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Miniaturization of electrochemical cells for mass spectrometry

Floris T.G. van den Brink *, Wouter Olthuis, Albert van den Berg, Mathieu Odijk

MESA + Institute for Nanotechnology and MIRA institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands

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ABSTRACT

The combination of electrochemistry (EC) and mass spectrometry (MS) (EC-MS) has proved to be powerful and versatile for important biological and chemical analyses, including the study of drug metabolism, the oxidation and the cleavage of proteins, and environmental research. The electrochemical-cell designs used in these studies are critical for the types of analyses that can be carried out using EC-MS instrumentation, and, to this end, miniaturization opens up a wide range of new possibilities. In this review, we identify the benefits associated with microfluidic electrochemical cells, and describe design and fabrication aspects of these devices. Next, we highlight the use of microfluidic electrochemical cells in EC-MS studies and specific trends in miniaturization that will expand the range of possible applications for these devices in EC-MS analysis.

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1. Introduction

Electrochemistry (EC) and mass spectrometry (MS) have been established as a powerful combination for analytical chemists who are interested in performing oxidation or reduction reactions followed by rapid, sensitive detection. This concept already serves a large variety of applications, a large part of which is covered in this Special Issue of ***TrAC*** and a recent review by Jahn and Karst [1]. Possible applications include those related to drug screening and proteomics, as new developments in EC combined with electrospray ionization (ESI)-MS are often driven by demands from these fields of research [2].

Routine EC-MS experiments in industrial and academic laboratories typically employ commercially available electrochemical cells that are connected to the ESI interface of mass spectrometers.

Postal address: University of Twente, Faculty of Electrical Engineering, Mathematics and Computer Science, BIOS chair, Carré 2.247, P.O. Box 217, Enschede 7500 AE, The Netherlands.
* Corresponding author. Tel.: +31 53 489 3706.
E-mail address: f.t.g.vandenbrink@utwente.nl (F.T.G. van den Brink).

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Although this type of set-up has been used successfully for a large variety of analyses, further developments are ongoing to satisfy the needs for reduced flow rates, shorter transit times and more innovative electrochemical cells. The use of microfluidics technology can facilitate meeting those demands. First, operation at low flow rates enables the use of nano-ESI, thereby increasing the ionization efficiency and the overall ratio of signal to chemical noise, especially in the presence of increased salt concentrations [3]. Second, the small volumes of miniaturized electrochemical cells reduce transit times, enabling the detection of short-lived reaction products. Third, microfabrication techniques facilitate further system integration by adding functionality (e.g., integrated sample preparation or separation), while parallelization can help to achieve the desired throughput. For example, microfluidic chips containing a sample-enrichment column, a nano-LC separation column and a nano-electrospray emitter are already commercially available [4].

In this review, we first describe design aspects, materials and fabrication technologies related to the development of miniaturized electrochemical cells, as well as some aspects of their interfacing with mass spectrometers. Following this, we explore trends observed in a variety of reported electrochemical cells, with a strong focus on microfluidic electrochemical reactors. Macro-scale cells and electro-active ESI emitters are reviewed by Baumann and Karst [5] and Prudent and Girault [6], so we discuss them only briefly, with a special focus on the materials and geometric aspects of those cells. Electrochemical detection and electrokinetic systems are excluded from this review, since a more general review on electrochemical microsystems is published by Zimmerman [7]. Moreover, many papers on electrochemical detectors for column or electrophoretic separations, or microreactors for electrosynthesis have been published since the end of the 1960s, and these have already been reviewed by Ewing et al. [8], and Ziogas et al. [9], respectively.

For this review, we focus on microfabricated microfluidic electrochemical systems aimed at conversions coupled to mass spectrometers for subsequent detection of reaction products.

2. Why miniaturize electrochemical cells?

Traditional reasons to use microfluidics instead of macro-scale reactors include the promise of using less sample, less reagents, creating less waste, and more effective heat transfer, while using (at least theoretically) low-cost, disposable devices if produced in large quantities [10]. However, for EC-MS, there are several additional advantages that clearly stand out. One of the most important arguments to miniaturize is based on geometric effects, which can be illustrated by the following equations in relation to Fig. 1. As a starting point, a microfluidic channel is considered with an electrode at the bottom [here, the working electrode (WE)], which is a thin-layer arrangement and a typical configuration for microfluidic electrochemical cells.

To achieve full conversion, diffusion towards the electrode surface has to take place within the time the analyte resides above the WE. In general, the diffusion time (t_d) scales quadratically with the diffusion distance (x_d):

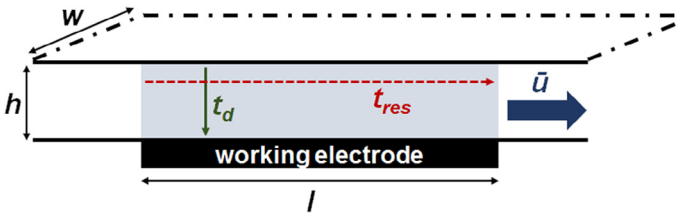

Fig. 1. A microfluidic channel with a working electrode (WE) at the bottom, which is a typical configuration for microfluidic electrochemical cells.

$$t_d = \frac{x_d^2}{2nD} \quad (1)$$

where D is the diffusion constant and n the dimensions in which diffusion takes place (1, 2 or 3).

In a microfluidic channel, the residence time is given by the length of the WE in contact with the solution (l) divided by the average linear flow velocity ($\bar{u}$), or by the channel volume above the WE (V) divided by the volumetric flow rate (Q):

$$t_{res} = \frac{l}{\bar{u}} = \frac{V}{Q} \quad (2)$$

In chromatography, the plate number represents the number of equilibrations during the residence time within the column and is approximated by Poppe [11] as:

$$N \approx \frac{t_{res}}{t_{eq}} \quad (3)$$

The equilibrium time (t_{eq}) (among other factors) depends on the diffusion coefficients and length of the diffusion path. In thin-layer flow cells, a similar situation is valid, since ions need to diffuse from the top of the channel to the bottom where the electrode is located. We can therefore define a plate number for thin-layer electrochemical flow cells, by replacing t_{eq} in Equation (3) with the diffusion time t_d as described in Equation (1), with x_d equal to the channel height h:

$$N_{tl} = \frac{t_{res}}{t_d} = \frac{2nDl}{\bar{u}h^2} = \frac{2nDV}{Qh^2} \quad (4)$$

This thin-layer plate number is a dimensionless number describing the electrochemical-conversion performance of a thin-layer electrochemical cell, analogous to the plate number in chromatography describing the separation performance of a column. In microfluidic channels, the surface area to volume ratio is very high (for the electrode and the channel volume above it this ratio scales with $\frac{1}{h}$) and the aspect ratio can be made low (height *versus* width of the channel, $\frac{h}{w}$). These properties are exploited to optimize electrochemical-conversion performance by locating electrodes at the bottom of shallow, wide channels (to minimize h and maximize V). According to Equation (4), thin-layer plate numbers can reach well above 1, while keeping total cell volumes low. This means that the microfluidic approach to electrochemical-cell design, in which electrodes are included in microfabricated channels, can result in both a high-performance electrochemical conversion and low consumption of analyte, which are beneficial for a variety of analytical applications, including EC-MS [12].

By careful design, the time between electrochemical reactions and MS detection can be reduced to a few seconds or less, allowing the study of reactive intermediates [13,14]. Moreover, flow rates in general are lower in microfluidic devices. Micro-scale EC is therefore more compatible with state-of-the-art nano-LC or nano-electrospray. Finally, the use of microfluidics allows chemical reactions under otherwise critical conditions to take place in a safe way, such as those involving highly reactive compounds or those taking place at high pressure [15]. It is for the latter reason that microfluidic chips can be used directly upstream of HPLC columns in an on-line approach.

3. Design aspects of miniaturized electrochemical cells

The design of a miniaturized electrochemical cell involves many aspects, including the choice of materials [substrate, WE, counter electrode (CE) and reference electrode (RE)], the cell geometry and