hexyl-1-decanol have been tested in EME as the SLM (Lee et al. 2009, Seidi et al. 2011a,b, Strieglerová et al. 2011a,b, Guo and Lee 2012, Seip et al. 2014a,b, Huang et al. 2015a,b,c,d,e,f, Suh et al. 2015a,b, Tak et al. 2015, Zhang et al. 2015a,b, Hosseiny Davarani et al. 2016, Rahmani et al. 2016, Zahedi et al. 2016). Both experiments with pure solvents and with carriers added to the solvent have been reported. Alcohols were found to be useful SLMs with/without carriers for EME of several acidic drugs, peptides, and metal ions because of their high hydrogen bonding acidity (α) and basicity (β) and high/moderate polarizability (π^*) (Balchen et al. 2007, Basheer et al. 2010, Payan et al. 2011, Strieglerová et al. 2011a,b, Tabani et al. 2013a,b,c, Koruni et al. 2014, Huang et al. 2015a,b,c,d,e,f). Among the aliphatic alcohols, 1-octanol (Figure 3) was one of the most frequently used EME SLMs with/without carriers to extract peptides (Balchen et al. 2012), metal ions (Kubáň et al. 2011, Hosseiny Davarani et al. 2015), acidic

drugs (Payan et al. 2011, Koruni et al. 2014), chlorophenols (Lee et al. 2009, Šlampová et al. 2013), and inorganic anions (Safari et al. 2013). 1-Nonanol (Figure 3) was used to replace 1-octanol to improve the stability of the EME system for peptides (Huang et al. 2015a,b,c,d,e,f, Huang et al. 2015a,b,c,d,e,f). 1-Nonanol provided a SLM of higher stability than 1-octanol due to lower water solubility. Besides 1-octanol, 1-heptanol (Figure 3) has been successfully used as the SLM to extract acidic drugs (Balchen et al. 2007, Huang et al. 2015a,b,c,d,e,f) and to extract inorganic anions (Kiplagat et al. 2011, Nojavan et al. 2014). 1-Butanol, 1-pentanol, 1-hexanol, and 2-ethylhexanol were not suitable SLMs for EME due to water solubility. 1-Decanol, 1-undecanol, 1-dodecanol, 2-undecanol, isoamylalcohol, 2-ethylhexanol, 2-octyl-1-dodecanol, and 2-hexyl-1-decanol were unsuccessful SLMs. Most of them are highly hydrophobic alcohols with relatively high viscosity and less prominent hydrogen bonding capability (α and β).

Phenols including eugenol, m-cresol, di-sec-butylphenol, 5-isopropyl-2-methylphenol, 2-isopropyl phenol, and 2-methoxy-4-methylphenol have been tested in EME for peptides and basic drugs without success because of partial water solubility and due to high current (Balchen et al. 2011, Seip et al. 2011, Seip et al. 2014a,b).

Other alcohols including benzyl alcohol, 2-phenylethanol,2-nitrophenylethyl alcohol, tetrahydrofurfuryl alcohol, furfuryl alcohol, (+)-santolina alcohol, (−)-perillyl alcohol, and cyclohexanol have been investigated in EME (Lee et al. 2009, Payan et al. 2011, Seip et al. 2011, Davarani et al. 2013a,b, Nojavan et al. 2013, Ramos-Payán et al. 2013, Seip et al. 2014a,b, Song et al. 2015). However, they were not useful SLMs because of high current and inefficient mass transfer (Seip et al. 2011, Seip et al. 2014a,b).

Ketones

Some ketones including 2-nitroacetophenone, 2-octanone, benzyl methyl ketone, acetophenone, 2-decanone,cyclohexanone, isophorone, methyl ethyl ketone, acetyl acetone, 2-nonaone, 2-undecanone, 6-undecanone, methylacetophenone, 2,6-dimethyl-4-heptanone, α-tetralone, 3,3,5-trimethylcyclohexanone, and 1-chloropinacolone have been tested as the SLM (Pedersen-Bjergaard and Rasmussen 2006, Balchen et al. 2007, Balchen et al. 2009, Seip et al. 2011, Strieglerová et al. 2011a,b, Ahmar et al. 2013, Seip et al. 2014a,b). Among these tested ketones, 2-octanone, 2-nonaone, 2-decanone, 2-undecanone, 6-undecanone, and 2,6-dimethyl-4-heptanone were efficient for EME of non-polar drugs. The other ketones mentioned were not suitable SLMs mainly because of the high current and due to significant water solubility (Seip et al. 2014a,b). In addition, with the assistance of an ion-pair reagent (DEHP), 2-octanone and 2-nonaone (Figure 3) were successful organic solvents for EME of several model peptides (Seip et al. 2011).

Aromatics and substituted aromatics

Benzene, benzene derivatives [1-ethyl-2-nitrobenzene (ENB), 1-isopropyl-4-nitrobenzene (IPNB), 2,4-dimethyl-1-nitrobenzene, nitrobenzene, 1,2,4-trifluoro-5-nitrobenzene, 1,2,4-trifluoronitrobenzene, (2,2-dimethyl-1-propyl) benzene, pentylbenzene, bromobenzene, and chlorobenzene], 4-nitro-m-xylene, o-xylene, toluene, 2-nitrotoluene, cumene, and 3-nitrostyrene have all been tested as SLMs in EME (Balchen et al. 2007, Balchen et al. 2009, Kubáň et al. 2011, Seidi et al. 2011a,b, Seip et al. 2014a,b). Most of them are not suitable, but some nitrobenzene derivatives, namely, IPNB, ENB, and 2,4-dimethyl-1-nitrobenzene (Figure 3), were found to be successful SLMs in EME because of high dipolarity-polarizability (π^*) and high hydrogen bonding basicity (β) (Gjelstad et al. 2009, Jamt et al. 2012, Šlampová et al. 2012, Eibak et al. 2014a,b, Seip et al. 2014a,b, Šlampová et al. 2014a,b). For example, IPNB was used to extract amitriptyline, fluoxetine, and haloperidol from undiluted human plasma and urine using 20 V (Eibak et al. 2014a,b). Stimulating drugs including cathinone; methamphetamine; 3,4-methylenedioxyamphetamine; 3,4-methylenedioxy methamphetamine; ketamine; and 2,5-dimethoxy-4-iodoamphetamine were extracted successfully from undiluted whole blood and post mortem blood by EME with an SLM of ENB (Jamt et al. 2012). ENB also has been used to extract some basic drugs from diluted human urine and serum (Šlampová et al. 2012). In addition, several basic drugs were extracted from undiluted biological samples including human urine and serum using μ-EME and ENB as the free liquid membrane (Kubáň and Boček 2014a,b).

Toluene has been studied intensively as the SLM in EME by different research groups (Basheer et al. 2008, Basheer et al. 2010, Alhooshani et al. 2011, Davarani et al. 2013a,b, Safari et al. 2013, Liu et al. 2014, Sanagi et al. 2014, Šlampová et al. 2014a,b, Zhang et al. 2015a,b). For example, toluene was used as the SLM in EME to determine the concentration of lead ions in amniotic fluid, blood serum, lipstick, and urine samples (Basheer et al. 2008). In another example, haloacetic acids and aromatic acetic acids were extracted from wastewater by EME with

an SLM of toluene (Alhooshani et al. 2011). In addition, simultaneous extraction of acidic and basic drugs at neutral sample pH was achieved with an SLM of toluene by EME under 300 V (Basheer et al. 2010). However, toluene is not recommended because of volatility, which might cause inconsistent results (Lee et al. 2009).

Alkanes and substituted alkanes

Alkanes and related derivatives including 1-nitropropane, nitropentane, 1-hexane, 1,10-dichlorodecane, dichloromethane (DCM), hexadecane, nitrocyclohexane, n-tetradecane, nitromethane, n-hexane, and kerosene (lamp oil) have been studied (Pedersen-Bjergaard and Rasmussen 2006, Kjelsen et al. 2008, Basheer et al. 2010, Alhooshani et al. 2011, Seidi et al. 2011a,b, Guo and Lee 2012, Nojavan et al. 2013, Seip et al. 2014a,b, Šlampová et al. 2014a,b, Mamat and See 2015, Suh et al. 2015a,b). However, very low or no recoveries were obtained from all cases. This was mainly due to high volatility causing serious losses of the SLM during EME (Basheer et al. 2010, Nojavan et al. 2013) or due to low values of α, β, and π*(Suh et al. 2015a,b).

Ionic liquids

Most recently, ionic liquids (ILs) including imidazoliumhexafluorophosphate-based ILs[C_nMI_m][PF_6] (n=4, 6, 8), 1-butyl-3-methylimidazolium-hexafluorophosphate ([C_4MI_m][PF_6]), 1-hexyl-3-methylimidazolium-hexafluorophosphate ([C_6MI_m][PF_6]) (Figure 3), and 1-octyl-3-methylimidazolium-hexafluorophosphate ([C_8MI_m][PF_6]) were applied for extraction of basic and acidic compounds under very low voltage conditions (Sun et al. 2014, Sun et al. 2015). With ionic liquid-based EME (IL-EME), strychnine and brucine were determined in human urine (Sun et al. 2014). In another work, IL-EME was used to determine chlorophenoxy acid herbicides in pig kidney (Sun et al. 2015). IL-EME has to be accomplished with very low voltage (1.5–7.5 V) to avoid high and unstable system-current due to high conductivity. However, it can also be a great advantage for EME that efficient EME can be obtained with very low consumption of energy by using ionic liquid as SLM.

Solvent mixtures

In addition, some mixed organic solvents have been tested for peptides and acidic drugs (Balchen et al. 2009, Balchen et al. 2010, Balchen et al. 2011, Payan et al. 2011, Seip et al. 2011, Balchen et al. 2012, Ramos-Payán et al. 2013, Tabani et al. 2013a,b,c, Huang et al. 2015a,b,c,d,e,f). For example, the mixture of 1-octanol with 4-nitro-m-xylene and di-isobutylketone, 1-octanol with di-isobutyl ketone, 4-nitro-m-xylene with di-isobutyl ketone, and 1-octanol with NPOE provided efficient EME of peptides from water samples (Balchen et al. 2009). Mixtures of organic solvents (a mixture of 1-heptanol and NPOE) were used to reduce and stabilize the system-current in EME (Huang et al. 2015a,b,c,d,e,f).

Miscellaneous solvents

Alkylated phosphates (including dibutyl phosphate, tributyl phosphate, triisopropyl phosphate, tris(2-butoxyethyl) phosphate, tris(2-ethylhexyl) phosphate (TEHP), di-(2-ethylhexyl) phosphate (DEHP), and trixylyl phosphate), tri-tert-butylborate, benzyl chloride, different amines (including trihexyl amine, tert-butylamine, dibenzylamine, 2-ethylhexyl-4-(dimethylamino) benzoate, and octylamine), carboxylic acids (including, 1-octanoic acid, linoleic acid, caprylic acid, and nonanoic acid), nitriles (including cinnamonitrile and 3-tolunitrile), aldehydes (heptane aldehyde, benzaldehyde, nonanal and undecanal), peppermint oil, silicone oil AS 4, and different esters (including dodecyl acetate, dibutyl phthalate, and dioctyl phthalate) have been investigated as SLM in EME but without major success (Balchen et al. 2007, Balchen et al. 2009, Seidi et al. 2011a,b, Seip et al. 2014a,b). Unsuccessful EME with the above tested organic solvents was mainly due to significant water solubility, causing high current and an unstable SLM system. Additionally, solidified solvents (polymer inclusive membranes) have also been used successfully in EME, where the organic solvent was mixed with cellulose triacetate and polymerized after the evaporation of dichloromethane (See and Hauser 2011, Schmidt-Marzinkowski et al. 2013, See et al. 2013, Mamat and See 2015).

Additives in the SLM

In most of the EME publications, EME was conducted using pure solvents as the SLM. However, addition of ion-pair reagents in the SLM is mandatory for EME of polar substances, and additives in the SLM could enhance the EME efficiency.

Alkylated phosphates are the most intensively studied ion-pair reagents in EME of basic drugs, peptides, amino acids, and metal ions. Investigated phosphates include di-(2-ethylhexyl) phosphate (DEHP), tris-(2-ethylhexyl)

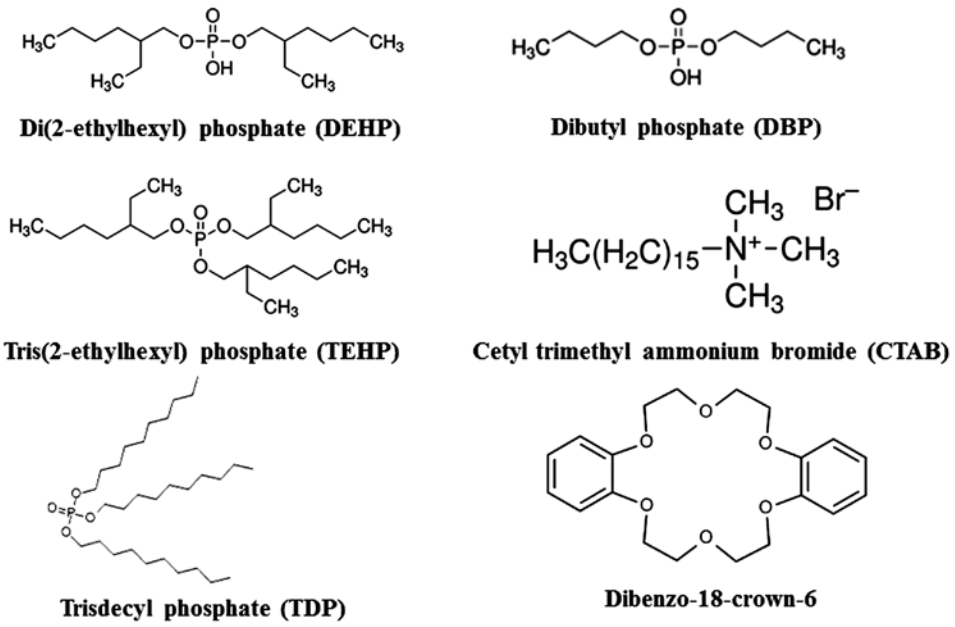

Figure 4: Structures for the representatives of additives in EME.

phosphate (TEHP), diphenylphosphate, tridecyl phosphate (TDP), dibutyl phosphate (DBP), trixylyl phosphate, triphenyl phosphate, dihexadecyl phosphate, dibenzyl phosphate, 2-cyanoethyl phosphate, 1-naphtyl phosphate, tris(2-butoksyethyl) phosphate, bis(4-nitrophenyl) phosphate, tri-isopropyl phosphate, tributyl phosphate, tri(8-quionlyl) phosphate, tri octyl phosphine oxide, hexamethylenediamine tetra (methylene phosphonic acid), amino tris (methylenephosphonic acid), and triethyl phosphate (Balchen et al. 2008, Seip et al. 2011, Davarani et al. 2013a,b). Among those DEHP, TEHP, TDP, and DBP, whose structure is shown in Figure 4, were the most efficient ones (Middelthon-Bruer et al. 2008, Seip et al. 2011, Strieglerováet al. 2011a,b, Rezazadeh et al. 2013a,b). For example, with pure NPPE as the SLM, only singly charged basic drugs with log P>2 were extracted by EME. However, the addition of TEHP in NPPE as the SLM was required for EME of medium polar basic drugs (1<log P<2), and addition of DEHP into the SLM was crucial for EME of the most polar drugs with log P<1 (Middelthon-Bruer et al. 2008). This main difference was due to the fact that DEHP can form complexes with positively charged species by ionic interactions, while TEHP can form complexes with the analytes by hydrogen bonding. Thus, for EME of hydrophilic substances like amino acids or peptides, DEHP is always present in the SLM (Balchen et al. 2008, Balchen et al. 2009, Balchen et al. 2011, Seip et al. 2011, Strieglerová et al. 2011a,b, Balchen et al. 2012, Seip et al. 2012, Rezazadeh et al. 2013a,b, Rezazadehet al. 2014a,b,c, Huang et al. 2015a,b,c,d,e,f, Rezazadeh et al. 2015a,b). In addition, in order to improve the affinity between the SLM and the analytes, the combination of DEHP (strong ionic interaction) and TEHP (strong hydrogen bonding) was used (Rezazadeh et al. 2012, Rezazadeh et al. 2013a,b, Ahmar et al. 2014, Fashi et al. 2015, Hosseiny Davarani et al. 2015, Rezazadeh et al. 2015a,b).

Amines including tetrabutyl ammonium hydroxide 30-hydrate, tetrabutylammonium phosphate, 1-hexyltriethyl ammonium phosphate, 1-octyltriethyl ammonium phosphate, 1-dodecyltriethyl ammonium phosphate, trimethyloctyl ammonium bromide, decyltrimethyl ammonium bromide, dodecyltrimethyl ammonium bromide, cetyltrimethyl ammonium bromide (CTAB), and tetraoctylammonium bromide have been tested as the carrier for EME of anions (Balchen et al. 2007, Lee et al. 2009, Tabani et al. 2013a,b,c, Suh et al. 2015a,b). However, in most cases, the addition of amines in the organic solvent was found to be unsuccessful because of high system-current, bubble formation in the EME system (Balchen et al. 2007), and too strong ionic interaction (Suh et al. 2015a,b). Most recently, CTAB (Figure 4) was successfully used as the carrier to extract polar acidic drugs in an all-in-one EME system (Koruni et al. 2014).

Nanoparticles have been introduced into the SLM to improve the EME performance for basic and acidic compounds by involving both solid-phase microextrcation(SPME) and EME principles (Hasheminasab and Fakhari 2013, Hasheminasab et al. 2013, Hasheminasab et al. 2014, Ramos-Payán et al. 2014, Song et al. 2015). Carbon nanotubes (CNT) were added into the

organic solvent to extract buprenorphine with success (Hasheminasab and Fakhari 2013). Nanotubes dispersed in 1-octanol was also used as the SLM to extract acidic drugs (Hasheminasab et al. 2013). In addition, some acidic drugs were extracted by EME using silver nanoparticles in the SLM (Ramos-Payán et al. 2014). The addition of nanoparticles in the organic solvent resulted in more efficient EME (Hasheminasab and Fakhari 2013, Hasheminasab et al. 2013, Ramos-Payán et al. 2014).

Other carriers such as tri-tert-butyl borate, dithizone, 8-hydroxyquinoline, acids (including sodium-2-ethylhexylsulphuric acid, triisopropylnaphtalenesulfonicacid, hydroxyisobutyric acid, 1-naphtoic acid, caprylic acid, stearic acid, phenylboronic acid, and hydroxyisobutyric acid), and crown ethers (including 15-crown-5 ether, 18-crown-6, benzo-18-crown-6, dibenzo-18-crown-6 (Figure 4), dicyclohexano-18-crown-6, and 4-amino-dibenzo-18-crown-6) have been tested for EME of peptides and metal ions (Balchen et al. 2008, Balchen et al. 2011, Kubáň et al. 2011, Seip et al. 2011, Šlampová et al. 2014a,b). Among all these tested carriers, crown ethers were useful for selective EME of hydrophobic peptides (Balchen et al. 2011) and K^+ (Šlampová et al. 2014a,b) due to the complexation.

Other parameters in EME

As discussed above, the system-current in the EME system and the EME efficiency strongly depends on the properties of the organic solvent. Besides that, to construct a stable and efficient EME system, some other operation parameters such as the SLM volume, extraction voltage, pH in sample and acceptor solution, acceptor solution composition, and extraction time also need to be optimized.

It has been found that the SLM volume also affects the system-current and the EME recovery of some small peptides (Huang et al. 2015a,b,c,d,e,f). Larger SLM volume (≥7.5 μl) could reduce and stabilize the system-current during EME. In addition, the recoveries of peptides were improved by using an optimal SLM volume of 10 μl.

Extraction voltage can affect the selectivity, efficiency, and stability in EME. In one example, all five basic drugs were extracted under higher voltage (50 V), whereas only two basic drugs possessing the lowest polar surface area were extracted with lower voltage (5 V) (Domínguez et al. 2012). Generally, high voltage resulted in higher EME recovery but also higher system-current. The latter affects the EME efficiency in turn. Normally, unstable EME system leads to a reduction in EME efficiency and also irreproducible results. Thus, the extraction voltage should be carefully optimized after the optimization of the organic solvent to propose the most efficient EME system but without causing any stability problems.

The pH in sample and in the acceptor solution should ionize the analytes of interests. In addition, buffer solution is preferable to be used to overcome the pH shift because of the electrolysis during the EME process (Šlampová et al. 2007, Huang et al. 2015a,b,c,d,e,f, Kubáň and Boček 2015, Šlampová et al. 2015). The composition of the acceptor solution affects the EME efficiency as well as the system-current (Huang et al. 2015a,b,c,d,e,f).

The optimal extraction time for EME depends strongly on the type of analytes and the parameters that we discussed above. For pharmaceuticals, normally, the optimal extraction time is within 15 min, and longer extraction time will result in lower recovery because of the back-extraction due to the pH shift in the acceptor solution. In a recent publication, the extraction time was reduced to 30 s (Song et al. 2015).

Future directions

As discussed in the current review, a large number of different organic solvents have been tested as the SLM in EME. Only a few of these solvents have been highly efficient, and this supports that several criteria have to be fulfilled for an EME solvent. Clearly, the solvent has to be immiscible with water (low polarity) and of low volatility in order to avoid leakage to the sample and evaporative losses. In addition, the successful EME solvent also has to be carefully balanced in terms of dipolarity-polarizability (π^*), hydrogen bonding acidity (α), and hydrogen bonding basicity (β). For future development of EME, the number of efficient EME solvents should definitely be increased, especially for anionic analytes and polar analytes. Thus, more research in this field is required. Further testing of pure organic solvents may be one approach, but testing of solvent additives insoluble in water may be even more interesting. Future additives may be based on ionic interactions, but also carriers with high α and β values should be tested. The latter type of carriers will not contribute to excessive current in the EME system, and this is an important practical point that should not be overlooked.

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