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Interfacing liquid-phase microextraction with electrochemical detection: A critical review

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ABSTRACT

The increasing interest in the development of rapid and efficient liquid-phase microextraction (LPME) approaches has led to a strong demand of fast, portable and decentralized detection methods as compelling alternatives to standard chromatographic and atomic spectrometric techniques. For this purpose, the coupling of LPME to electrochemical detection (ECD), including mostly cyclic, differential pulse, and stripping voltammetric techniques, has been explored in recent years for sensing of various analytes, including ions and drugs, in samples of varying matrix complexity. This review is aimed at critically surveying the current state of the art of the LPME-ECD hyphenation within the timeframe of 2010–2022 by pinpointing (i) smart configurations for *in-situ* micro-extraction and detection, (ii) experimental parameters for amelioration of analyte extractability and detectability, (iii) the compatibility of the solvent and analyte-enriched phase with the ensuing detection step, and (iv) analytical strategies and guidelines to cope with sensitivity, and selectivity demands. In addition, analytical validation and real life application of the LPME-ECD methods are critically evaluated and some future perspectives in the field of 3D printing and the development of integrated fluidic platforms are provided.

1. Introduction

Liquid phase microextraction (LPME) approaches have been most commonly interfaced to chromatographic detection systems, such as gas chromatography (GC) with mass spectrometric (MS) detection, and high-performance liquid chromatography (HPLC) with ultraviolet–visible (UV-Vis), MS, or atomic absorption/emission detection systems. Despite their separation power, these instrumental apparatuses are bulky, with high start-up and running costs, require technical support and service frequently and do not allow decentralized analyses [1,2]. In fact, in-situ/in-loco analytical detection has attracted much attention over the recent past with a promise of point of need analysis [3]. Different technologies such as wearable and implantable sensors have been developed for this purpose [3]. Regarding transduction, electrochemical detection (ECD) features unique opportunities in terms of simplicity, low cost, short analysis time, and flexibility, which originates from the diversity of electroanalytical techniques that can be fit for purpose [4,5]. This versatility enables determination of a broad range of environmentally and clinically relevant analytes as well as ease of miniaturization. However, some major drawbacks include the incorporation of expensive electrodes such as platinum and gold in some applications, or lengthy operational procedures for fabrication, activation and modification of electrodes to overcome selectivity issues and maximize sensitivity. Electrode-related challenges can be, in some instances, avoided by the use of screen printed electrodes (SPEs), e.g., carbon based electrodes, that work for low volume sample analysis, and might be disposed, whenever needed, after every single use. Selectivity issues can be alleviated by (micro-scale) extraction methods that have been suggested to minimize or eliminate interfering compounds from matrixes of real samples whenever they are carried out prior to ECD. In the field of LPME, variants that have been fully leveraged as a front end to ECD include single drop microextraction [6,7], dispersive liquid-liquid microextraction (DLLME), also incorporating switchable solvents, deep eutectic solvent and ionic liquids (ILs) [8–21], supported liquid membrane (SLM) in a hollow fiber or flat sheet configuration [22–33], and electromembrane extraction (EME) using an electrical potential difference as a driving force for charged species [34–45].

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Acronyms

ASV	Anodic stripping voltammetry
NPs	Nanoparticles
BDDE	Boron doped diamond electrode
[C8mim][PF6]	1-octy-3-methylimidazolium hexafluorophosphate
DLLME	Dispersive liquid-liquid microextraction
DPASV	Differential pulse anodic stripping voltammetry
DPV	Differential pulse voltammetry
ECD	Electrochemical detection
ECL	Electrochemiluminescence
EME	Electromembrane extraction
SFFTCCV	Stripping fast Fourier transform continuous cyclic voltammetry
FFTSWV	Fast Fourier transform square wave voltammetry
GC	Gas chromatography
GCE	Glassy carbon electrode
GDE	Gold disk electrode
HF-LPME	Hollow fiber-liquid phase microextraction
[Hmim][NTf2]	1-hexyl-3-methylimidazolium bis [(trifluoromethyl)sulfonyl]imide
HPLC	High performance liquid chromatography
ILs	Ionic liquids
LPME	Liquid-phase microextraction
MS	Mass spectrometry
NPOE	2-nitrophenyl octyl ether
Pot	Potentiometry
SLM	Supported liquid membrane
SPCE	Screen printed carbon electrode
SPE	Screen printed electrode
SPME	Solid-phase microextraction
SWASV	Square-wave anodic stripping voltammetry
SWV	Square wave voltammetry
UV–Vis	Ultraviolet–visible spectroscopy

Table 1 comprehensively overviews the analytical performance of the LPME-ECD couplings over the last thirteen years (2010–2022) using cyclic voltammetry (CV), differential pulse voltammetry (DPV), square wave voltammetry (SWV), electroluminescence (ECL), linear sweep voltammetry (LSV) and potentiometry (Pot) detection. Recent articles in the LPME-ECD arena are mostly focused on two main groups of analytes: The first group includes narcotic drugs (e.g., tramadol, morphine, and dextromethorphan), which normally feature well-established electrochemical behavior and compatibility with most LPME techniques. The second noticeable category deals with determination of trace metals and metalloids (Hg, Pb, Cu, As, Al) by leveraging anodic stripping voltammetric (ASV) methods. In case of non-electroactive species (e.g., disease biomarkers), electrode surfaces could be modified with biomolecules, yet little effort has been dedicated to combine electrochemical biosensors with LPME approaches as of yet. Distribution of papers in four categories of LPME methods and six categories of ECD techniques are shown in Fig. 1.

In this review, recent developments in LPME-ECD couplings are critically surveyed in terms of analytical aspects and performance, and sample processing needs, including evaluation of operational parameters and analytical properties, *viz*., selectivity and sensitivity issues for complex matrices, and throughput. Aiming at comprehensively covering the literature in the field, Table 1 contains detailed information as to the extraction methodologies, detection techniques and analytical figures of merit.

2. Hyphenation of LPME with ECD

2.1. Coupling requirements

2.1.1. Detectability of the analytes

To transcend the limitation of non-electroactive analytes in ECD, researchers opted for modification of the electrode surface with electroactive groups, biomolecules (e.g., enzymes) or nanomaterial mimics (e.g., nanoenzymes) that catalyze reactions yielding electrochemically active products in the presence of target analytes, or their electrochemical behavior undergo some changes in the presence of the analyte. This strategy is normally used in enzymatic electrochemical biosensors and electrochemical immunosensors [46]. An example referring to LPME-ECD coupling is the electrocatalytic determination of propylthiouracil on a catechol modified screen printed carbon electrode (SPCE) (Fig. 2A) [39]. It was reported that sulfhydryl compounds such as propylthiouracil boosted the anodic current of the electroactive catechol moieties while minimizing the cathodic peak.

2.1.2. Extractability of the analytes

Every single LPME method serves as a suitable platform for extraction of a range of analytes regardless of the ensuing ECD method. For instance, EME could be one of the best options for easily ionized analytes. For basic compounds containing free electron pairs, efficient electromigration can be achieved by acidifying both the donor and acceptor solutions as demonstrated by the EME of morphine and dextromethorphan with extraction recoveries of 71% and 97% by applying electrical voltages of 90 and 110 V for 24 and 20 min, respectively [38,44]. Although rarely used in LPME-ECD couplings, acidic analytes, such as diclofenac, could be qualified for EME by using an alkaline acceptor solution. Hollow fiber-liquid phase microextraction (HF-LPME) or DLLME, in contrast, are usually implemented by converting the analytes into their neutral form by appropriate acidification or alkalization of the sample or the incorporation of ligands (e.g., chelates in Ref. [13]) or carriers in the supported organic phase or donor solutions [22]. It is important to note that strong acidic or alkaline conditions that might not fully cope with green chemical principles are predominantly required in the corresponding acceptor phases in HF-LPME and EME to enable uni-directional transport of the analytes.

2.1.3. Compatibility of extracting solvents with ECD

The physicochemical properties of the extracting solvent might significantly influence the ECD response, especially in the case of organic solvents. Electrochemists mostly prefer to work in aqueous solutions in which the analytes undertake well-controlled redox reactions, and the manipulation of the ionic strength of the sample/extract solution is straightforward. In fact, there are only a few studies on the direct application of organic solvents in ECD. Some solvents such ILs are usually not amenable to injection in GC, and might shorten the column life and lead to peak resolution problems in HPLC [10]. However, they can be used as appealing alternative electrolytes in electrochemical devices due to their intrinsic conductivity, and wide electrochemical window [10]. An interesting application of ILs is the *in-situ* formation of (1-hexyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl]imide, [Hmim][NTf_2] in a DLLME format for 2,4,6-trinitrotoluene determination [10]. [Hmim][NTf_2] was used as both the extracting solvent and the

Table 1
Analytical performance and relevant features of representative articles coupling liquid-phase microextraction with electrochemical detection.

Extraction method	Extraction phase/derivatization reaction	Electrochemical method	Working electrode	Electrode modifier	Analyte	Linear dynamic range ($\mu g\ L^{-1}$)	LOD[a] ($\mu g\ L^{-1}$)	EF[i]	RSD %	ER %	samples	REF
SDME[b]	Aliquat tetrachloromanganate(II) in ethanol	Differential pulse voltammetry	Carbon paste	TiO_2 nanoparticles	Ascorbic acid	0.26–7	0.076	127	3.2	–	Vitamin C tablets and orange juice	[6]
HS-SDME[c]	Total strength adjustment buffer (sodium chloride, trisodium citrate, and acetic acid in deionized water)	Potentiometry	LaF_3/Titania nanotube array	–	Fluoride	1–10000	0.4	–	–	–	Milk	[7]
DLLME[d]	1-hexyl-3-methylimidazolium bis [(trifluoromethyl)sulfonyl]imide	Square-wave anodic stripping voltammetry	Screen-printed carbon	Gold nanoparticles	Mercury(II)	0.5–10	0.2	25	–	–	Tap water, bottled water, river water and industrial wastewater	[12]
DLLME	1-hexyl-3-methylimidazolium bis [(trifluoromethyl)sulfonyl]imide	Square-wave voltammetry	Screen-printed carbon	Gold nanoparticles	Mercury(II)	–	0.5–1.5	20–31	–	–	Urine	[13]
DLLME	1-hexyl-3-methylimidazolium bis [(trifluoromethyl)sulfonyl]imide	Differential pulse voltammetry	Screen-printed graphite	–	2,4,6-trinitrotoluene	10–80	7	–	7	–	Tap water and wastewater	[10]
DLLME	N-octylpyridinium tetrafluoroborate and N-octylpyridinium trifluoromethylsulfonate	Differential pulse stripping voltammetry	Gold disc	–	Mercury(II)	–	0.05	17	–	–	Tap, pond and wastewater	[8]
DLLME	1-octy-3-methylimidazolium hexafluorophosphate	Square-wave anodic stripping voltammetry	Gold disc	–	Aluminum(III)	0.0001–0.0012	–	–	–	–	Commercial distilled water	[9]
DLLME	N,N-dipropylamine with hydrochloric acid	Differential pulse voltammetry	Glassy carbon	–	Nitrazepam	0.03–20 and 20–450	0.009	–	7.4	87–91	Urine	[11]
DLLME	Triton X-100 in sodium chloride	Square wave voltammetry	Pre-treated boron-doped diamond	–	Methyl parathion	26–526	1.6	6.1	–	–	Honey	[14]
DLLME	N,N-dipropylamine with hydrochloric acid	Differential pulse voltammetry	Glassy carbon	Multi-walled carbon nanotubes	4-nitrobenzaldehyde	1.0–350	1.0	–	6.2–7.8	–	Drinking water, tap water and river water	[15]
DLLME	Deep eutectic solvent (menthol, formic acid and water)	Square wave anodic stripping voltammetry	Screen-printed carbon	–	Lead(II) and cadmium(II)	0.03–50 and 0.02–50	0.01 and 0.006	–	<6	36–39	Vegetable oil	[16]
DLLME	Deep eutectic solvent (choline chloride and urea)	Differential pulse voltammetry	Gold disc	–	Aflatoxin B1	0.2–80	0.05	–	3.4		Cereal samples	[17]
FM-LPME[e]	Sodium dodecyl sulfate in 10% (v/v) octanol/water	Differential pulse voltammetry	Pencil graphite	RuO_2-graphene oxide	Insulin	4.6–116 and 116–5800	0.14	–	3.7	–	Human urine and plasma	[22]
HF-LPME[f]	Butyl benzoate	Differential pulse voltammetry	Cathodically pre-treated boron doped diamond	–	Vanillylmandelic acid	99–19800	99	–	7.9	–	Urine	[24]
HF-LPME	Propyl benzoate	Differential pulse voltammetry	Graphite pencil lead	–	Desipramine	1.33–1332	0.21	301	6.2	–	Plasma and urine	[25]
HF-LPME	Propyl benzoate containing 1-(2-pyridylazo)-2-naphthol	Differential pulse anodic stripping voltammetry	Pt-wire	Gold nanoparticles	Mercury(II)	0.04–6	0.012	277	6.2	98	Fish and rice	[26]
HF-LPME	Butyl benzoate	Differential pulse voltammetry	Boron doped diamond	–	Homovanillic acid	219–18218	73	–	9.3	–	Urine	[28]
HF-LPME	1-octyl-methylmidazolium hexafluorophosphate	Electrochemiluminescence	Glassy carbon	–	Kanamycin sulfate	2–100	0.7	–	–	–	Milk and water	[31]
HF-LPME	Isoamyl benzoate	Differential pulse voltammetry	Carbon paste	Multi-walled carbon nanotubes	Trimipramine	1.47–14722 and 14722 –147217	0.6	16.3	4.3	–	Plasma and urine	[30]
HF-LPME	Propyl benzoate	Potentiometry	Ion selective	–	Desipramine	9–7992	0.08	296	4.5	98	Plasma and urine	[20]
FM-LPME	1-octanol	Fast Fourier transform stripping cyclic voltammetry	Carbon paste	Reduced graphene oxide	Diclofenac	1000–2500	100	–	5.5	32	Whole blood	[32]
HF-LPME	Propyl benzoate	Differential pulse voltammetry	Pencil lead	–	Buprenorphine	0.00046–0.050 and 0.050–51	0.00028	25	–	–	Urine and plasma	[27]
HF-LPME	1-octanol	Fast Fourier transmission square wave voltammetry	Carbon paste	Cerium carbonate nanospheres	Estradiol valerate	10–500	2			52	Whole blood	[29]

(*continued on next page*)

Table 1 (*continued*)

Extraction method	Extraction phase/derivatization reaction	Electrochemical method	Working electrode	Electrode modifier	Analyte	Linear dynamic range (μg L^{-1})	LOD[a] (μg L^{-1})	EF[i]	RSD %	ER %	samples	REF
FM-LPME	Propyl benzoate containing 1-(2-pyridylazo)-2-naphthol	Anodic stripping voltammetry	Pt	3-Trimethoxysilyl-1-propanethiol and gold nanoparticles	Lead(II)	0.21–62	0.02	–	6.0	–	Fish,rice, and wastewater	[23]
FM-LPME	Dihexyl ether	Square wave voltammetry	Gold electrode	–	P-coumaric acid	41–123	–		–	–	Cell culture supernatant	[33]
FM-EME[g]	1-octanol	Stripping fast Fourier transform continuous cyclic voltammetry	Carbon paste	–	Diclofenac	5–1000	1.0	2.4	–	24	Whole blood	[35]
HF-EME[h]	2-nitrophenyl octyl ether	Differential pulse voltammetry	Screen-printed carbon	Multi-walled carbon nanotubes	Sufentanil	24–1400	8	122	5.7	61	Urine and plasma	[36]
HF-EME	1-octanol	Square wave anodic stripping voltammetry	Glassy carbon	Gold nanoparticles	As(III)	0.5–10 and 10–600	0.18	60–64	6.7–8.5	60–64	Tap water, river water	[41]
FM-EME	2-nitrophenyl octyl ether	Fast Fourier transform square wave voltammetry	Carbon paste	Terbium carbonate ($Tb_2(CO_3)_3$) nanoparticles	Estradiol valerate	0.1–1300 and 1300–10,000	0.01	2	<4.2	67	Whole blood	[37]
HF-EME	2-nitrophenyl octyl ether containing 10% tris-(2-ethylhexyl) phosphate and 10% di-(2-ethylhexyl) phosphate	Differential pulse voltammetry	Screen-printed carbon	–	Morphine	0.005–2.0	0.0015	142–152	7.1	71–76	Urine	[38]
HF-EME	Nitrobenzene	Differential pulse voltammetry	Screen-printed electrochemical strips	–	Propylthiouracil	50–5000	20	200	5.7	80	Urine	[39]
HF-EME	2-nitrophenyl octyl ether	Linear sweep voltammetry	Pencil lead	Reduced graphene oxide	Tramadol	10–500 and 500–50000	3	94–101	8.1	–	Urine	[40]
HF-EME	2-Nitrophenyl octyl ether	Differential pulse voltammetry	Pencil lead	–	Clozapine	3–1500	0.9	114	3.5	42	Human plasma	[42]
FM-EME	2-nitrophenyl octyl ether	Fast Fourier transform stripping square wave voltammetry	Carbon paste	–	Amlodipine	0.1–10 and 10–1000	0.05	61	4.5	–	Whole blood	[43]
HF-EME	2-nitrophenyl octyl ether	Differential pulse voltammetry	Screen-printed carbon	Reduced graphene oxide	Dextromethorphan	5–1500	1.5	260	6.2	97	Plasma and urine	[44]
FM-EME	1-octanol	Anodic stripping voltammetry	Glassy carbon	Gold nanoparticles	Mercury(II)	0.2–10	0.01	102–108	7.5–8.7	41–43	Tap water, river water	[45]
FM-EME	1-octanol	Fast Fourier transform square wave voltammetry	Carbon paste	–	Glibenclamide	10–1000 and 1000–10,000	3	–	3.8	26	Blood	[34]

[a] LODs were mostly reported based on a signal-to-noise ratio (S/N) of 3.
[b] Single-drop microextraction.
[c] Head space-single-drop microextraction.
[d] Dispersive liquid-liquid microextraction.
[e] Flat membrane-liquid three-phase microextraction.
[f] Hollow fiber-liquid phase microextraction.
[g] Hollow fiber-electromembrane extraction.
[h] Flat membrane - electromembrane extraction.
[i] Enrichment Factor

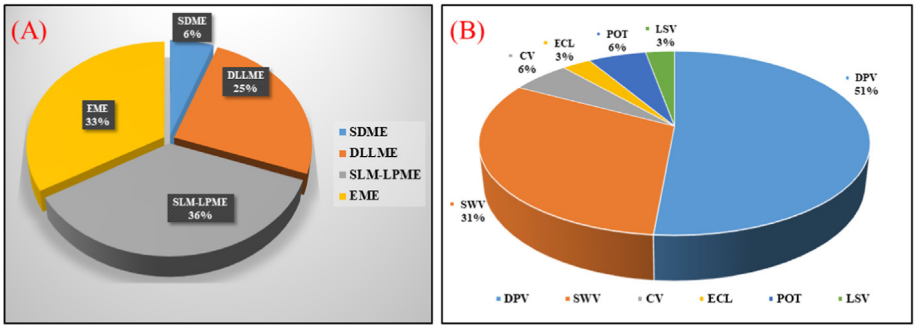

Fig. 1. Distribution of LPME-ECD couplings from 2010 to 2022 based on A) extraction methods and B) ECD techniques.

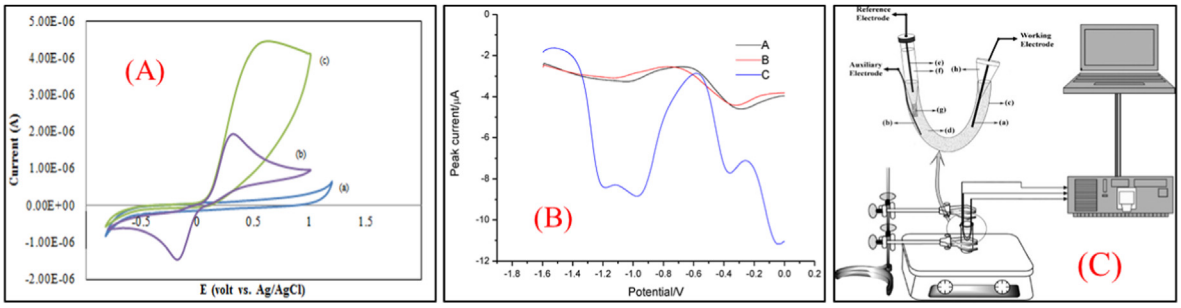

Fig. 2. A) Cyclic voltammograms of SPCE in the presence of a) only 1 mM propylthiouracil, b) only 1 mM catechol and c) 1 mM catechol and 1 mM propylthiouracil [reproduced from Ref. [39] with permission from Elsevier], **B)** The SWASV on GDE: (A) [C_8mim][PF_6]; (B) oxine in [C_8mim][PF_6]; (C) IL-with 0.4 ng L^{-1}Al(III) and oxine [reproduced from Ref. [9] with permission from Multidisciplinary Digital Publishing Institute (MDPI)], and **C)** Different parts of the equipment used for HF-LPME with in-situ DPV detection: (a) graphite pencil electrode; (b) platinum wire microelectrode; (c) polypropylene hollow fiber; (d) acceptor phase; (e) Ag-wire coated with an AgCl thin film; (f) saturated KCl/AgCl solution; (g) agarose gel; (h) 10-μL polypropylene micropipette [reproduced from Ref. [25] with permission from Elsevier].

non-water miscible electrolyte solution in ECD. A well-defined cathodic peak was obtained in DPV at −0.80 V, which was associated to the reduction of one of the three nitro groups of the molecule. However, no comprehensive study of the behavior of the IL in the presence of electroactive matrix interfering species was undertaken. In fact, the direct electrochemical detection of Hg extracted by [Hmim][NTf_2] was reported not to be suitable and thus back-extraction to aqueous sample was deemed necessary for voltammetric analysis [12]. Taking into account the fact that back-extraction methods are tedious and time-consuming, a more efficient DLLME of Hg using IL as a 'front end' to ECD was proven feasible by simply diluting the Hg-laden IL with acetonitrile. The IL/acetonitrile mixture was amenable to direct ASV on a gold disc electrode (GDE) [8]. Based on a comprehensive study of solvents for ECD of Hg, researchers encountered no stripping peak in dimethyl sulfoxide and ethanol, a weak stripping peak in isopropanol and propylene carbonate, and a clean and sharp peak in acetonitrile. Interestingly, no signal of Hg in organic media was found in glassy carbon electrode (GCE), while gold remained its redox and complexation/amalgamation capability with atomic mercury in organic solvents [8].

With respect to the ECD of metal species, the hydrogen evolution reaction might deteriorate the detectability of metals with high electronegative potential, such as barium and aluminum, in aqueous solutions. This shortcoming was elegantly circumvented by Al(III) chelation with 8-hydroxyquinoline with further IL-LPME extraction and direct detection of the Al-laden 1-octy-3-methylimidazolium hexafluorophosphate ([C_8mim][PF_6]) by square-wave anodic stripping voltammetry (SWASV) [9](see Fig. 2B).

All LPME studies concerning the compatibility of the extract/acceptor phase with ECD have been carried out by DLLME methods using organic solvents, while EME and HF-LPME have been excluded, probably due to the partial solubility of the organic phase in SLMs (1-octanol and 2-nitrophenyl octyl ether (NPOE)) into the acceptor phase that might deteriorate the baseline and response in ECD. However, this possibility should be reconsidered, as there are a few reports on three phase HF-LPME using acetonitrile as an acceptor phase [47].

2.1.4. pH control of the extraction and detection steps

Considering the extraction mechanism of three-phase LPME/EME methods, pH of the acceptor phase is usually fixed using strong acids or alkaline solutions. Therefore, the acceptor solution must be in most instances diluted and adjusted to a customized pH value for optimal ECD detection notwithstanding of the deterioration of the enrichment factors [38]. In one interesting HF-EME-ECD coupling for the clean-up and preconcentration of tramadol in urine samples [40], the effect of the strong acidity of the acceptor phase on ECD was alleviated by adsorption of the drug on a graphene modified pencil lead electrode used as the cathode inside the lumen of the hollow fiber whereupon the electrode was removed from the extraction cell and immersed into the electrochemical cell to record ECD signals. Because the pH values were separately optimized for the microextraction and ECD steps, this could be seen as a universally enabling strategy in LPME-ECD coupling.

2.1.5. Electrode selection and configuration

Different types of electrodes have been accommodated in LPME-ECD couplings based on the volume of acceptor/diluent phase available, analyte class, cost of electrodes, and portability. In many studies, commercial SPEs, such as carbon based-SPEs, have been exploited for determination of drugs such as dextromethorphan, or sufenantil because of easy handling and compatibility with small

volumes [36,44]. Usually extracted/acceptor solutions from HF-LPME, EME, and DLLME with volumes ranging between 15 and 20 μL have been manually injected onto the SPE (2–4 mm diameter for the working electrode), in many cases, without dilution with a buffer solution, because this would in fact jeopardize the pre-concentration factors achieved by LPME [38]. Carbon paste electrodes has also much to offer in LPME-ECD hyphenation, because of facile manipulation to confer specific shapes, formats or bespoke chemical composition [32]. In case of simultaneous LPME and ECD, the electrode size and shape play a pivotal role in proper design. For example, the in-situ HF-LPME with ECD detection of desipramine [25] was proven feasible by incorporating three microelectrodes including a platinum wire (0.25 mm O.D.) as the counter electrode, a graphite pencil lead (0.35 mm O.D.) as the working electrode, and a homemade Ag/AgCl-wire (0.5 mm I.D.) as the reference electrode into the hollow fiber lumen containing 10 μL acidic acceptor solution (Fig. 2C). Elevated preconcentration factors (257–296) are reported because the dilution of the acceptor phase is circumvented.

Another possibility is to perform off-fiber, on-drop detection following HF-LPME on a vertically standing working electrode (e.g., boron doped diamond electrode (BDDE)), by immersing the reference and counter electrode into the drop of acceptor phase [28]. This system was applied to the determination of homovanillic acid as a tumor biomarker (Fig. 3A). However, due to the repulsion between homovanillic acid as an anion in the neutral or alkaline hollow fiber extract and negatively charged surface of O-terminated BDDE, a cathodic pre-treatment of BDDE to produce H-terminated surface at - 1.0 V for 15 s was proposed for reliable analysis. Using this coupling, an RSD% of 9.3% was reported, which is slightly higher than those of alternative ECD methods, and this could be attributed to technical issues for repeatable handling and *in-situ* analysis of droplets. A similar on-drop analysis was developed using EME prior to ASV determination of As(III) using a gold nanoparticles modified GCE (AuNP-GCE) [41]. These reports demonstrated that ECD offers inherent flexibility regarding the size of the extract/acceptor phase to be analyzed.

The physicochemical properties of the analytes also play a crucial role in the selection of the working electrode aiming at ameliorating detectability. However, because the electrochemical behavior of drugs on carbon based electrodes is very well investigated [48], these electrodes are frequently used in LPME-ECD couplings [36,44]. In fact, carbon based electrodes are at least two to three times more affordable than the gold or platinum based counterparts.

2.2. Sensitivity caveats in LPME-ECD couplings: How to get them addressed?

2.2.1. Increase of the extraction efficiency

Several articles indicate that standard LPME methods cannot serve as universal protocols for extraction of analytes prior to ECD [38,39]. A potential strategy involves the addition of a carrier to the SLM for improvement of extraction, in particular, for polar or ionized species [38]. For example, carriers such as bis(2-ethylhexyl) phthalate and tris (2-ethylhexyl) phosphate containing hydrophobic alkylated moieties and hydrogen acceptor groups are proven to ameliorate mass transfer of morphine in EME. However, the electrical current changes during morphine extraction in real samples were not studied after addition of carrier to the SLM. This is an issue of major concern inasmuch as there are high amounts of salts in biological samples, especially urine samples, that might give rise to high currents. In fact, the addition of a carrier could either burn the SLM, or promote leaking of the SLM, thus increasing the probability of mixing of donor and acceptor phases.

Aiming at improving extraction efficiencies, the SLM in EME could be reinforced with carbon or metal nanoparticles (e.g., CuNPs) as demonstrated by the determination of propylthiouracil in urine samples [39]. The high affinity of propylthiouracil toward

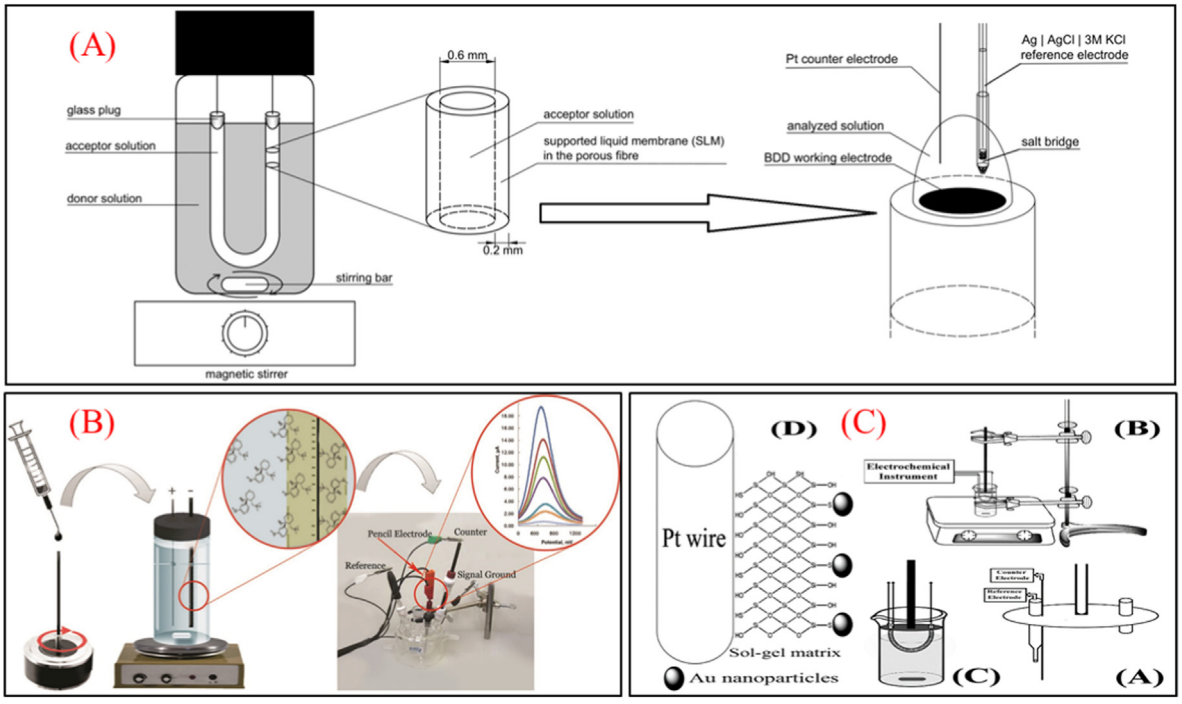

Fig. 3. A) Representation of an HF-LPME extraction cell (left side) and on-drop three electrode detection system (right side) [reproduced from Ref. [24] with permission from Elsevier], **B)** Schematic representation of an EME-SPME-ECD hybrid system with a chemically modified electrode [reproduced from Ref. [40] with permission from Elsevier], **C**) (A) Designed assembly for microextraction and in-situ voltammetric detection; (B) and (C) schematics of the equipment used for HF-LPME and in-situ DPASV, respectively; and (D) schematic of the working electrode [reproduced from Ref. [26] with permission from Elsevier].

CuNPs was explained by the interaction of Cu with the thiol moieties. Even though the addition of CuNPs to SLM was also aimed at improving selectivity, there was only one thiol containing compound among the studied interfering agents. In fact, there are a large number of sulfur containing species that co-exist in urine, such as metabolites of cysteine [49], that could interfere with the extraction of the target analyte. It should be also born in mind that the CuNP shell is most likely composed of sodium ascorbate used in the synthetic route (Zeta potential $\neq 0$), and thus the current level through EME might increase, and as a consequence, trigger the electrolysis of water with the subsequent unwanted change of the pH in the sample and/or acceptor solutions.

Another strategy to boost the sensitivity of the extraction system is coupling of LPME with another sample treatment step (liquid-liquid extraction, solid phase extraction, or membrane extraction) [50] in a serial mode. However, to the best of our knowledge this hyphenation has not been exploited so far in combination with ECD.

2.2.2. Increase of sensitivity in the ECD step

2.2.2.1. Physicochemical modification of the electrode. To alleviate sensitivity issues of LMPE-ECD methods, the detection system can be tweaked to obtain enhanced response. For example, modification of SPCE with catechol was shown to enhance the electrochemical responses for detection of propylthiouracil in urine through electrocatalysis (See Fig. 2A) [39]. However, metal nanoparticles and carbonaceous nanomaterials are frequently used modifiers aimed at increasing the surface area, enhancing mass transport and catalytic activity, and improving signal to noise (S/N) ratios [51]. For example, AuNPs were proposed for the modification of SPE for Hg determination after DLLME [12]. It was reported that the gold amalgam formed on the surface of the electrode shifted the deposition potential of mercury at a more positive potential than that of standard conditions. The novelty of this work relied upon the *in-situ* synthesis of AuNPs onto the SPCE surface from $AuCl_4^-$ in 0.1 M HCl by applying -100 μA constant current for 180 s. However, the experimental ECD signals obtained before and after the electrode modification with AuNPs were not regrettably presented.

Another possibility is to decorate the electrode inside the hollow fiber with graphene or graphene oxide for *in-situ* EME-solid-phase microextraction (SPME) for enhanced extraction efficiency with further electrochemical detection using the EME electrode (Fig. 3B) [40], thereby exploiting the inherent elevated conductivity and surface area of the nanomaterial. However, the stability of the nanomaterial-modified electrode has not been thoroughly investigated in the literature [40].

2.2.2.2. Optimization of the ECD step. Optimizing the ECD based on DPV, SWV, Pot, or ECL might aid obtaining the required detectability for real sample analysis. Scrutinizing the papers on LPME-ECD coupling, one can realize that the detection parameters of ECD methods have been mostly taken from the literature and there has not been a comprehensive optimization study on the detection step except in a few cases. For example, fast Fourier transform square wave voltammetry (FFTSWV) based methods have been developed to ameliorate the ECD sensitivity of drugs in whole blood analysis [37] using a large frequency for current measurements. It is supposed that this might help getting better S/N ratios by efficient removal of noise. This improvement could however be shown experimentally by comparing normal SWV against FFTSWV signals. Increasing the amplitude up to 100 mV is proven to enhance the FFTSWV readouts, yet the kinetic limitation of the diffusion process decreases the analytical response at higher amplitudes. Comparing with conventional CV, stripping fast Fourier transform continuous cyclic voltammetry (SFFTCCV) harnesses an additional time axis that serves as a time window for the experiment run. As a consequence, SFFTCCV could help monitoring the extraction process and visualizing concentration changes of the analyte at real time [35].

In-situ potentiometry using bespoke ion selective electrodes is another yet technique that can leverage HF-LPME [20]. Dedicated polyvinyl chloride membranes with ion-pair reagents can straightforwardly decorate Pt-wire electrodes by dip coating before in-fiber ECD detection.

In the literature, there is only one paper on the coupling of ECL with HF-LPME using IL as the liquid membrane. After extraction, $Ru(bpy)_3^{2+}$ and tripropylamine were added into 10 μL of the acceptor solution into the ECL cell, followed by addition of 1 mL phosphate buffer (pH = 8) [31]. The dilution carried out in the last step (>100 times) could however jeopardize the enrichment factor and method's sensitivity, and this might shed light into the fact that no target analyte was detected in the analysis of real samples.

2.2.2.3. Accumulation and stripping for preconcentration in the ECD step. Accumulation methods are frequently adopted in ECD for tailoring method's sensitivity [36]. However, stripping of some metal ions or metalloids might not be selective enough whenever metal species with close reduction potential co-exist in the sample. To solve this problem, a modified electrode or a specific ligand for metal ion extraction in the LPME step could be used for reliable analysis. For example, HF-LPME with 1-(2-pyridylazo)-2-naphthol as a chelating agent coupled with differential pulse anodic stripping voltammetry (DPASV) of mercury on AuNP sol–gel modified Pt-wire electrode is an example of both electrode modification and derivatization in microextraction to assure sufficient sensitivity and selectivity (Fig. 3C) [26]. Gold electrodes have shown to provide better ASV response than that of alternative working electrodes, such as Hg or Pt for As detection. In fact, Au–As inter-metallic compounds are formed, thus enhancing the efficiency of cathodic preconcentration of As(0), as demonstrated by hyphenating EME with SWASV for trace As(III) detection [41].

2.3. Selectivity caveats in LMPE-ECD couplings: How to get them addressed?

2.3.1. Selectivity issues across the extraction step

Selectivity in LPME is method-dependent. For example, basic drugs in EME are positively charged at acid/neutral pH and thus might be efficiently extracted while the negatively charged and neutral analytes remain in the sample solution after application of a potential difference across the liquid membrane. In the case of urine, the interference of major neutral or anionic components (e.g., uric acid and, ascorbic acid) is thus entirely overcome [40]. Regarding HF-LPME or DLLME, analytes should normally be in their neutral form for efficient partitioning into the organic phase. As for metal ions (e.g., mercury), the use of a prior derivatization reaction with dithiocarbamate or oxine moiety-containing ligands to yield a neutral chelate might assist alleviating interference effects of normally co-existing ions in the blood or urine samples [26]. However, interference studies usually lack systematic evaluation, do not show ECD readouts for real samples and are only limited to a few number of interfering agents [32,39]. It is certain that the microextraction step might potentially eliminate many interfering agents by clean-up into the ECD, yet there are still compounds that can be possibly preconcentrated along with the target analytes. One of the problems regarding the papers published in this area is that direct ECD analysis of real samples has not been compared with that of the LPME-ECD combination [26,27,32]. Therefore, one might argue that the interfering effect of some compounds in high matrix samples could have been even magnified on account of the

preconcentration step.

2.3.2. Selectivity issues across the ECD step

In those situations in which there are some coextracted compounds in the acceptor/diluent LPME phase, a crucial decision is to select the most appropriate ECD technique. For example, DPV has the intrinsic advantage over CV of the potential separation signals of coextracted analytes [38,52]. Electrochemically active acidic compounds, such as uric acid, ascorbic acid, and tartaric acid coexist in their negative forms in urine at a pH of 5 [35], and thus they could be simultaneously extracted by EME with acidic drugs (e.g., diclofenac), and consequently interfere in the ECD. The use of cyclic voltammetry [35] does not seem a good option because of poor separation power, and thus accurate quantification of acidic drugs might be jeopardized by interfering electroactive anions. With respect to cationic species, DPV has proven to selectively detect a target drug (morphine) against concomitantly extracted basic species in EME (noscapine, cocaine, codeine or tramadol) [38]. It should be considered that analytes, such as morphine, might have been involved in several redox reactions but the authors in Ref. [37] did not explain the reasons for selection of a certain ECD signal against others in terms of selectivity. Another aspect that is normally neglected but it is of utmost relevance in interfering studies is the effect of the dissolved solvent (e.g., NPOE for basic species and 1-octanol for acid compounds in EME) in the acceptor phase on the ECD signals and background. In fact, the majority of reports on LPME-ECD neglected the investigation of solvent and matrix extracted compounds in the ECD step [12].

3. Validation of LPME-ECD methods

Analytical figures of merit in LPME-ECD methods normally include limit of detection and quantification, dynamic range, intraday repeatability, preconcentration factor, electrode stability, and absolute and relative recovery. However, inter-day repeatability (reproducibility) has been frequently neglected. In addition, RSD% should have been reported for two or three concentration levels to cover the entire linear calibration range and both in standard solutions and real samples. Examples of the lack of performance data can be seen in the paper using EME-SFFTCCV for determination of diclofenac in which inter-day RSDs were not reported neither for standards nor real samples [35]. Some inconsistences throughout method validation are also identified in the literature. For example, Mofidi *et al.* [35] analyzed as much as 12 mL of diluted whole blood containing diclofenac using 5 mL of acceptor solution. A preconcentration factor of 2.4 was reported, thus suggesting that the extraction recovery should have been 100%, rather than 24% as indicated across the paper.

Another problem regarding analytical validation is the insufficient number of spike levels to cover the calibration range. This is observed in a number of papers in the field dealing with the EME-DPV of propylthiouracil in urine [39], EME-LSV of tramadol in urine [40], and HF-LPME coupled with ECL for kanamycin sulfate determination in water and milk [31]. Because ECD is significantly affected by the components of complex biological (e.g., whole blood or urine) and environmental/industrial samples (e.g., wastewaters) extracted into the acceptor/diluent phases and by remnants/dissolution of organic phases, a matrix matched calibration seems to be the method of choice for investigation of method trueness and analysis of samples. However, very few examples reported the analysis of real samples with incurred analytes [26], thus indicating that the sensitivity of the LPME-ECD coupling might not suffice for trace level analysis. In addition, statistical comparison of the ECD results against those of alternative chromatographic or spectroscopic detection systems is not usually tackled. Two examples potentially demonstrating the applicability of LPME-ECD to cope with the maximum allowed concentrations by international regulations include the determination of As and Hg in drinking waters at $< 10\ \mu g\ L^{-1}$ [41] and $<2\ \mu g\ L^{-1}$ [12], respectively. However, it should be born in mind that the maximum allowed concentration refers to the total concentration of metal, yet the authors analyze concentrations of only As(III) [41] and Hg(II) [12] ions. In the case of Hg, no analyte was found in the real samples and the lack of comparison with a standard method casts doubt on the reliability and applicability of the proposed system.

3.1. Extraction and detection times/sample throughput

Normally ECD is very fast. Therefore, the total analysis time will rely on the LPME method, and the post-processing steps for ECD. Based on literature data, extraction times for HF-LPME spanned from 15 to 240 min [25,32]. It is a general assumption that the extraction time of HF based methods is greater compared to that of EME systems. However, this is only in few studies, such as the determination of diclofenac in whole blood sample [32] or determination of buprenorphine in urine and plasma samples [27], while in other papers, extraction times in HF-LPME are more or less the same as in EME [20,39]. An interesting comparison across different microscale extraction methods including HF-LPME, EME, and DLLME is available in the literature for determination of Hg(II). Extraction times for HF-LPME [26], EME [45], and DLLME [12] were 27 min, 12 min, and ca. 30 min, respectively. To assure compatibility of the extraction solvent with the ensuing detection, DLLME with switchable solvents seems to be an appealing alternative for high-throughput analysis. For example, the determination of 4-nitrobenzaldehyde in waters was carried out by combination of dipropylamine based DLLME with ECD on multiwalled carbon nanotubes modified electrode in just 2 min [15]. To ensure appropriate enrichment factors, however, the switchable solvent containing analyte might need to get evaporated until a few μL before transferring onto the surface of the electrode [15]. These additional steps can lengthen the total analysis time.

3.2. Comparing LPME-ECD against LPME-UV-Vis

There is not a vast amount of literature reporting a critical comparison of LPME-ECD against alternative optical detection methods (e.g., spectrophotometry) because each detection technique is specifically selected according to the particular physicochemical properties of the target compounds. By taking Hg(II) as a model analyte, the analytical performance of HF-LPME-UV-Vis for detection after derivatization with dithizone [53] is proven to exhibit a poorer LOD as compared to EME-ECD [26], with values of 20 and 0.01 $\mu g\ L^{-1}$, respectively. Similarly, the LOD of a HF-LPME-ECD method using a Pt wire modified with AuNPs was $0.012\ \mu g\ L^{-1}$ [45], which is almost 1700 times better than that of HF-LPME-UV-Vis [53]. Though ECD demonstrated better analytical performance than UV−Vis in the above examples, there is no universal rule with respect to superiority of one method over the other in terms of detectability. Selectivity issues in both detection systems without a prior separation column could be ameliorated by derivatization and masking reactions in UV−Vis detection and nanoparticle-modified electrodes in ECD, the latter usually selected for amelioration of ECD sensitivity as well.

4. Perspectives

This manuscript critically surveys the advantages and pitfalls of LPME-ECD couplings in terms of analytical features. Each side of this conjugation can benefit the other. Electrochemistry is

amenable to fast and portable/decentralized detection, while micro-scale extraction bearing green chemical credentials can fuel clean-up and sensitivity enhancements. On the other hand, (i) the long extraction times in LPME, even EME, to ensure acceptable extraction recoveries [38,44], (ii) the need of large sample volumes and impossibility of using undiluted samples in the extraction side in many studies [35,38], (iii) the short electrochemical window of water, (iv) the selectivity and S/N ratio issues in ECD from co-extracted species [9,24,35], and (iv) the difficulty of multianalyte analysis on ECD have, to some extent, hindered the progress in this research area. To the authors' viewpoint, LPME-ECD hyphenation can leverage the current progress in millifluidic/flow injection and microfluidic approaches for downscaling and automation of the entire analytical process encompassing on-line sample preparation and detection [54,55] as demonstrated with centrifugal analyzers accommodating SLM and ECD [33].

The advent of additive manufacturing (3D printing) has also opened up new avenues in the ECD field for fast prototyping on account of the cost-effectiveness of consumer-grade fused deposition modelling printers and the availability of thermoplastics with conductive properties that can be readily decorated with metal nanoparticles. This enables facile fabrication of fit-for-purpose working electrodes (notwithstanding electrode post-processing, polishing and activation might be still required) with an extra degree of freedom for the entire fabrication of the electrochemical sensing platform including chemically inert electrochemical cells and the reference and auxiliary electrodes [56]. Therefore, the development of novel 3D printed (fluidic) platforms integrating LPME-based approaches with printed ECD components is foreseen in the near future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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