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ELECTROEXTRACTION AND ELECTRO MEMBRANE EXTRACTION, ADVANCES IN HYPHENATION TO ANALYTICAL TECHNIQUES-A CRITICAL REVIEW

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ABSTRACT
Electro membrane extraction or EME, is a miniaturized liquid-liquid extraction technique developed for sample preparation of aqueous samples prior to analysis by chromatography, electrophoresis, mass spectrometry, and related techniques in analytical chemistry. EME involves the use of a small supported liquid membrane (SLM) sustained in the wall of a porous hollow fiber, and application of an electrical field across the SLM. Electroextraction (EE) and electromembrane extraction (EME) are sample preparation techniques that both require an electric field that is applied over a liquid-liquid system, which enables the migration of charged analytes. First, the theoretical aspects of concentration enhancement in EE and EME are discussed to explain extraction recovery and enrichment factor. Authors described the overviews are provided of the techniques based on their hyphenation to LC, GC, CE, and direct detection.

KEYWORDS: Electroextraction, Electro membrane Extraction, Hyphenation, Analytical Techniques, Critical Review.

1. INTRODUCTION
Target compounds are extracted from an aqueous sample, through a µL-volume of organic solvent sustained as a thin supported liquid membrane (SLM) in the pores in the wall of a porous hollow fiber, and into an acceptor solution inside the lumen of the hollow fiber. Extraction is based on electrokinetic migration in an electrical field sustained across the SLM. The volume of the acceptor solution is typically 5-25 µL. The acceptor solution is an aqueous solution, and can be analysed by liquid chromatography (LC) or capillary electrophoresis (CE).

2. METHODOLOGY
A diagram of an electroextraction apparatus is shown. The apparatus consists of a vial with a conical bottom, a grounded platinum electrode, a capillary to inject the aqueous solution, and an adjustablem gold anode with a circular bottom that contacts the entire organic phase. EE is also often performed in a capillary electrophoresis capillary. This is referred to as capillary electroextraction, or cEE. In this set up, shown in figure 2, a capillary containing aqueous phase is placed in a vial of organic phase and surrounded by a hallow cathode. The outlet of the capillary is then grounded.

When EE is coupled to isotachophoresis coupled to capillary electrophoresis, limits of detection decrease to the nanomolar range and isotachophoresis takes only a few minutes to complete. Similar limits of detections are obtained when EE is coupled to liquid chromatography-mass spectrometry. Similar limits of detections are obtained when EE is coupled to liquid chromatography-mass spectrometry.

3. Advantages
The extraction is performed under the influence of an electrical field, the extraction selectivity can be controlled by the direction and the magnitude of the electrical field.

4. Applications
Electroextraction has been successfully employed in the separation of dyestuffs from wastewater. Electroextraction is better suited over other techniques for its ability to extract small amounts of dye from very dilute solutions. EE has also been effectively used in the separation of amino acids. This separation was done using an aqueous two-phase system of dextran-polyethylene glycol-water to stabilize the amino acids. The velocity of a particle crossing the phase barrier is directly proportional to the strength of the applied

electric field, so 100% separation is achieved with a strong enough field. EE is ideal for pharmaceuticals with low concentrations of active ingredient, such as those containing proteins and peptides, because of its ability to lower limits of detection for liquid chromatography and capillary electrophoresis. In addition, sample enrichment by EE helps overcome the low injection volumes and short optical path length of UV-Vis detectors that accompany CE. EE coupled to CE has been used to separate and analyse antisense oligonucleotides. Antisense oligonucleotides inhibit protein expression from their complementary base pair sequence and can treat certain diseases and genetic disorders.EE coupled to liquid chromatography also successfully detects low concentration metabolites in urine for the purpose of studying metabolic processes. EE-ITP CE has been used in the determination of the drugs clenbuterol, salbutamol, terbutaline, and fenoterol.

5. Description of various drugs analyzed by electromembrane extraction

1. Amar Oedit∗ et al., reported electroextraction (EE) and electromembrane extraction (EME) with the title "Electroextraction and electromembrane extraction: Advances in hyphenation to analytical techniques "is described as follows: Electroextraction (EE) and electromembrane extraction (EME) are sample preparation techniques that both require an electric field that is applied over a liquid-liquid system, which enables the migration of charged analytes. Furthermore, both techniques are often used to pre-concentrate analytes prior to analysis. In this review an overview is provided of the body of literature spanning April 2012–November 2015 concerning EE and EME, focused on hyphenation to analytical techniques. First, the theoretical aspects of concentration enhancement in EE and EME are discussed to explain extraction recovery and enrichment factor. Next, overviews are provided of the techniques based on their hyphenation to LC, GC, CE, and direct detection. These overviews cover the compounds and matrices, experimental aspects (i.e., donor volume, acceptor volume, extraction time, extraction voltage, and separation time) and the analytical aspects (i.e., limit of detection, enrichment factor, and extraction recovery). Techniques that were either hyphenated online to analytical techniques or show high potential with respect to online hyphenation are highlighted. Finally, the potential future directions of EE and EME are discussed.[1]

2. Stig Pedersen-Bjergaard et al., reported the recent trends in electromembrane extraction (EME) with the title "Electromembrane extraction–Recent trends and where to go" is described as follows: Electromembrane extraction (EME) is an analytical microextraction technique, where charged analytes (such as drug substances) are extracted from an aqueous sample (such as a biological fluid), through a supported liquid membrane (SLM) comprising a water immiscible organic solvent, and into an aqueous acceptor solution. The driving force for the extraction is an electrical potential (dc) applied across the SLM. In this paper, EME is reviewed. First, the principle for EME is explained with focus on extraction of cationic and anionic analytes, and typical performance data are presented. Second, papers published in 2016 are reviewed and discussed with focus on (a) new SLMs, (b) new support materials for the SLM, (c) new sample additives improving extraction, (d) new technical configurations, (e) improved theoretical understanding, and (f) pharmaceutical new applications. Finally, important future research objectives and directions are defined for further development of EME, with the aim of establishing EME in the toolbox of future analytical laboratories.[2]

3. Nicolas Drouin, et al,. reported liquid phase microextraction (LPME) techniques with the title "Electromembrane extraction: Overview of the last decade'' is described as follows: Sample preparation is a crucial step in any bioanalytical workflow. Nowadays, microextractions are very popular because of the reduction of the organic solvent and sample volumes, the analysis time, and the operating costs. Electromembrane extraction (EME) is one of the most recently reported liquid phase microextraction (LPME) techniques and was first described in 2006. It is based on the application of an electric field between two aqueous compartments separated by a layer of water-immiscible organic solvent, reducing the time needed for the extraction process to a few minutes, enabling extraction selectivity towards a broad range of molecule polarity ($-5 < \text{Log } P < 5$), recoveries up to 100%, and enrichment up to 100-fold. In this paper, EME literature was reviewed with special emphasis on recent mass transfer theory, and how this theory affects method development and the different technical configurations.[3]

4. Stig Pedersen-Bjergaard et al,. reported the analytical microextraction techniques with the title "Electromembrane extraction—looking into the future" Analytical microextraction techniques, including solid-phase microextraction (SPME) Arthur & Pawliszyn (Anal Chem 62:2145–2148, 1990), stir bar sorptive extraction (SBSE), Baltussen et al. (J Microcol 11:737–747, 1999), single-drop microextraction (SDME) Jeannot & Cantwell (Anal Chem 68:2236–2240, 1996), hollow-fiber liquid-phase microextraction (HF-LPME) Pedersen-Bjergaard & Rasmussen (Anal Chem 71:2650–2656, 1999), dispersive liquid-liquid microextraction (DLLME) Berijani et al (J Chromatogr A. 1123:1–9, 2006), and electromembrane extraction (EME) Pedersen-

Bjergaard & Rasmussen (J Chromatogr A 1109:183–190, 2006) have gained considerable interest in recent years. The latter technique, EME, differs from the others by the fact that mass transfer and extraction is facilitated by electrokinetic migration. Thus, basic or acidic analytes are extracted in their ionized form from aqueous sample, through an organic supported liquid membrane (SLM) and into an aqueous acceptor solution under the influence of an electrical potential. EME provides pre-concentration and sample clean-up, and can be performed in 96-well format using only a few microliters organic solvent per sample (green chemistry). Extraction selectivity is controlled by the direction and magnitude of the electrical field, by the chemical composition of the SLM, and by pH in the acceptor solution and sample. This trends article discusses briefly the principle, performance, and current status of EME, and from this future directions and perspectives are identified. Unlike traditional extraction methods, EME involves electrokinetic transfer of charged analyte molecules across an organic phase (SLM) immiscible with water. This process is still not fully characterized from a fundamental point of view, and more research in this area is expected in the near future. From author's point of view, such research at the interface between electrophoresis and partition will be highly important for future implementation of EME.[4]

5. Wajid AliKhan et al., reported liquid-phase microextraction and electromembrane extraction (EME) with the title ''Hollow fiber-based liquid phase microextraction followed by analytical instrumental techniques for quantitative analysis of heavy metal ions and pharmaceuticals" is described as follows: Hollow-fiber liquid-phase microextraction (HF-LPME) and electromembrane extraction (EME) are miniaturized extraction techniques, and have been coupled with various analytical instruments for trace analysis of heavy metals, drugs and other organic compounds, in recent years. HF-LPME and EME provide high selectivity, efficient sample cleanup and enrichment, and reduce the consumption of organic solvents to a few micro-liters per sample. HF-LPME and EME are compatible with different analytical instruments for chromatography, electrophoresis, atomic spectroscopy, mass spectrometry, and electrochemical detection. HF-LPME and EME have gained significant popularity during the recent years. This review focuses on hollow fiber-based techniques (especially HF-LPME and EME) of heavy metals and pharmaceuticals (published 2017 to May 2019), and their combinations with atomic spectroscopy, UV-VIS spectrophotometry, high performance liquid chromatography, gas chromatography, capillary electrophoresis, and voltammetry.[5]

Table 1: Critical review of methods.[6,7,8]

S. no.	Drugs	Hyphenated Techniques	Sample type	Remarks
1.	Acylcarnitines	Three phase Electroextraction	Plasma	Limit of detection: 90-330; Ejection fraction:2-7; Extraction time: 9min; Standard time: NA; Extraction Voltage: 140V
2	Anti-depressant drugs (Desipramine, Sertraline, Clomipramine, Citalopram)	Electromembrane extraction	Urine sample	Detection limit – 0.9-1.5ng/ml; Extraction potential- 190V
3	Bismuth subcitrate tablet	Electromembrane extraction	Human plasma sample	Assay 2.1-800ng/ml; Detection limit- 1ng/ml; Enrichment factors- 151- 187
4	Methadone	Electromembrane extraction	Plasma	Recovery 30%; Relative standard deviation- 9%
5	Ketoprofen, Ibuprofen, Citaprolam, Sertraline	EME + LPME	Plasma	Limit of detection-0.79-6.2; Ejection fraction – 3.8-57
6	Diclofenac	Electromembrane extraction	Urine	Recovery – 89%; Relative standard deviation -7%; Extraction time – 15min
7	Loperamide, Methadone, Haloperidol, Nortryptiline,	Electromembrane extraction	Urine	Limit of detection: 0.41-60 Nm; Ejection fraction: 25- 196; Extraction time- 2min; Standard time- 25min;

	Pethidine			Extraction voltage:200V
8	Stearoylcaritine, hexanoylcaritine, acetylcaritine	Electro extraction	Urine	Limit of detection- 1.4-390Nm; Ejection fraction- 175-970; Extraction time- 6min; Standard time- 30min; Extraction voltage- 15000V
9	Naltrexone, Nalnefene	Electromembrane extraction	plasma	Limit of detection- 2.9Nm; Ejection fraction- 100-199; Extraction time- 20min; Standard time- 12min; Extraction voltage: 100V.
10	Aspargine, Glutamine	Electromembrane extraction	gelatin	Limit of detection- 189-342nM; Ejection fraction- 29-53; Extraction time- 20min; Standard time- 20min; Extraction voltage - 137V
11	Nalmefene, Diclofenac	Electromembrane extraction	Urine	Limit of detection: 5.9- 1.4nM; Ejection fraction-300-350; Extraction time-14min; Standard time-12min; Extraction voltage -40V
12	Strychnine, Brucine	Electromembrane extraction	Urine	Limit of detection- 6.9-21; Ejection fraction - 114- 122; Extraction time- 10min; Standard time- 13min; Extraction Voltage- 1.5V
13	Methadone, Nortriptyline, Pethidine	Electromembrane extraction	Dried bloodspots	Limit of detection- 0.3- 3.6; Ejection fraction- 44-50; Extraction time- 25min; Standard time- 26min; Extraction Voltage- 100V
14	Citaprolam, Methadone, Loperamide, Sertraline	Electromembrane extraction	Dried bloodspots	Limit of detection1.2-1.7; Ejection fraction- 6.3- 16; Extraction time- 10min; Standard time- 24min; Extraction Voltage- 100V
15	Imipramine, Clopramine	Electromembrane extraction	Plasma	Limit of detection- 1.7-2.5;Ejection fraction- 215- 250; Extraction time- 20min; Standard time- 5min; EV-200V
16.	Drugs And Amino Acids	Electromembrane extraction	Urine	Limit of detection: 2.1- 2500; Ejection fraction- 0.35- 39; Extraction time: 5min; Standard time: 4min; Extraction Voltage: ±4/±40

6. CONCLUSION

EME and EE are highly promising electromigration-based sample pretreatment techniques with excellent prospects for online hyphenation to analytical separation and detection techniques. In this technique sample cleanup and analyte enrichment are integrated with high performance separation and selective, sensitive detection.

7. ACKNOWLEDGEMENT

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8. CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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