



## Review

## Electrochemistry coupled to (liquid chromatography/) mass spectrometry—Current state and future perspectives

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## ABSTRACT

The coupling of electrochemistry (EC) to different mass spectrometric (MS) techniques in off-line and especially in on-line approaches is a quickly growing research field in analytical chemistry with numerous distinct objectives. Depending on the analytical problem, a separation step can be further integrated according to the instrumental set-up and, most frequently, liquid chromatography (LC) is selected for this purpose. In this review, various scientific areas of application for this EC/(LC)/MS hybrid method are presented and discussed in detail. Therefore, one major division is made between those applications which are already successfully used on a large scale (current state), and those which have shown promising results for future utilization (future perspectives). The reader shall be provided with a thorough overview on the capabilities of the combination of EC/(LC)/MS and the drawbacks which result in further optimization and exploration of this technique. The major topics addressed in this review include the role of EC/(LC)/MS for drug metabolism studies, peptide, protein and DNA (deoxyribonucleic acid) research and quantification strategies. Promising future applications that are presented and evaluated comprise the fields of toxicology and forensics, targeted product synthesis and environmental analysis.

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## 1. Introduction

During the last four decades, the range of methods and applications of electrochemistry (EC) coupled on-line or off-line to mass spectrometric methods, especially electrospray ionization–mass spectrometry (ESI–MS) and inductively coupled plasma–mass spectrometry (ICP–MS), has dramatically increased [1,2]. By now, this versatile group of techniques has successfully been used in many different research areas including drug metabolism studies [3], peptide, protein and DNA (deoxyribonucleic acid) analysis [4–6], quantification of biomolecules [7] or even in sample pretreatment procedures [8]. Next to these fields, in which substantial explorative and investigative work has already been accomplished, electrochemical applications are also gaining interest in various other domains such as toxicology and forensics [9], environmental analysis [10,11] or for preparative-scale synthesis and characterization of target molecules [12]. Thus, there is a broad range of analytical challenges for which EC in combination with MS, often extended by liquid chromatography (LC), can provide important benefits. Particularly within the last ten years, the advantages and disadvantages of this method have been subject to a number of reviews, yet with differing emphases [1,2,13–24]. Diehl et al., for instance, focused on the instrumental and method development of the on-line hyphenation between EC and (LC)/MS with respect to the determination of non-volatile compounds and structured their review by increasing complexity of the employed system [13], whereas in the article of Hayen et al., the discussion of EC is only incorporated as one of several approaches for the LC/MS analysis of non-polar substances [14]. In contrast, the review of Roussel et al. exclusively deals with this group's work on the electrochemical generation of mass tags toward cysteine residues in peptides and proteins, exploiting the inherent oxidation processes of ESI in a microfabricated microspray emitter [15]. While Zhou is nicely summarizing latest developments on the basis of EC coupled to elemental mass spectrometric methods as ICP/MS for trace-metal analysis and investigations of electrode processes [2], the more recent publications are primarily dedicated to the role that EC/(LC)/MS plays in drug metabolism studies [16,19,22–24]. Additionally, drug stability assessment [20], protein research [17] and electrochemical cell types [19] are addressed in some cases. Finally, the review article of Prudent and Girault is of a rather technical focus, demonstrating the versatility of electrospray emitters by taking advantage of the microfluidic, the electrochemical or the aerosol nature of ESI (functionalization) for different applications [18]. Gun et al. also concentrated on mechanistic and technical details when describing the challenges in combining EC effectively with MS instruments [21].

The aim of the present review is to offer an overview on the various current applications, but also on the potential future use of EC/(LC)/MS in analytical chemistry. Hence, the role of this promising method is evaluated and discussed while focusing on the specific scientific area, for which it possibly proves useful, rather

than going into detailed electrochemical fundamentals, concerning instrumental improvements and cell types. The reader shall eventually be equipped with the knowledge of where EC/(LC)/MS can already be called an efficient means today and what will be the upcoming utilities of this technique as demonstrated by first achievements. Therefore, this review is divided into two major parts, dealing with the current state on the one hand, and with future perspectives on the other hand. Each part is then further subdivided into corresponding sections of major interest. Prior to this partitioned discussion, though, some of the early and pioneering EC/MS studies shall briefly be presented at this point, in order to provide a quick historical introduction into this field of research, talking about how and by whom the EC/(LC)/MS approach was originally performed in its emergent phase.

The first documentation of a study that used an electrochemical cell coupled to a mass spectrometer dates back to 1971 when Bruckenstein and Gadde investigated the oxidation and reduction behavior of perchloric acid, leading to oxygen and hydrogen release, respectively [25]. They used a porous platinum electrode that contacted the electrolyzed solution on the one side and the MS vacuum on the other. Similar reports for the analysis of volatile compounds followed, especially from the groups of Bruckenstein [26], Heitbaum [27,28], Anderson [29] and Vielstich [30]. This technique is nowadays referred to as differential electrochemical mass spectrometry (DEMS), however, further details will not be covered within this review, but can be found in an early article of Chang et al. [31] and the recent review from Lev's group [21]. In 1986, it was again Heitbaum, together with Hambitzer, who combined EC and thermospray (TSP) MS for the first time, aiming at the detection of non-volatile substances [32]. This approach was later pursued by Brajter-Toth and co-workers for studying redox reactions of biological compounds, employing a commercially available flow-through cell and comparing the results with enzymatic processes [33,34]. Moreover, they did pioneer work in integrating an LC system into the on-line EC/TSP–MS set-up and, thus, successfully separated and identified the oxidation products of different purines [35–37]. The hyphenation of EC to a mass spectrometer was eventually extended to instruments with fast atom bombardment (FAB) [38–40], particle beam (PB) [41–44] and atmospheric pressure chemical ionization (APCI) [45,46] interfaces. Finally, emphasis is laid on efforts from Zhou and Van Berkel in 1995, who were the first to combine different EC cell types with ESI–MS, the most widely used ionization method for non-volatile, polar and thermally labile compounds [47]. They impressively demonstrated, at an early stage of EC/MS development, the utility and versatility of this method by carrying out the following three exemplary applications: (1) ionization of neutral analytes for effective detection via ESI–MS, (2) investigation of the products of electrode reactions, including transient species, and (3) enhanced determination of metals by coupling anodic stripping voltammetry with ESI–MS. For these studies, perylene, nickel(II)octaethylporphyrin,  $\beta$ -carotene as well as elemental silver served as model systems.

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