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Review

A review of microdialysis coupled to microchip electrophoresis for monitoring biological events

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ABSTRACT

Microdialysis is a powerful sampling technique that enables monitoring of dynamic processes *in vitro* and *in vivo*. The combination of microdialysis with chromatographic or electrophoretic methods with selective detection yields a "separation-based sensor" capable of monitoring multiple analytes in near real time. For monitoring biological events, analysis of microdialysis samples often requires techniques that are fast (<1 min), have low volume requirements (nL–pL), and, ideally, can be employed on-line. Microchip electrophoresis fulfills these requirements and also permits the possibility of integrating sample preparation and manipulation with detection strategies directly on-chip. Microdialysis coupled to microchip electrophoresis has been employed for monitoring biological events *in vivo* and *in vitro*. This review discusses technical considerations for coupling microdialysis sampling and microchip electrophoresis, including various interface designs, and current applications in the field.

Contents

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1. Introduction

Continuous monitoring of biomolecules in living systems is important for understanding neurological disorders, evaluation of drug delivery systems, determination of pharmacological responses to drugs and environmental factors, and bioreactor monitoring. Sensors provide a popular approach for monitoring biomolecules *in vivo* and *in vitro*, and commercially available sensors have been developed for many bioactive analytes [1–3]. These include sensors for glucose, nitric oxide, glutamate, and dopamine [4]. However, a major drawback of these sensors is that they are generally limited to detection of a single analyte. It is also not possible to monitor a group of structurally related compounds, such as a drug and its metabolites, in a single assay.

Microdialysis sampling was first introduced by Ungerstedt in 1974 as a method for continuous sampling of the extracellular fluid of the brain [5–9]. This sampling technique has enjoyed wide applicability and has been extensively employed in both research laboratories and clinics [10–17]. Microdialysis sampling is accomplished based on diffusion of molecules across a size-selective membrane. Therefore, microdialysis acts as a "generic" sampling system, in that the dialysate includes all the small molecules present in the extracellular fluid of the tissue that is being interrogated. The resulting dialysate is then collected and can be analyzed by a variety of techniques optimized for the compounds of interest. A major advantage of microdialysis sampling is that it makes it possible to monitor multiple analytes simultaneously (within a single analysis) as long as these analytes can be detected individually. Separation-based analytical systems, in particular, can provide the ability to monitor multiple analytes from a single microdialysis sample. These "separation-based sensors" (Fig. 1) have been used to continuously monitor multiple neurotransmitters in the brain, drug metabolism, and biomarkers of disease.

Analysis of microdialysis samples can be performed either off- or on-line. The most common method used for off-line separation-based analysis is liquid chromatography [15,18]. However, over the past twenty years, capillary electrophoresis has become increasingly popular [15,18–20]. An advantage of capillary electrophoresis for off-line analysis is that, because this technique requires only nanoliter amounts of sample, a single 1–10 μL microdialysis sample can be analyzed for several different classes of analytes by multiple capillary electrophoresis methods [21–23]. However, a major drawback of off-line analysis is that fairly large volume samples (1–10 μL) need to be collected to be compatible with the instrumentation and avoid evaporation during sample handling.

In order to avoid the issues with the manipulation and analysis of sub-microliter samples and provide a method for near real-time continuous monitoring, on-line separation-based systems have been developed (Fig. 1). Microdialysis has been coupled to liquid chromatography [14,15,18,24–27] and capillary liquid chromatography [28] for continuous monitoring of drug metabolism and neuropeptides. In 1994, microdialysis was first coupled to capillary electrophoresis and used to monitor the metabolism of an anticancer drug [29]. Later, it was coupled with on-line derivatization to monitor the release of aspartate and glutamate with 1 min temporal resolution [30].

Lab-on-a-chip devices were introduced in the early 1990s as a way to integrate multiple chemical processes into a single device [31]. Microchip electrophoresis was initially described by Harrison and Manz in 1992 [32–35], and the first high speed separations were published by Ramsey's group in 1994 [36,37]. The microchip format has all the advantages of capillary electrophoresis for on-line analysis of microdialysis samples, including efficient separations and ease of fluid handling, as well as the unique ability to integrate components such as mixers and detection directly on-chip. The first report of microdialysis coupled to microchip electrophoresis was demonstrated by monitoring an enzyme reaction in 2004 [38]. Since that time, there have been many papers describing new approaches and applications of this technique for monitoring biomolecules *in vivo* and *in vitro*. This review will describe the different approaches that have been developed for coupling microdialysis to microchip electrophoresis, as well as applications of this approach for on-line monitoring.

2. Microdialysis sampling

The key system components required to perform microdialysis (MD) sampling include connecting tubing, the sampling probe, and a perfusion pump. The probe consists of a semipermeable membrane that is attached to inlet and outlet tubing. In the case of animal studies, the probe is surgically placed into the tissue or organ of interest and perfusate is pumped through the tubing and into the probe. In most cases, the composition of the perfusate is as similar as possible to that of the extracellular fluid in the area of interest so as not to disrupt the biological system being interrogated. Compounds outside the probe diffuse across the semipermeable membrane based on their concentration gradient and are pumped to a fraction collector or on-line analysis system (Fig. 2). There are many membrane materials available for the fabrication of microdialysis probes, including polyacrylonitrile (PAN), polyarylethersulfone (PAES), cuprafan (CUP), and polyethersulfone (PES) [39]. These materials differ in charge and hydrophobicity and, therefore, impart some selectivity in the sampling process. The probes are also manufactured with a specific molecular weight cut-off (MWCO), which allows only molecules smaller than the cut-off to diffuse across the membrane. Commercially available probes have molecular weight cut-offs ranging from 6 to 100 kDa (Table 1).

Table 1
Commercially available microdialysis probes.

Probe type	Selected areas sampled	Membrane (MWCO)
Linear	*In vitro*, homogenous tissue	CUP (6 kDa), PES (55 kDa), PAN (30 kDa)
Rigid cannula	Brain	PAES (20 kDa), PES (100 kDa), CUP (6 kDa), PAN (30 kDa), Cellulosic (38 kDa)
Flexible cannula	Vasculature, soft tissue	PAES (20 kDa), PES (100 kDa), PAN (30 kDa)
Shunt	Bile	PAN (30 kDa)