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Electromembrane extraction (EME): Fundamentals and applications

Rafael Oliveira Martins [a], Giovanna Lopes de Araújo [a], Rosineide Costa Simas [b,*], Andréa Rodrigues Chaves [a]

[a] Instituto de Química, Universidade Federal de Goiás, Avenida Esperança s/n, Campus Samambaia, Goiânia, GO 74690-900, Brazil
[b] Escola de Engenharia - Faculdade de Química, Universidade Presbiteriana Mackenzie, São Paulo, SP 01302907, Brazil

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ABSTRACT

Conventional sample preparation methods are commonly used to ensure the best analytical response of the method. However, these methods still include large solvent and sample consumption, and lengthy operation time, among other drawbacks, contributing to the unfriendly environmental status of such approaches. On the other hand, the miniaturization of such conventional methods can lead to procedures that use less or no volume of organic solvents as well as the automation of such methods resulting in less environmentally harmful methodologies. Electromembrane extraction (EME) is a miniaturized liquid phase extraction, that uses an electrical field to drive the analytes from the sample (donor phase) to an acceptor phase through a hydrophobic membrane containing a supported organic solvent on its porous membrane. Since its introduction, the technique has shown great potential in the preconcentration and clean-up of complex matrices, such as biological fluids and environmental analyses. However, the performance of the method includes many parameters and theoretical understanding to improve the analytical performance of the method. With the increasing number of studies reporting EME application for different matrices, this review has as its main goals to bring an overview of the fundamentals involved during the EME extraction, from the theoretical point-of-view to the current applications of these methods for the evaluation of different complex matrices. We believe that this overview of the fundamentals and current application of EME extraction can be used as a guide to inspire the development of new and advanced EME methods.

1. Introduction

Over the decades, the application of analytical strategies has been demonstrated as the perfect approach to provide the qualitative and quantitative evaluation of organic and inorganic compounds of many matrices [1]. Nevertheless, this evaluation is always a challenge, especially while analysing complex matrices, such as biological samples [2,3]. Matrices of this kind, have in their composition several endogenous compounds, and most of the time, low concentration of the target analyte(s) in the samples, which affects the analytical performance of the method [4]. To overcome the complexity of the sample, usually, a sample preparation step is performed before the analysis itself. The sample preparation step is responsible for ensuring the selectivity and analytical sensitivity of the method, ultimately reflecting on the analytical system integrity [5]. Regarding this, conventional sample preparation techniques, for instance, liquid-liquid extraction (LLE) have been extensively used over the decades to reduce the complexity of many matrices and contribute to the success of proposed analyses, allowing the obtention of reliable results and better analytical response [6].

LLE is a classic sample preparation technique used for the extraction and pre-concentration of analytes in different matrices. This technique is based on analyte partition equilibrium. In a medium composed of two immiscible liquids, the extraction of the target analyte is favored according to its partition coefficient between the two liquids [7]. Although the technique has excessively been applied since its introduction, this conventional method requires a large use of organic solvent, leading to a high-cost performance. Besides, LLE methods are time-consuming and extremely difficult to work with automatic methods. The aforementioned drawbacks contribute to the environmentally unfriendly status of LLE methods [8,9].

Therefore, there has been greater investigation for analytical procedures that use less, or no volume of organic solvents, combined with a reduction in the volume of samples required, what is also expected is a

* Corresponding author.
E-mail address: 1165652@mackenzie.br (R.C. Simas).

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sample preparation technique that provides a shorter operating time and ensures greater selectivity and/or specificity in extraction. In this sense, the miniaturization of analytical systems includes sample preparation techniques. These methods propose the development of procedures that are less harmful to the environment and exhibit extraction efficiency equivalent to or better than those already obtained by the application of conventional methods [10,11].The spotlight on the application of miniaturized methods only came after the introduction of solid-phase microextraction (SPME) in 1990 by Pawliszyn et al. [12–15]. On the other hand, it was only in 1996 that the first studies describing the use of liquid-phase microextraction (LPME) systems were reported by Dasgupta et al. [8,16] and Cantwell et al. [17] demonstrating large applications [18–23,13,24–26,25,27]. Since then, several miniaturized systems, each one with a distinct characteristic, have emerged.

Concerning the introduction of new LPME methods, electromembrane extraction (EME) has been featured over the years as one of the most promising approaches to solving the matrix complexity of many samples [28]. This miniaturized procedure was first described by Pedersen-Bjergaard and Rasmussen (2006)[31] as an approach for sample preparation of biological fluids. The extraction is based on the application of a potential difference across a membrane immobilized with an organic solvent, called supported liquid membrane (SLM), immersed in the sample solution. Inside the membrane, there is a solution called the acceptor phase. To ensure the ionization of the target analyte(s) the pH of both the acceptor and donor phases (sample) is controlled according to the type of analyte involved in the extraction. The system involves the presence of two inert electrodes, each of them in contact with their respective phase (donor and acceptor). After the application of the potential in the electrodes, it is expected that the compounds migrate from the sample pole (donor solution) to the pole inside the membrane (acceptor solution) [29,30]. The involved phenomena will be discussed in the next session of this review.

Since its introduction in 2006, more than 600 studies using the technique have been published according to the platform *Web of science*. Most of the reported papers describe the application of EME as a sample preparation step for different biological matrices [31–34]. Although there is a high level of applying EME for biological fluids, the technique has also been reported as a powerful analytical approach to the sample preparation of other complex matrices, such as food [35–37] and environmental samples [38,39]. Regarding the potential of the technique, this study aims to bring an overview of the main theoretical fundamentals of the technique. Moreover, the application of the method as a green analytical procedure to deal well with the complexity of different matrices ensures the analytical performance and instrument integrity of the method.

1.1. BASIC principles of EME extraction

Since its introduction, many efforts have been made to understand the EME procedure. Nowadays, it is agreed that the EME procedure involves two known concepts, that is the, partition (diffusive migration) and the electrophoresis procedures (electrokinetic migration) [40]. Although each process occurs during the EME extraction, it is the electrophoresis process that is the main carrier process responsible for driving the analytes from the donor to the acceptor solution. We can describe the EME system considering the following parts: (I) Donor phase: an aqueous phase that represents the sample, as a consequence, it contains the target analyte(s). (II) a hydrophobic porous membrane that contains an organic solvent supported in its porous. (III) Acceptor phase: an aqueous phase in which the analytes will migrate after the application of the voltage. That being established, it is also important to highlight that the electrokinetic migration of the analytes will only occur in their ionic form, which can be achieved by the pH control of the donor and the acceptor phases. For the extraction of acid analytes, the pH of the acceptor and donor phases must be above the pKa value of the target analyte(s), and vice-versa for the extraction of basic compounds. The

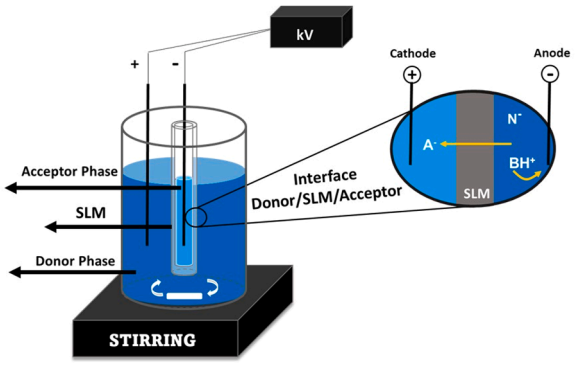

Fig. 1. Schematic Illustration of the experimental arrangement of the electromembrane extraction system.

ionized analytes from the donor solution are then driven to the donor/SLM interface, crossing the membrane. Accordingly, due to their distribution coefficient, and especially the electrical field, they are finally released in the aqueous phase. The migration of the analytes from the sample to the organic phase of the SLM also the considers distribution coefficient between the two phases, which is strongly linked to the physicochemical properties of the analyte(s). As was discussed, pH control represents a fundamental parameter to be evaluated during the EME performance. To overcome the difficult task of ensuring the ionization of the target analyte(s), in EME extraction, this pH control is commonly performed by the utilization of dilute acid and alkaline solutions or buffers solution [29]. The representation of the EME system is illustrated in Fig. 1.

The electrokinetic migration is driven by the application of a DC electric potential. This potential is applied to the two inert electrodes that come in contact with the donor and acceptor phases. The electrodes are positioned according to the objective of the extraction [41]. In the case of extraction of acidic analytes, where the conjugate base is negatively charged, the anode is placed in the acceptor phase solution and the cathode in the sample solution. Similarly, for the analysis of compounds with basic characteristics, the positively charged conjugate acid is attracted to the cathode inside the membrane containing the acceptor phase. As a result, due to the polarization of the electrodes, the electrokinetic migration of the charged compounds from the electrode to the solution immersed in it will occur [29].

Experimentally, initially, the SLM membrane is impregnated with the organic solvent, by immersion for a few seconds in a suitable solvent. Then, the acceptor solution is inserted inside the hollow fiber (HF). The membrane previously impregnated with a solvent that also contains the internal acceptor phase is immersed in a support-carrying the sample. Following that, the electrodes are then positioned into the corresponding solutions, and the potential is finally applied to the system. The system can be stirred by means of a magnetic bar. After extraction, the acceptor phase is collected with the aid of microsyringes and sent to the analytical system, which can be liquid chromatography (LC), gas chromatography (GC), and mass spectrometry (MS) systems, among others [42].

Following this principle of extraction, Shang et al. [43] postulated the main advantages of the EME process, some of which include:

(I) Extraction time: Comparing the EME technique and some conventional LPME methods, the application of the electric field in EME increases the extraction speed. The mass transfer between the donor and the acceptor phase is potentially improved as well, which in turn, causes time extraction of EME methods performed normally < 20 min.

(II) Clean-up: The hydrophobic membrane used in the extraction acts as a physical barrier against the matrix endogenous compounds, thus, performing the clean-up of the sample.

(III) Selectivity: The selectivity of the technique is ensured by two parameters, the pH control, and the accurate SLM solvent choice. Ensuring adequate pH control promotes the ionization of the target analytes, making them able to cross the membrane reaching the acceptor phase. The SLM solvent needs to be chosen according to the properties of the target analyte, therefore, choosing the right SLM solvent will allow only the desired analyte (s) crossing this solvent to reach the acceptor phase.

(IV) Enrichment of trace-level compounds: The preconcentration ability of the technique is mainly linked to the ratio of donor/acceptor phase volume. Huang et al. [44] pointed out preconcentration factors of 108–140 using 3 mL of sample solution. The acceptor phase volume will depend on the volume properties of the membrane; however, commonly used volumes are in the μL range.

Although these advantages, the extraction of some species can be challenging by EME. In general, high-polarity species do not exhibit excellent extraction efficiencies in EME. Molecules with acidic sites are further affected by these disadvantages, since there are no solvents to assist mass transfer, such as 2-Ethylhexyl phosphate (DEHP) for basic compounds. Therefore, simultaneous extraction of high and low-polarity compounds is hardly achievable with EME [43]. Another limitation of EME is related to its restricted application to analytes present in aqueous samples. In this regard, some studies have been demonstrating the use of a portion of organic solvent in the donor phase. However, this type of approach can generate an unstable system by increasing the current when dissolving the SLM. Thus, its implementation in non-aqueous matrices is still a major challenge [44].

In summary, the application of EME as a sample preparation step can ensure the preconcentration of the analytes through the application of the electrical field, which will drive the charged compounds to the acceptor phase [45]. In addition, the clean-up process of the technique can be of great service when dealing with challenging matrices, such as biological and environmental samples [46]. On the other hand, this technique includes the evaluation of many parameters, which directly affects the analytical performance of the method.

2. MASS transport in EME extraction

We can assume the EME process is a hybrid process composed of both the electrophoresis and the distribution mechanisms. Although these two processes occur at the same time, electrokinetic migration is the main mechanism responsible for driving the analytes from the donor to the acceptor phase. In 2016 Huang et al. [44] described the use of a steady-state model to describe the mass transport of the analyte across the membrane.

According to the authors, applying such an approach reduces the complexity of understanding the involved calculations, especially since these models are based on the Nernst-Planck flux equation. Eq. (1) represents the analyte flux J_i (in moles per unit time and area) across a hydrophobic membrane.

$$Ji = \frac{-Di}{h}\left(1+\frac{v}{lnx}\right)\frac{(x-1)}{x-expexp\,(-v)}\,(Cih - Ci0\ exp\ exp\,(-v)\,) \tag{1}$$

Following Eq. (1), D_i represents the diffusion coefficient of the molecule, h is equal to the thickness of the SLM, v is equal to the dimensionless driven force, which is defined by Eq. (2), and ✗ is the ion balance between the donor and acceptor phase. Finally, the second part of Eq. (1) shows the C_{ih} represents the analyte concentration at the SLM/sample interface. C_{i0} refers the concentration of the target analyte at the acceptor-SLM interface.

$$v = \frac{ZiF\Delta_{\varphi}}{RT} \tag{2}$$

In Eq. (2) *Zi* represents the charge of the analyte, F is the know Faraday's constant, Δ_{φ} is in reference to the potential differences across the SLM, R is the gas constant, and finally, T is the temperature. Observing and interpretating Eq. (1) it is correct to assume that the analyte migration from the donor phase to the acceptor phase through the SLM membrane, is linked to the following parameters: (I) the analyte's diffusion coefficient in the SLM, (II) the thickness of the SLM, (III) the ion balance across the SLM, (IV) the temperature of the medium and (V) The applied voltage.

Although Eq. (1) can be used to describe the movement of the analyte across the membrane, it doesn't include the time dependent on the analyte to cross the SLM membrane. Bearing this in mind, we can add the time-depending assuming the following points:

(I) The analyte(s) takes some time to cross the SLM which corresponds to the SLM lag time.

(II) The mass transfer from the analyte between the two phases is mainly affected by the transport trough the SLM.

(III) The convection from the sample and acceptor phase is efficient, and the bottleneck of the mass transport is crossing the SLM.

(IV) The analytes are unidirectionally driven and completely recovered in the acceptor phase.

Assuming such points in the time-dependent model, we can describe the concentration of the analyte in the acceptor phase by Eq. (3).

$$\mathbf{C}_{\mathbf{A}i}(\mathbf{t}) = \frac{\left(V_D C^0_{Di} \;-\; C^0_{Di} * expexp \;-\; \left(\; A_f * P_i^{D\ \to A} * t\right)\; \left(V_D + K^*_d *\; V_m\right)\right.}{V_A} \tag{3}$$

In Eq. (3) we have V_D as the total volume of the sample, C^0_{Di} the initial respective concentration of the analyte present in the sample, A_f represents the active surface of the SLM membrane, $P_i^{D\ A}$ the SLM permeability of the analyte from donor to acceptor phase, V_m is the volume of the SLM, V_A is equal to the acceptor volume, and finally, K_d* is the distribution coefficient.

Theoretically, many parameters affect the mass transfer of the analyte through the SLM between the two phases. Nonetheless, according to Droin et al. [28] experimentally, we can assume the major parameters being , (I) the SLM composition, (II) the extraction time, and (III) the extraction voltage. Despite the fact that these parameters are the ones that most affect mass transport, a complete study involving other parameters is commonly applied.

3. EME optimization

The success of the method is linked to the optimization of the main variables involved during the extraction. A theoretical study was demonstrated by Seip et al. [47] of some parameters that influence mass transfer during EME extraction. The first parameter to be considered is the equilibrium time between the analyte(s) and the acceptor phase. According to the study, the acceptor phase starts to have the first analyte concentrations from 5 to 15 s after the start of the extraction (lag time). Increasing the tension to a certain level favors the migration of species.

The decrease in sample volume is associated with the increase in recovery and contributes to the increase in the surface area of the membrane used. On that account, the influence of some parameters such as SLM, acceptor phase composition, extraction time, voltage, stirring speed, the effect of the salt addition, and membrane type always need to be evaluated.

3.1. Supported liquid membrane

We can describe the SLM as a thin organic solvent layer that is immobilized in a porous hydrophobic membrane [48]. The membrane itself acts as a physical barrier against the matrix endogenous compounds and suspended particles [49]. However, the application of the SLM allows the transport of the analytes after the application of an electrical field from the donor to the acceptor phase. When selecting the SLM solvent some aspects need to be ensured (I) low water solubility; (II) low vapor pressure; (III) high polarity polarizability; (IV) high hydrogen bonding capability (high hydrogen bond basicity for cations and high hydrogen bond acidity for anions); and (V) reasonable hydrophobicity ($6 > \log P > 2$) [28,50].

For the extraction of basic low polarity compounds ($\log P > 1.5$) the literature has been highlighting the application of 2-nitrophenyl pentyl ether (NPOE). The application of NPOE has shown potential effects on the mass transfer of basic low-polarity compounds with $3 < \log P < 5.5$. However, when applied to more polar compounds ($\log P < 1.5$) the mass transport of the analytes through the NPOE solvent is not as efficient [28,51]. For the extraction of such compounds, adding a hydrophobic ion-pairing reagent is the favored decision. Normally, DEHP is used to improve the extraction of more polar compounds. For the extraction of basic compounds with different polarities, the mixing of NPOE and DEHP has been reposted as an efficient strategy [52,53]. When there is a focus on the evaluation of acid analytes, it is expected that the SLM solvent has a strong bond acidity. Some alcohols, such as 1-octanol and 1-nonanol have been showing compelling potential for the extraction of acid compounds [28].

3.2. Composition of the donor and acceptor phases

In EME, the composition of both phases plays a key role in the efficiency of analyte extraction. The solvent used as SLM must present the following specifications: low or no solubility in aqueous solutions, low vapor pressure, low viscosity, low conductivity, and high purity. For the success of the extraction, both phases must have the pKa under control, as they must guarantee the ionization of the analytes present in the donor phase, as the extraction is favored with the analytes in their ionic form. For the procedure, analytes with basic characters are extracted in the SLM with a positive electrode placed in the sample and a negative electrode placed in the acceptor solution. The reverse configuration is valid for the extraction of compounds wiacidic characters. In both phases, it is necessary to avoid sudden changes in pH, especially after the application of electrical potential. It was demonstrated through a study with acid-base indicators [54] that the process of electrolysis by applying the potential can change the pH of the medium. Therefore, it is recommended to use buffer solutions capable of ensuring the stability of the pH of the phases (donor and acceptor) during the extraction process [55].

According to Eq. (1), the ion balance ✗ between the donor and acceptor phase affects the mass transport of the analyte. We can describe the ✗ as being the division of the total ionic concentration of the donor phase by the total ionic concentration of the acceptor phase (Eq. (4)).

$$\chi = \frac{\sum i\, C_{ih} + \sum k C^*_{kh}}{\sum i C_{i0} + \sum k\, C^*_{k0}} \tag{4}$$

In Eq. (4) we have C^*_{kh} is the concentration of the kth anionic analyte in the donor phase, and the C^*_{k0} is the kth anionic concentration of the analyte in the acceptor phase. Although Eq. (4). Can be used to describe the partition coefficients of the ions into the SLM, it describes as being equal for cations and anions. To describe the ✗ it should consider individual partition coefficients for the cations (i^{th}) and anions (j^{th}) as is presented in Eq. (5).

$$\chi = \frac{\sum i\, C_{ih}\, K_{ih} + \sum i C^*_{jh}\, K_{jh}}{\sum i C_{i0} K_{i0} + \sum i C^*_{j0}\, K_{j0}} \tag{5}$$

In Eq. (5) we have K_{ih} and K_{jh} representing the distribution coefficients for cations and anions in the SLM. The sample/SLM interface concentrations of the analytes are represented by C_{ih} and C^*_{jh}. The corresponding distribution coefficient in the SLM/acceptor interface of cations and anions are K_{i0} and K_{j0}, respectively. Finally, the SLM/acceptor interface concentration of the charged analytes is given by the C_{io} and C^*_{jo}. After analysing both Eqs. (1) and (5), it is correct to assume that the mass transport of the analytes increases with (a) voltage increases, (b) rising diffusion coefficient, and (c) reduction of the SLM thickness.

3.3. Voltage

Concerning the basics of EME extraction, electrokinetic migration is the main process that drives the analytes from the donor to the acceptor phase through the SLM. In 2007, Gjelstad et al. [56] described for the first time, the simulation of the analyte flux in the system based on the Nernst-Planck equation. According to the authors, we can describe the steady-state flux J_j of an ionic analyte J though the SLM under an electrical field (E) by the Nernst-Planck equation:

$$J_j = -D_j \frac{d_{Cj}}{dx} + \frac{D_{jzje} E_{cj}}{kT} \tag{6}$$

In Eq. (6) D_j is defined as the diffusion coefficient of the ionic compound, Zj is the analyte's charge, Cj represents the analyte's concentration in the SLM interface, X is the distance from the SLM/acceptor interface, k is the symbol for the Boltzmann's constant, e represents the elementary charge, and finally, T is the absolute temperature.

As can be seen in Eq. (6) the first term described in the equation regards the diffusion of the charged analytes in the SLM while the second term is presented to describe the electromigration of the analyte(s) in the EME system. The study could experimentally prove that the transport flux of five drugs was strongly dependent on the potential difference applied over the donor/SLM/acceptor interface.

Normally, a very high electrical current is not used. Systems submitted to a high voltage are more susceptible to electrolysis processes, and because of that, the stability of the system can be affected by the presence of bubbles [9]. Electrolysis is a common process, observed at the cathode and anode during EME extraction, that is also observed in EME devices using free liquid membranes (FLM). To minimize the electrolysis process, buffer solutions are commonly used. However, increasing the presence of ions in the donor and acceptor phases can lead to an ion competition between the ions from the buffer and the ones from the donor phase. The ion competition between the buffer and the donor phase can lead to a decrease in the mass transport of the analytes from the sample, therefore, consequently decreasing the analytical performance of the extraction [55].

3.4. Extraction time

According to Douin et al. [28], the ideal extraction time is achieved when the EME system reaches its equilibrium. As a result, the extraction recovery factor is directly linked to the minimum time that the system takes to reach extraction equilibrium. On account of the voltage application in EME systems, extractions using this approach tend to be faster than hollow fiber liquid-phase microextraction (HF-LPME) methods. On average, EME extractions do not take more than 15 min to reach

extraction equilibrium. Meanwhile, HF-LPME methods require extraction times ranging from 30 to 60 min depending on the characteristics of the analyte and the geometry of the system.

3.5. Stirring speed

According to Rouhollahi et al. [57] agitation in the EME system promotes an increase in mass transfer speed and electromigration, reducing the thickness of the double layer around the SLM, and increasing the mass transfer rate of analytes from the donor to the acceptor phase. Moreover, the authors confirm that a high agitation speed influences the stability of the system, so it must be evaluated in order to maintain the integrity of the system and contribute to a reduction in the extraction time.

3.6. Salt addition

As in HF-LPME, the addition of salts in EME extraction changes the ionic strength of the system, in order to increase the extraction recovery rate. Seip et al. [58] evaluated the effect of the addition of 2.5% NaCl (m/v) on the extraction of 8 basic drugs. The salt addition had a negative effect on the extraction yield due to the increase of ions in the sample solution, causing an ion competition between the ions of the sample and the ones from the salt. The same behavior was observed by Rouhollahi et al. [57] during the extraction of clozapine from human plasma samples. According to the author, the presence of salt increases the ionic substances in the sample leading to a consecutive increase in the ionic balance, resulting in competition between interfering ions and the charged analytes from the sample. Therefore, the addition of salt in EME systems should always be carefully evaluated.

3.7. Membrane type

EME extraction can be classified according to the type of membrane. The configurations can be classified into membranes, known as SLM and FLM (Fig. 2). The SLM configuration comprehends devices that use a supported solid as a membrane, which has an organic solvent impregnated in its porous. The most commonly used material as SLM is porous polypropylene (PP), found in the hollow fiber (HF) form or a thin membrane. This material is generally used for being cheaper, which is a technical requirement, mainly because they are discarded after extraction. Alternatively, other materials can be used as porous supports, such as polyvinylidene fluoride (PVDF) or polytetrafluoroethylene (PTFE). The volume of acceptor placed on the membrane depends on the dimensions, thickness, and porosity of the material used, ranging from a few microliters for thin membranes to tens of microliters for HF membranes [28]. Another option for EME extractions is the use of a device that does not use physical support to stabilize the organic layer, termed free liquid membranes. For FLM methods, the study of the solvents needs to consider the characteristics of the target analyte ensuring the integrity of the extraction system in question. Some of the most used solvents in the literature are aliphatic alcohols, for instance 1-octanol and 1-heptanol, together with water for the formation of the immiscible system [30].

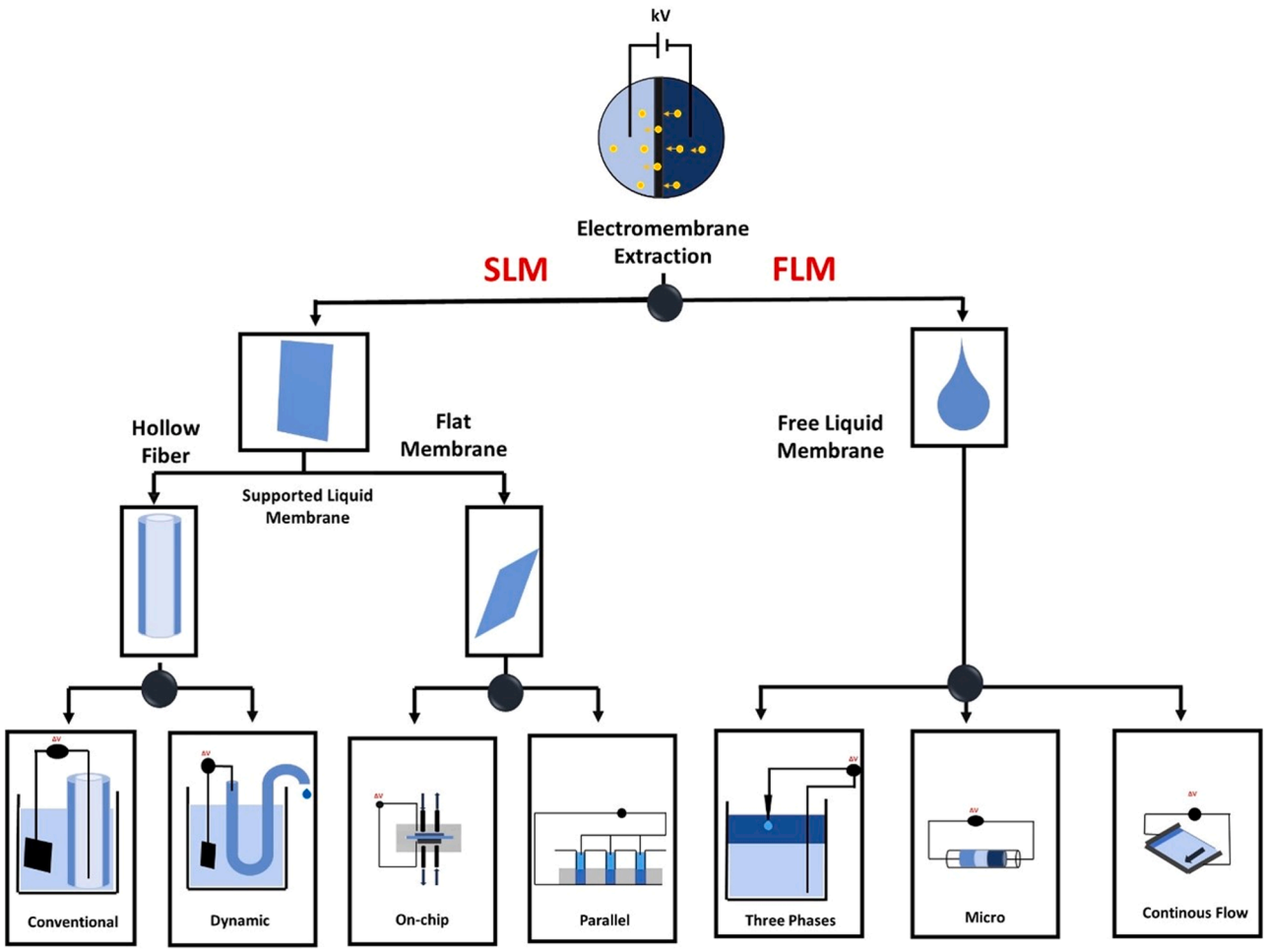

Fig. 2. Possible configurations for electromembrane extraction according to the mode of liquid membrane used. Adapted from Drouin et al. [28].

4. EME analytical Configurations

4.1. SLM mode

Extraction assays using an SLM in HF have become more popular due to their great versatility and application [59]. Although this method was initially the most widespread, the literature points the increasing publications testing of some modifications of the conventional approach to improve the extraction efficiency for different analytes [55,60,61]. Recently, Tahamasebi et al. [62] described the determination of propylthiouracil (PTU) with high polarity in urine samples, using a membrane modified with copper nanoparticles (CuNPs). The authors reported an 80.0% recovery, and a detection limit (S/N ratio 3: 1) of 0.02 μg mL^{-1}. Their results demonstrated that the modification of the conventional HF could lead to better analytical performance for the analysis of a such complex sample. Additionally, the methods showed great capacity to carry out the PTU evaluation, which could help in the monitoring of such compounds in urine samples.

Dynamic mode electromembrane extraction (DEME) was introduced in 2015 by Yamini et al. [34]. This operating mode was initially proposed to analyze ionized compounds in different biological matrices. In this system, the HF is impregnated with an immiscible organic solvent. The solution containing the sample is pumped into the cell located on the outside of the membrane, with the aid of a peristaltic pump. The upper end of the membrane is connected to a micro syringe pump, and the lower end is directed to a microvolume tube, which acts as an acceptor phase. This small volume is pumped through the interior of the fiber (lumen). The continuous movement of the donor and acceptor phases ensures an increase in extraction efficiency in comparison to the conventional method, and a consequent decrease in extraction time (Fig. 2) [34].

Commercial polypropylene hollow membranes have been widely used for their great versatility [63]. However, this material suffers greatly from the influence of applied voltage in some direct current (DC) systems. Due to the small dimensions of the membrane, it is usual to observe the formation of bubbles in the acceptor phase after the application of the potential, which can decrease the extraction recovery [64]. In 2008, flat membrane-based EME (FM-EME) systems were introduced [65] the use of such membranes demonstrated a better performance compared to the conventional system using the hollow membrane [64].

In 2010, an electromembrane extraction system in the form of a chip (On-chip electromembrane extraction) (Fig. 2) was introduced by Basheer et al. [66]. The proposed device comprised of a 25 μm polypropylene flat membrane, between two polymethylmethacrylate (PMMA) plates with channel structures linked toward the membrane. In the experiment, the membrane pores were filled with 2-nitrophenyl octyl ether (NPOE). The solution containing the sample (donor solution) was pumped through the flat membrane. After the application of 15 kV as the potential the basic drugs were selectively extracted from the donor solution to the acceptor solution, and the acceptor solution was collected and analysed by capillary electrophoresis. The chip format system brought some advantages, for example 1) The sample solution and the acceptor phase were supplied in a continuous flow. (2) Real-time online analyses could be used to monitor metabolic reactions (3) Mass transfer was favored due to the greater proximity between phases [67].

Another approach introduced in 2013 by Gjelstad et al. [68] is known as Parallel Artificial Liquid Membrane Extraction (Pa-EME) [68]. In this mode, a plate containing the donor solution and another plate containing an aqueous acceptor solution are separated by a polyvinylidene fluoride membrane, where the organic solvent is impregnated to form the SLM. The pH plays an important role in this approach. For analysis of basic analytes, the pH of the donor solution is adjusted to maintain the analytes in their neutral form. The pH of the acceptor solution is also adjusted to ensure the ionization of these compounds and prevent the compounds from returning to the donor phase [69].

4.2. FLM mode

Despite the popularization of the SLM mode, there were still controversies regarding the immobilization of the solvent in the membrane pores [70]. In an attempt to overcome these difficulties, FLM devices were introduced. This category includes devices that do not use physical support for stabilization. The system consists of the use of solvents capable of exhibiting low solubility, favoring the formation of phases. Systems operating in FLM mode are known as three-phase, micro, and continuous flow [28].

In the three-phase configuration, as well as the others that use the FLM principle, there is no stabilization of the organic layer by any polymeric support. This mode is characterized by the use of three phases in a vertically structured system (Fig. 2), in which the phases are separated according to the density and miscibility of the liquids involved in the system. After structuring the system, the acceptor phase is introduced in the form of an aqueous micro drop at the tip of a micropipette. The optimized extraction mode can offer process automation and MS coupling is also possible for direct analysis, and an enrichment factor of the target analyte(s) in the matrix of up to 80 times is usually observed [71].

The micro mode, also known as μ-EME, uses a structuring of the system in the form of a horizontal sandwich, with the organic layer between the acceptor and donor solutions (Fig. 2). The great advantage of this system in relation to the others is the amount of volume that the method requires, being able to perform the procedure with a low sample volume (volumes less than 1 mL) [28,55,72].

In continuous flow electromembrane extraction (CF-EME), the system is assembled in the form of a chip (Fig. 2). The donor phase containing the ionized analyte flows through the cell while an interface between the aqueous and organic phases is maintained due to the difference in surface tension between the two liquids. After the ions come into contact with the electric field which is perpendicular to the direction of the flow, they are directed to the acceptor phase. The method takes its name precisely because the sample is constantly renewed with the aid of a syringe pump. Like other techniques, continuous flow extraction uses a low sample volume [73].

The search for different materials for membranes has generated an increasing introduction of new EME approaches. One of these approaches is the use of biopolymer-based membranes (or biomembranes) to perform the extraction of charged analytes. The method using biomembranes has been considered an almost solvent and an ion-pairing reagent-free approach. It has proven great potential as a greener analytical approach [74].

4.3. Gel-Electromembrane extraction

According to Tabani et al. [74], the first study reporting biomembranes in gel electromembrane extraction (G-EME) was described in 2015 by Hidalgo et al. [75] in which the authors reported an agarose film with silver nanoparticles (AgNPs) as gel-based in sheet shape for supporting dihexyl ether (DHE). In this approach, DHE acted as the organic extractant for the extraction of non-steroidal anti-inflammatory drugs. The agarose films of 20 μm thickness were compared with conventional polypropylene membranes (450 μm and 100 μm) and showed 10–70% more extraction efficiency in comparison with the traditional membranes. The authors also reported in 2017 the agarose gel for the extraction of basic drugs (rivastigmine, verapamil, amlodipine, and morphine) in wastewater [76]. The application of the method could perform the extraction of the drugs without the use of any solvent. The illustration of the device is presented in Fig. 3. The system involved the basics of EME in which we have a donnor and an acceptor phase. However, unlike SLM which is solid support, here a gel is in contact with both phases. Furthermore, most of the time, no organic solvent is necessary, making G-EME a greener approach in comparison with traditional and some miniaturized sample preparation methods.

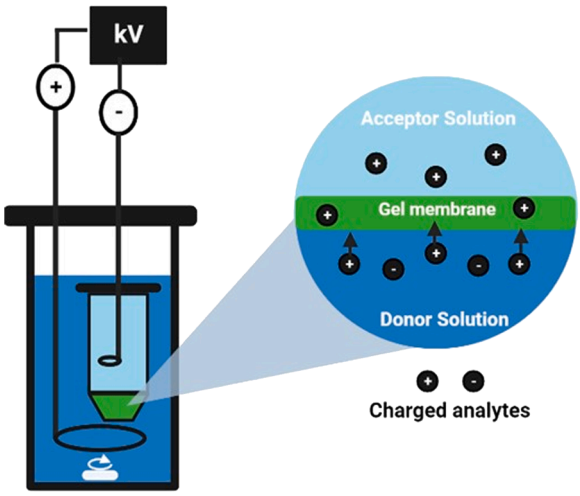

Fig. 3. Schematic illustration of the G-EME apparatus.

5. Reported EME applications

One of the main reasons that contributed to the advance in the use of miniaturized techniques in the liquid phase was the reduction of the amount of solvent used, compared to conventional extraction techniques. In this context, EME presents necessary attributes for the analysis of compounds at trace levels even in complex samples, such as biological and environmental samples. Table 1 shows a brief description of some literature reports on the types of EME used for determinations of different analytes in complex matrices.

5.1. SLM mode

The conventional EME using hollow fiber (Fig. 1) combines simplicity in its system and application for different analytes. In 2019, Mahadavi et al. [78] studied for the first time the effect of adding sugar (sugaring-out effect) instead of adding salt (salting-out effect) in the donor solution for the extraction of four basic drugs (pseudoephedrine, lidocaine, propranolol, and ketoconazole) in human plasma and urine. For the study, different types of sugars were evaluated at different concentrations, including glucose (0–30% w/v), fructose (0–30%), galactose (0–25%), and sucrose (0–30%) added on donor solution containing the sample. The authors observed a high number of hydroxyl groups (OH) in the structure of these sugars established, a strong tendency towards hydrophilicity, leading to a considerable increase in the mass transfer from the donor to the acceptor phase. The addition of 5 to 20% glucose was not only able to improve the transfer of analytes through the SLM but also improved the stability of the extraction system. However, concentrations above 20% of glucose led to an increase in sample viscosity, which reduced the recovery of the studied compounds. Under the optimized conditions of the extraction method, a linearity range was also obtained in the range of 5.0–1000.0 ng mL^{-1} and limits of quantification (LOQ) and detection (LOD) in the range of 5.0–10.0 ng mL^{-1} and 1.5–3.0 ng mL^{-1}, respectively. Along with this, recovery in the range from 41.2 to 80.8%, reveals the possible application of sugars as an option to improve the conventional EME extraction system.

Still using hollow fiber, Rahimi, et al. [98] performed the extraction of basic drugs (propranolol, diltiazem, and lidocaine) in plasma and urine. The authors used a combination of liquid-phase microextraction of single interface hollow fiber and electromembrane using DEME mode. The DEME extraction was optimized for the following parameters: applied voltage, extraction time, and pH of the acceptor solution. The optimized condition of the method consisted of using a voltage of 100 V, extraction time of 2 min, and acceptor solution at pH 12. The LOD for the optimized method was in the range of 0.12–0.36 ng mL^{-1}. Finally, the quantification of propranolol, diltiazem, and lidocaine in urine and plasma samples was performed, with the relative recovery obtained varying from 94.1 to 105.4%,

Extraction in food matrices was similarly reported using the flat membrane SML mode. Kamankesha, et al. [85] reported the use of a lab-on-chip device with the use of a flat membrane coupled to an LC system, for the extraction and determination of heterocyclic aromatic amines in grilled meat. The optimization of the extraction methodology adopted important parameters: the applied voltage (50–150 V), extraction time (10–30 min), the concentration of the donor phase (0–100 mmol L^{-1}), and 100 mmol L^{-1} for the acceptor solvent. The optimized methodology offered recovery values between 95% to 98% in three concentration levels (low, medium, and high). The detection limits obtained were between 0.9 to 1.7 ng g^{-1} for the 4 heterocyclic aromatic amines. The application of the EME extraction method proved to be efficient for the trace-level determination of analytes in grilled meat samples.

Although the application of on-chip electromembrane extraction has many advantages, the application of constant voltages can increase the joule heating through the SLM also leading to the increase of the electrolysis reactions. To avoid this drawback, in 2017 Karami et al. [82] reported the use of on-chip pulsed electromembrane extraction for the analysis of codeine, naloxone, and naltrexone in biological fluids. For the developed microsystem (Fig. 4) some important parameters were evaluated, the composition of the SLM, the pH effect of the sample and the acceptor phase, the effect of the applied voltage, the pulse frequency, and the flow rate. As specified by the authors, the application of a potential of 110 V led to better analytical results. Having established that, of this value, the analytical performance of the method was compromised due to the presence of the electrolysis process. The application of a pulsed voltage also increased the recovery of the analytes, in which a maximum extraction was achieved by the application of voltage for 12 s and an outage time of 6 s. Finally, the application of the method in real samples led to the obtention of recovery values ranging from 28.8 to 32.9% and LODs values ranging from 5 to 10 μg L^{-1} and 2–5 μg L^{-1} in plasma and urine samples, respectively.

PALME extraction was reported by Drouin et al. [99] for the extraction of highly polar compounds in plasma samples. The developed PALME system consisted of a donor and acceptor 96-well-plate device with conductivity provided by a piece of aluminum foil with 0.14 of thickness. The application of the PALME system could offer recovery values of up to 100% with low variability (<2%). Another PALME application was described by Olsen, et al. [100] in which the authors applied EME extraction in parallel mode for the extraction and identification of selective serotonin and serotonin-noradrenaline reuptake inhibitors in human plasma, in addition to proposing the automation of the extraction method using a 96-well pipettor for handling liquids. The optimized methodology proved to be efficient for the extraction of 8 analytes in 125 μL of human plasma, with recovery values ranging from 72 to111% and detection limits values in the range of 0.13 to 1.11 ng L^{-1} for the inhibitors studied. The automation of the extraction method with a semiautomatic pipettor still led to a considerable reduction in the total analysis time, and satisfactory application for real samples.

5.2. FLM mode

This operating mode has already been used for the extraction or clean-up of various analytes in complex matrices.

Oedit, et al. [90] described the use of an FLM system known as three-phase micro-electroextraction, or also as three-phase extraction. The authors reported the use of this mode for the determination by capillary electrophoresis of the biogenic amines: serotonin, tyrosine, and tryptophan, in urine samples. The modification of the system for the application of capillary electrophoresis allowed the formation of an electric field from the donor phase through the FLM to the acceptor drop (acceptor phase constituted by water and 1 M of formic acid). Under

Table 1
Applications of EME for the determination in complex matrices.

Analyte	Sample	Configuration	Sample volume	Solvent volume	LOD	LOQ	Rec. (%)	Refs.
Phenytoin	Plasma and Urine	conventional EME	3 mL	–	3.0 ng mL^{-1}	10.0 ng mL^{-1}	88–92	[77]
Pseudoephedrine, lidocaine, propranolol and ketoconazole	Plasma and Urine	conventional EME	8 mL	–	1.5–3.0 ng mL^{-1}	5.0–10.0 ng mL^{-1}	41.2–80.8	[78]
Chrome	Water	conventional EME	4.5 mL	–	0.006 ng mL^{-1}	0.02 ng mL^{-1}	70.6	[79]
Propylthiouracil	Urine	conventional EME	5 mL	–	0.02 μg mL^{-1}	–	80	[62]
Imatinib	Plasma	EME conventional	5 mL	2.5 mL	6.24 ng mL^{-1}	20 ng mL^{-1}	98–106	[80]
neuropeptides	Cerebrospinal fluid	(DEME)	250 - 1000 μL	500 μL	–	–	–	[81]
Ionized Species	Plasma and Urine	(DEME)	30 μL	–	0.5–1.0 μg L^{-1}	2.0 μg L^{-1}	–	[34]
Ephedrine and clonidine	Plasma and Urine	on-chip	2 mL	–	7.0 and 11 μL^{-1}	10 and 30 μg L-1	94.5–105.2	[52]
Codeine, Naloxone and naltrexone	Plasma and Urine	on-chip	2 mL	–	5–10 μg L^{-1} and 2–5 μg L^{-1}	10–15 and 15–20 μg L^{-1}	28.6–32.9	[82]
Mefenamic Acid, Diclofenac and Betaxolol	Plasma and Urine	on-chip	1 - 1.02 mL	–	2.0–5.0 μg L^{-1}	5.0–10.0 μg L^{-1}	–	[83]
Histamine	Urine	on-chip	1 mL	110 μL	4.0 and 10.0 μg L^{-1}	–	–	[84]
Biogenic Amines	sausage and Kielbasa	on-chip	2 mL	–	3.0–8.0 μg L^{-1}	10.0–25 μg L^{-1}	>95	[53]
Heterocyclic aromatic amines	Grilled meat	on-chip	60 μL	–	0.9–1.7 ng g^{-1}	2.9–5.6 ng g^{-1}	95 and 98	[85]
Atenolol, Betaxolol and propranolol	Plasma and Urine	on-chip	–	–	< 10 mg L^{-1}	–	30–39	[72]
Perchlorate	seafood	(Pa-EME)	25 mL	–	0.04 μg g^{-1}	0.125 μg g^{-1}	90–106.3	[86]
amitriptyline, Fluoxetine and Haloperidol	Water, Plasma, and Urine	(Pa-EME)	250 μL	4 μL	–	–	82–85	[87]
Basic polar compounds	Plasma	(Pa-EME)	300 μL	3 μL	–	–	90	[88]
Antidepressant medications	Plasma	(Pa-EME)	237 μL	3 μL	0.02–0.28 ng mL^{-1}	0.08–0.94 ng mL^{-1}	15–33	[89]
Acylcarnitines	Plasma	EME Three Phases	50 μL	150 μL	90–290 nM	–	–	[71]
Serotonin, Tyrosine, Tryptophan	Urine	EME Three Phases	375 μL	725 μL	15–33 nM	–	–	[90]
Nortriptyline, Haloperidol, loperamide	Human serum and urine	μ-EME	1.5 μL	1 μL	0.2–1.0 mg L^{-1}	–	19–52	[91]
nortriptyline, papaverine, Loperamide, Haloperidol	blood and urine	μ-EME	500 μL	14 μL	< 25 ng mL^{-1}	–	49–100	[92]
Ibuprofen, Ketoprofen, Naproxen, Diclofenac	Standard solutions, urine samples, human serum, and wastewater.	μ-EME	3 μL	3 μL	4–20 ng mL^{-1}	–	60–97	[30]
nortriptyline, Papaverine, Haloperidol	Standard solutions containing salt and protein, urine, and human plasma	μ-EME	1.3 μL	2.5 μL	0.1 to 0.15 mg L^{-1}	–	79–102	[93]
Chromium	Industrial Wastewater	μ-EME	60 μL	1 μL	0.06 ng mL^{-1}	0.20 ng mL^{-1}	91	[94]
Rivastigmine, Haloperidol, Verapamil, Clomipramine	Urine and Wastewater	CF-EME	2 mL	–	2.4 ng mL-1	8.0 ng mL^{-1}	8–10	[95]
Psychotropic drugs	Urine	G-EME	5 mL	–	15 μg L^{-1}	–	95.9–101.1	[96]
Morphine and codeine	Plasma and Urine	G-EME	7 mL	–	1.5 ng mL^{-1}	5.0 ng mL^{-1}	67.7–73.3	[97]

EME: Electromembrane extraction; DEME: Dynamic electromembrane extraction; Pa-EME: Parallel electromembrane extraction; μ-EME: Micro-EME, CF-EME: Continuous-flow electromembrane extraction; G-EME: Gel electromembrane extraction.

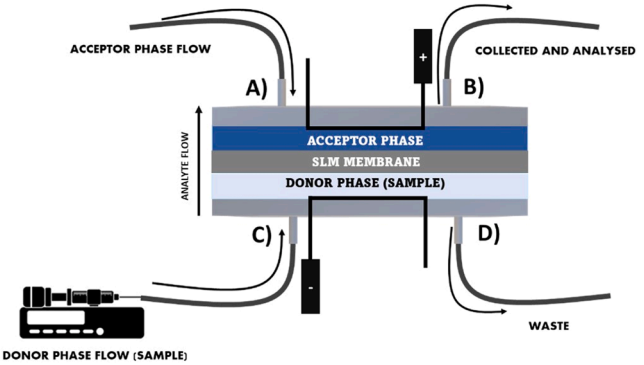

Fig. 4. Schematic illustration of the On-chip electromembrane system.

optimized conditions, the method was able to offer LODs of 15 nM and 33 nM for serotonin and tyrosine, respectively. These values were compared to those of other methodologies, showing equivalence between the existing methodologies.

The determination of basic drugs has also been described using an FLM system. Slampová and Kuban [92] described the use of the μ- EME system for the extraction and analysis of four basic drugs (nortriptyline, papaverine, loperamide, and haloperidol) in human urine samples and dried bloodstains. The system consisted of a glass vial containing the donor solution (aqueous phase) and a drop of organic solvent (acceptor phase) which appeared in the form of a free liquid membrane in the system. The optimized methodology (tension, stirring speed, extraction time, and pH of the aqueous phase) showed recovery values between 49 and 100% and a LOD in the range of 5–28 ng mL^{-1}. The authors stated that, due to the geometry of the droplet FLM system, the active area of

the interface between the FLM and the donor solution increased and ensured the rapid migration of analytes from the aqueous phase to the organic phase.

Dvorak et al. [93] also described the application of the μ- EME system for the extraction of basic drugs (nortriptyline, papaverine, and haloperidol) in biological fluids. For the assays, a three phases system was constructed, with a few microliter volumes of donor solution, FLM, and acceptor solution. The main optimized parameter was the solvents of the three-phase system. According to the results, the best analytical performance was achieved using 1.3 mL of acidified donor solution (10 mM HCl) across 2.5 mL of FLM (1-ethyl-2- nitrobenzene) into 1.3 mL of acidified acceptor solution (25 mM HCl) in 10 min at 150 V. Finally, the application of the developed methodology in real samples (human plasma and urine samples) led to the obtention of recovery values ranging from 79 to 102% and LOD values $\leq$ 0.15 mg L^{-1}. According to the authors, the methodology was successfully applied for the extraction of drugs in biological matrices, which could improve de detection of such compounds in low concentrations in such complex matrices.

Another application of an FLM system for basic drugs was carried out by Nojavan et al. [95]. The authors compared the use of continuous flow extraction and conventional EME extraction for the determination of four basic drugs (rivastigmine, haloperidol, verapamil, clomipramine) in urine and wastewater samples. Under optimized conditions, CF-EME extraction and conventional EME were able to extract the compounds of interest from complex matrices. However, when comparing the two methods, the conventional EME extraction method achieved higher extraction efficiency, lower detection limit, and higher pre-concentration factor than the CF-EME extraction methods. The methods showed detection and recovery limit values of 2.4 ng mL^{-1} and 8 and 10% for CF-EME extraction, respectively, and 0.6 ng mL^{-1} detection limit and 42–60% for recovery for the conventional EME method. Despite the conventional method having surpassed the CF-EME method, it was still able to efficiently extract and concentrate the analytes of interest in the studied matrices. This conveys that the used method, along with other FLM methods is a potential approach for the extraction of analytes in matrices as complex as biological and environmental ones.

5.3. G-EME applications

As described before, G-EME has been highlighted as one of the greenest analytical approaches to be applied to complex samples. In 2021, Abbasi and Seyed [96] reported the use of G-EME combined with emulsification-based microextraction (ME) by rhamnolipid bio aggregates for the evaluation of psychotropic drugs in urine samples by liquid chromatography-ultraviolet detection (LC-UV). According to the authors, the method could increase the mass transfer of the analytes by reducing the thickness of Nernst's diffusion film around the membrane/acceptor phase interface. Not to mention, in this configuration the use of a rotating cathode electrode plays a key role in the flux of the analyte between the phases, hence, reducing the time extraction. The analytical performance of the method showed LOD values of 1 and 5 μg L^{-1}. Finally, the application of the method in real samples demonstrated recoveries values ranging from 95.9 to 101%. The authors also claim that the application of rhamnolipid biosurfactants could effectively interact with the psychotropic drugs through hydrogen bonding and hydrophobic interactions, which increase the extraction recovery after G-EME. The method could be compared with some traditional approaches reported in the literature, such as Fakhari et al. [101] in which the researchers applied conventional EME for the extraction of psychotropic drugs in plasma and urine. In comparison with the traditional approach (25 min), the application of G-EME could offer an extraction time of 15 min and be performed without the use of an organic solvent. Besides, when comparing the analytical performance, the combination of G-EME with ME extraction provided the means to obtain a LOD of 15 μg L^{-1} in real urine samples, a lower value than the one obtained by the use of conventional EME (27,003,000 μg L^{-1}) by Fakhari et al. [101].

Rahimi et al. [97] described the use of a new G-EME approach, called "inside" gel-EME (IG-EME) for the extraction of morphine and codeine from biological fluids. In this study, the authors reported the application at the same time of the agarose gel membrane as both the gel membrane and acceptor phase. The optimization of the method considered the study of the donor phase (6.0), composition of the agarose gel (agarose concentration: 1% (w/v) in aqueous medium pH 3.0 and 15 mm of thickness), voltage (25 V), and extraction time (30 min). The optimized method could offer a LOD value of 1.5 ng mL^{-1} and a recovery value in the range of 67.7 to 73.8%. The greatest gain from this new configuration of G-EME was the ability to avoid unwanted changes in the acceptor phase volume.

In 2020, the same group reported another modification of the conventional G-EME. Behpour et al. [102] claimed the use of a rotating electrode gel electromembrane extraction (RE-G-EME) for the extraction of naloxone, naltrexone, and nalbuphine from urine samples. The developed device used a rotating electrode in contact with the acceptor phase. Based on their findings, the application of such an approach could improve the mass transfer between the gel membrane and the aqueous phase. The efficiency of the mass transfer was reflected in the obtained analytical performance. The optimized method showed LOD and LOQ values ranging from 0.3 to 1.5 ng mL^{-1} and 1.0 to 5.0 ng mL^{-1}, respectively. Recovery values were acquired in the range of 81.1–96.6% demonstrating its potential application for real urine samples. The authors also indicated the real influence of the rotation of the electrode in the aqueous phase in comparison with the traditional G-EME method. The study was performed in a time range of 5–30 min. According to the results, in low extraction time (<10 min) the extraction efficiency was almost similar to the RE-G-EME and G-EME. However, when the RE-G-EME device was applied in longer extraction times (25 min) a significant increase in extraction recovery in comparison with the G-EME method was observed.

As could be noticed, the application of conventional G-EME methods, shows a promise to be modified and improved. Although the method is still new in comparison with other EME configurations, G-EME has been widely applied, especially for the sample preparation of biological fluids. Even so, there are some relevant aspects to keep in mind. More research on this topic is necessary, particularly in applying the technique in different scientific fields. The introduction of new biomembranes, could result in a better application of such methods.

6. Comparisons between the configurations

Summarizing the advantages and drawbacks of the EME methods is a difficult task. Selecting the device or configuration will depend mostly on the objectives and the goals of an analytical method. However, we can try to highlight the advantages and the possible challenges of each configuration in an attempt to compare the best application for each system. Since its introduction, the HF-EME configuration has been widely reported. Therefore, many efforts have been done to compare the efficiency of the method against other EME configurations. In 2017, Nojavan et al. [95] compared the traditional HF-EME and CF-EME for the evaluation of basic drugs in urine and wastewater samples. Comparing those configurations, In HF-EME (SLM) we have the presence of the donor phase in a non-dynamic condition with the application of certain stirring movements. On the other hand, for CF-EME (FLM), the sample is constantly renewed in a continuous flow. According to the results, the application of conventional HF-EME could achieve better analytical performance for the evaluated compounds. The obtained results showed that the HF-LPME method demonstrated better LOQ and recovery values than the continuous flow, 0.6 ng mL^{-1} - 42–60% and 2.4 ng mL^{-1} - 8–10%, respectively. The authors described that for the extraction of basic drugs, the stirring of the donor phase was more efficient than flowing the sample.

Working with a low available quantity the sample is always

challenging. The use of some FLM-based devices can overcome the drawback of the sample amount, mainly since in this category samples in the μL range are commonly used. In 2020, Šlampová and Kubáň [92] reported the use of a two-phases μ-EME for the extraction and evaluation of basic drugs in biological samples by UV detection. The method was developed considering the use of 500 μL of sample volume for the entire process. The optimized method could demonstrate LOD values ranging from 5 to 28 ng mL^{-1} and recovery values of 49–100%. These values were close to the LOD values and better than the recovery values described by Karami et al. [82] (2–10 μg L^{-1} and 28.6–32.9%, respectively) for the extraction of basic drugs in biological fluids using an on-chip electromembrane approach with UV detection. The greatest advantage of the μ-EME approach in comparison with the SLM configuration is the use of μL of the sample. Šlampová and Kubáň [92] reported similar values using four times less volume than Karami et al. [82], 500 μL and 2 mL, respectively. Additionally, FLM configuration can achieve similar values to SLM configurations without the use of the supported membrane, which represents fewer costs for the methodology.

According to Drouin et al. [28], we can evaluate the advantages and drawbacks of EME configurations by considering the enrichment, recovery, low sample volume, throughput, infusion, and automation. Using Table 2, it is possible to have a critical view of some EME configurations, and help us review the positive and the negatives aspects of such devices.

In 2020, Aranda-Merino et al. [103] reported the investigation of the analytical performance of three EME configurations for the extraction and evaluation of non-steroidal anti-inflammatories (NSAIDs) in urine samples. The authors evaluated the use of HF-EME configuration, the μ-EME, and an SLM device which the authors denominated by flat membrane device (FL-EME). The authors stated that the geometry of μ-EME allowed continuous flow movement, which reflected on the surface contact of the analyte during the extraction by using low sample and acceptor phase volume. Although the μ-EME could achieve recovery values near 100%, as can be seen in Table 2 the μ-EME approach cannot ensure the preconcentration of the sample, especially because of the ratio between the two phases. For the SLM devices, such as HF-EME and FL-EME is hard to achieve recovery values near 100%. This observation was confirmed by the authors in which HF-EME and FL-EME achieved recovery values ranging from 17.2 to 26.9% and 22.7 to 34.3%, respectively. This finding was explained considering the large migration distance of HF-EME and FL-EME between the donor and acceptor phases, which is further than the μ-EME configuration. On the other hand, both HF-EME and FL-EME devices achieved high preconcentrate values, 85.6–134.3% and 8.8–13.7%, respectively than the μ-EME configuration, 0.93–1.03%. Finally, the study concludes that each configuration has its advantages and drawbacks, however, for obtaining low analyte concentration values, the methods of HF-EME and FL-EME can be the best option. Additionally, if high concentrations are expected, and the available sample volume is limited the application of μ-EME can be considered.

As mentioned in topic 3.1 for extraction of basic compounds the ideal SLM solvent must consider the polarity of the target compounds. Such limitation makes it hard the identification of compounds with different polarities from the same sample. With this in mind, since its introduction, G-EME has shown great potential to overcome such issues. Recently, Abbasi et al. [104] compared G-EME based on a solid agarose membrane while using deep eutectic solvents (DESs) as a liquid membrane for the determination of polar and non-polar bases drugs from biological fluids. According to the authors, both methods could extract base compounds with different ranges of polarity. Although EME performed with DES could lead to a better interaction with a large range of

Table 2
Features of EME configurations.

Parameter	HF-EME	Dynamic EME	On-chip EME	Parallel EME	Continuous Flow	μ-EME
Enrichment	+++	++	++	+	+++	+
Recovery	++	++	++	++	+	+
Low sample volume	++	++	+	+++	+	+++
Throughput	–	–	–	+	–	–
Infusion	–	–	–	–	–	+
Automation	–	+	–	+	–	+

Table 3
Advantages and drawbacks of some reported EME configurations.

EME Configuration	Advantages	Drawbacks
Conventional HF-EME	The use of μL of SLM solvent and acceptor phase; Use of sample volume ranging from μL to mL; Enrichment of trace level compounds; high recovery (up to 100%)	Normally performed with off-line methods; membrane cost and compatibility with organic solvents; In two phases HF-EME is necessary instrumental compatibility with organic solvents
DEME	The continuous movement of the donor and acceptor phases; The use of μL of SLM solvent and acceptor phase; Use of sample volume ranging from μL to mL; Automated and integrated methods	Membrane cost and compatibility with organic solvents; Low throughput
On-chip	Online methods and automated extraction; Pulsed voltage; The use of μL of SLM solvent and acceptor phase; Use of sample volume ranging from μL to mL; Possibility to the reduction of acceptor solution volume to nanoliter scale Enrichment of trace level compounds; high recovery (up to 100%)	Membrane cost and compatibility with organic solvents; Dead volume in the channels; When not fixing the system accurately, leaks can be observed
PALME	High throughput in comparison if HF-EME; reusable plate; SLM surface area is about 3 to 4 times smaller than in HF-EME; The use of μL of SLM solvent and acceptor phase; Use of μL as sample volume; Reduction on electrolysis and pH variation	Membrane compatibility with organic solvents; Difficult to automate
Three Phases	The use of μL of the sample, and organic solvents during the whole extraction process; Enrichment up to 80-fold because of the ratio between sample and acceptor phases; the possibility of automation and integrated methods	Difficult handling; Solvent selection needs to be carefully evaluated
μ-EME	Sample volume < 1 μL, all operation solutions can be evaluated after the extraction	Difficult handling; Low throughput; low enrichment of the analytes in comparison with the HF-EME
CF-EME	Extraction performed in a continuous flow of the sample; High enrichment of the compounds; The use of μL of the sample, and organic solvents during the whole extraction process	The selection of the solvents used needs to be carefully evaluated, Low throughput, and hardly automated
G-EME	Use of sample volume ranging from μL to mL; modification possibility of the gel membrane; no or almost no use of solvent volume	The applicability of the gel as a membrane; the viscosity of the gel can influence the mass transfer; hardly automated

HF-EME: Hollow fiber-Electromembrane extraction; DEME: Dynamic electromembrane extraction, Pa-EME: Parallel electromembrane extraction; μ-EME: Micro-EME; CF-EME: Continuous-flow electromembrane extraction; G-EME: Gel electromembrane extraction.

polarity compounds due to cation- π and π-stacking interaction, the use of agarose membrane in G-EME leads to an interaction by a hydrogen bond with polar and non-polar compounds. The application of such methods, especially G-EME can lead to the introduction of more green analytical approaches, without using conventional SLM and FLM solvents.

As described at the beginning of this topic, the comparison between the EME devices is extremaly challenging. The choice of the mode and geometry of the device has to take into account the goals, the analytical performance, and the costs of the method. In this study, a briefly discussion was presented in order to better comprehend the advantages and drawbacks of EME devices. As far as it is known, EME devices can be summarized by Table 3.

7. Conclusions and future perspectives

Since its introduction, EME has been presenting itself as a powerful and viable microextraction technique. The wide application of such a method can be observed by increasing diffusion in laboratories whose main objective is the efficient preparation of samples in complex matrices. As was presented in this review study, one of the greatest advantages of the technique is the availability of several modes of operation, additionally, the report of different devices for extraction. EME has brought the achievement of fast analyses compared to conventional sample preparation methods, namely resulting from the application of a voltage in the system. There is great potential for online coupling with the main detection methods. Due to the availability of several modes of operation, the technique can be applied to various matrices, whether environmental, biological, food, etc. According to what was discussed in this review study, extraction by EME still has the possibility of developing new devices and modes of operation. The research and development of new SLM's and FLMs along with biomembranes to be applied in G-EME methods holds challenges and future approaches, in order to obtain membranes with greater specificity for the target molecules. Another challenge for EME devices is the commercialization of these systems, as currently, most EME extraction systems are currently lab-made devices. The commercialization of these devices represents the development of devices that allow automatic sampling to reduce the number of manual operational steps, which in many cases LPME techniques require. Thus, greater availability of these automated and robust systems to serve more laboratories is expected, ultimately establishing these systems among the techniques for preparing miniaturized samples.

Declaration of Competing Interest

The authors have declared no conflicts of interest.

Data availability

No data was used for the research described in the article.

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