Modular, Lightweight, Wireless Potentiostat-on-a-Disc for Electrochemical Detection in Centrifugal Microfluidics

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Article

Modular, lightweight, wireless potentiostat-on-a-disc (PoD) for elec-trochemical detection in centrifugal microfluidics

Sriram Thoppe Rajendran, Ermes Scarano, Max H Bergkamp, Alessandro M Capria, Chung-Hsiang Cheng, Kuldeep Sanger, Giorgio Ferrari, Line H Nielsen, En-Te Hwu, Kinga Zór, and Anja Boisen

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Abstract figure

76x43mm (600 x 600 DPI)

Figure 1. A) A simplified block diagram of the PoD unit; B) photographs of the main circuits of the PoD, the core circuit (platform) and shield (C) with indication of the electronic components.

211x50mm (600 x 600 DPI)

Figure 2. (A) Experimental setup with spindle motor, microfluidic disc assembled with the F-on-a-disc (PoD) and control software interface; (B) Exploded view of the assembled PoD with the LoD device.

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Figure 3. (A) Representative CVs of 1 mM FiC with PoD and commercial potentiostat, Au WE area: 50 mm², applied potential vs. pseudo Au-RE, Au-CE. The CVs were performed at a scan rate of 50 mV/sec; (B) Oxidation and reduction peak currents as a function of the square root of the scan rate; (C) SWVs of 10 mM ascorbic acid, (Carbon WE area: 50 mm², applied potential vs. Ag-RE, carbon CE). The SWVs were recorded with a potential step 0.004 V, frequency 10 Hz, amplitude 0.025 V; (D) Calibration plot recorded for different concentrations of ascorbic acid; (E) Calibration curve of paracetamol obtained with PoD and commercial potentiostat, using Au WE (area: 50 mm²), Au-CE and Au-RE. Applied potential +0.4 V vs. pseudo Au-RE; (F) CVs were recorded at various rotation speeds at 100 mV/sec scan rate in 1 mM FiC, Au WE area: 0.69 mm², applied potential vs. pseudo Au-RE, Au-CE. All measurements were performed in PBS as supporting electrolyte, pH 7.4 and standard deviation were calculated based on triplicates (n=3).

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Figure 4. Baseline noise measured during rotation in fluidics using PBS at applied potential of + 0.4 V vs. pseudo-Au-RE recorded with PoD and commercial potentiostat using the Au electrodes (WE area: 0.69 mm², pseudo-Au-RE, Au CE) pat-terned on PMMA.

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Figure 5. (A) Multichannel amperometric measurement in the LoD platform of 500 μ M FiC in PBS, pH 7.4 as supporting electrolyte at an applied potential of -0.4 V vs. pseudo-Au RE, using on PMMA patterned Au electrodes (WE area: 0.69 mm², pseudo Au-RE, Au CE) under 1, 1.5 and 2 Hz; (B). Calibration plot, showing the normalized current changes, recorded for different concentrations of FiC during rotation at 1, 1.5 and 2 Hz, (n=3).

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Figure 6. (A) Exploded view of the microfluidic disc; (B) View of the assembled microfluidic disc, with a highlighted measurement unit; (C) A cartoon showing one measurement unit with its functional parts

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Figure 7. (A) Optical measurements of flow rate vs. rotation frequency ($n=3$), for LoD platforms with microchannels in 86 μm thick PSA; (B) Amperometric release and dissolution of FiC in PBS, pH 7.4 as supporting electrolyte, at a potential of +0.4 V vs. Au pseudo-RE. PMMA patterned fabricated gold Au electrodes (WE area: 0.69 mm^2 , pseudo Au-RE, Au CE).

84x152mm (600 x 600 DPI)

Modular, lightweight, wireless potentiostat-on-a-disc (PoD) for electrochemical detection in centrifugal microfluidics

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ABSTRACT: Interfacing electrochemical sensors in lab-on-a-disc (LoD) system with a potentiostat is often tedious and challenging. We here present the first multichannel, modular, lightweight and wirelessly powered, custom-built potentiostat-on-a-disc (PoD) for centrifugal microfluidic applications. The developed potentiostat is in the form factor of a typical DVD and weighs only 127 g. The design of the potentiostat facilitates easy and robust interfacing with the electrodes in the LoD system, while enabling real-time electrochemical detection during rotation. The device can perform different electroanalytical techniques such as cyclic voltammetry, square wave voltammetry, amperometry while being controlled by custom-made software. Measurements were conducted with and without rotation using both in-house fabricated and commercial electrodes. The performance of the PoD was in good agreement with the results obtained using a commercial potentiostat with a measured current resolution of 200 pA. As a proof-of-concept, we performed a real-time release study of an electrochemically active compound from microdevices used for drug delivery.

Electrochemical (bio) sensors ^{1,2} have been successfully used in biomedical application ³, for food analysis ^{4,5}, environmental monitoring ⁶ as well as for drug development ^{7,8}. These sensors have been proposed suitable for integration in microfluidics ^{9,10} and were used in point of care devices ¹¹, cell-based assays ⁸ and in combination with wireless data transmission ^{12,13}. The electrochemical transducer (electrode) and instrumentation (potentiostat) can be miniaturized without losing performance ^{10,14–16} at a relatively low cost with a minimal power demand ^{17–19}. Therefore, electrochemical detection proved to be suitable for integration with microfluidics when developing portable, affordable devices for point of care, point of need or on-site analysis.

Centrifugal microfluidic platforms or so-called lab-on-a-disc (LoD) systems gained interest in both academic research and industry ^{20–25}. These microfluidic devices require relatively simple instrumentation for liquid handling, i.e., a spinning motor. The

miniaturization and automation of the motor facilitates a simple, compact and inexpensive system enabling the execution of complicated liquid handling steps ^{24,26} on a small footprint such as a compact disc. LoD devices are mainly used in combination with contact-free optical detection ^{27–32}. Typically, in the case of optical sensing, the transducer is not in direct contact with the detector. Therefore, the measurement could be easily performed by the addition of a peripheral optical device. However, the spinning of the disc should be stopped for optical measurements. Measurements during rotation are particularly challenging when there is a need for direct contact between transducer and detector. There are several examples describing the integration of electrochemical ^{31,33–37} detection in LoD devices. In certain cases, the measurements are performed in static condition, at end-point after fluidic operations were carried out ^{34,37,38} or during rotation with the help of a slip ring, ^{31,33,35,37,39} which was in turn connected to a commercial potentiostat.

Figure 1. A) A simplified block diagram of the PoD unit; B) photographs of the main circuits of the PoD, the core circuit (platform) and shield (C) with indication of the electronic components.

Nevertheless, both methods create complications in handling and necessitate more time for a measurement. Although a slip ring enables real-time measurements, it adds additional complexity to the experimental setup and severely limits the number of possible electrical contacts. Moreover, the brush connector in the slip ring wears out with time and hence, limits rotational frequency of LoD devices⁴⁰.

We have previously used mercury based slip rings, which has lower resistance in comparison to the typical slip rings with brush connectors³⁵, however even for single channel measurements, the interfacing with a commercial potentiostat was rather bulky and complex^{35,37}. In certain applications, e.g. immunoassays, end point measurements are suitable and there is no need for real-time detection. However, when the detection needs to be carried out on-site or a reaction must be followed in real-time, there is a need for a platform, which can be portable, enables straightforward interfacing and reliable detection during rotation. There are several application of the LoD devices, for point of care applications^{20,41–43} on-site^{44,45}, at-line^{28,37,46} and in-line⁴⁷ monitoring. However, portable electrochemical analyzers used in combination with LoD systems, which enable real-time, detection during rotation are scarce.

In the last few years there have been major developments in creating a compact, modular, portable centrifugal platform with integrated power generation and wireless communication system^{40,48–51}. The electrified-Lab-on-a-Disc (eLoaD)⁴⁹ offers various detection possibilities^[51] as well as temperature and valve control⁵⁰. More recently, a portable battery powered commercial potentiostat was integrated on the disc for real-time measurements⁵². This approach is a step closer in solving the interfacing challenge. Although, it eliminates the need for slip rings, it still suffers from the trivial problem of having a reliable electrical interface between the electrode and the potentiostat. As it has been highlighted by Bauer et al.⁵², due to poor contacts, significant noise can be generated during spinning, thus requiring fast Fourier transform data treatment. Moreover, the weight of the placed device affects inertia during spin, particularly when there is a need for quick acceleration and deceleration. In addition, the complex casing around the disc prohibits the view of the channels during spin.

This further emphasizes the need for a solution for improved interfacing of potentiostats with LoD devices.

Despite the development in this area, to our knowledge, there are no reports of a custom-designed potentiostat for LoD devices, which enables accurate electrochemical detection during rotation. Here, we present the development and performance of a wirelessly powered potentiostat integrated with LoD system with embedded electrodes. The performance of the potentiostat-on-a-

disc (PoD) has been compared with a commercial potentiostat and we

carried out a proof-of-concept study, evaluating release from drug delivery microdevices.

EXPERIMENTAL SECTION

Fabrication of PoD. The disc shaped platform and the PoD shield circuits were designed with a computer aided design (CAD) software Altium (Altium LLC, La Jolla, USA). The platform is controlled by an ATmega2560 microcontroller, which integrates a 205 kHz inductive wireless power receiver, a low noise power regulator, single channel 14-bit digital-to-analog converter (DAC)/ analog-to-digital-converter (ADC), two input/output pin headers and a 2.4 GHz Bluetooth wireless communication module. The microcontroller firmware was programmed with an Arduino (Arduino, Turin, Italy) integrated development environment. All the electronic components were purchased from RS components (RS Components, Corby, UK) and Digi-key (DigiKey Electronics, Minnesota, USA). In addition the multichannel shield composed of four potentiostat circuits, each of them in the three operational amplifier buffered reference configuration driven by the same input potential, and a digitally controlled analog switch for output multiplexing. The printed circuit boards (PCBs) were from ShingTech, Taiwan. The components were assembled and tested in-house.

Fabrication of LoD. The centrifugal microfluidics device with eight detection units, consisting of gold (Au) electrode arrays (working electrode (WE), counter electrode (CE) and pseudo-reference electrode (pseudo-RE)). The electrodes patterned on the bottom of the poly(methyl methacrylate) (PMMA) substrate were fabricated as described earlier^{37,53,54}, using e-beam evaporation (20 nm Cr adhesion layer / 200 nm Au). The LoD device was designed using software Solidworks 2017 (Dassault Systèmes, Vélizy-Villacoublay, France). The optical grade PMMA (Evonik Industries AG, Essen, Germany) was cut using a computer-controlled Epilog Mini 18 laser cutter equipped with a 30 W CO₂ laser (Epilog Laser, Houten, The Nederland). One PMMA layer has been designed to have pores of 160 μm $\varnothing$, with 0.5 mm spacing, to act as filters to physically prevent the microcontainers from blocking the channels connecting the loading to the detection chamber. Two different double-sided pressure sensitive adhesive (PSA) tapes each of 140 μm thickness (ARcare 90106, Adhesive Research, Limerick, Ireland) and 84 μm thickness (ARcare 7840, Adhesive Research, Limerick, Ireland) were cut using a precision blade cutter (CE-40, Graphtech, USA). The PMMA layers of the LoD system were bonded together via the

PSA and placed in the hydraulic bonding press (PW20, Paul-Otto Weber GmbH, Remshalden, Germany) at 15 N/m² for 1 min.

Fabrication of open vial LoD. A PMMA layer (2 mm) was designed and cut in such a way that it acts as a reservoir when placed above the electrodes patterned on PMMA (1.5 mm). These two PMMA layers are held together using a layer of PSA. There are three different open vials LoD used in the present study. The open vial LoD-1 was interfaced with large (area 50 mm²), while LoD-2 with small (area 0.69 mm²) Au electrodes, patterned on PMMA. The open vial LoD-3 has an additional middle layer of PMMA (0.6 mm) to hold the commercially available screen printed carbon electrode (area 50 mm²) (DRP 110, Metrohm-Dropsens, Llanera, Spain) in place.

Figure 2. (A) Experimental setup with spindle motor, microfluidic disc assembled with the F-on-a-disc (PoD) and control software interface; (B) Exploded view of the assembled PoD with the LoD device.

Electrical measurements. The characterization of the voltage generation circuit was performed by measuring the voltage of the "analog output" pin of the platform with a benchtop digital multimeter (973A, Hewlett Packard) and mapping the measured value with the corresponding 14-bit DAC code. For the characterization of the measured current in the circuit (transimpedance amplifier + 14-bit SAR ADC) the shield was set in the 2-electrodes configuration (RE and CE shorted) with WE and CE connected through a reference resistor (R_x). The applied potential pin of the potentiostat shield was connected to waveform generator (embedded waveform generator of the DSO 2WAVEGEN Oscilloscope, Keysight (Santa Rosa, USA)) to generate the reference input voltage (V_x). The ADC output is

mapped to the reference input current (I_x), since I_x is given by dividing V_x with R_x .

Electrochemical measurements. The electrochemical measurements were performed in a conventional three-electrode setup with both the PoD system and with a commercial potentiostat (CHI660C, CH Instruments Inc., Austin, USA) for comparison, when applicable. Cyclic voltammograms (CVs) were recorded from -0.4 V to $+0.4$ V vs. Au pseudo-RE in 1 and 10 mM potassium ferricyanide (FiC)/ potassium ferrocyanide (FoC) with phosphate buffered saline (PBS) (10 mM phosphate, 137 mM NaCl, 2.7 mM KCl), pH 7.4, as supporting electrolyte, at various scan rates (10, 25, 50, 100 mV/sec) with open vial LoD-1. Square wave voltammetry (SWV) with a step potential of 1 mV, square-wave frequency of 10 Hz and amplitude of 50 mV was carried out using different concentrations of ascorbic acid from 0.1 M to 10 mM using open LoD-2. CVs were recorded both in static and fluidics, while SWVs were only recording in static condition. Amperometric measurements were carried out both in static and in fluidics (during spin) with custom made Au electrodes (area 0.69 mm²). Detection of paracetamol from 0.15 mM to 3.3 mM in static was carried out at $+0.55$ V vs. Au pseudo-RE. In addition, calibration in flow during rotation, was performed using amperometric detection with the multi-channel shield, using FiC in the range from 0.1 mM to 10 mM at -0.4 V vs. Au pseudo-RE. The rotation of the LoD at different frequencies (1 and 1.5 Hz) was achieved with a spindle motor (RE 35, Maxon motor AG, Sachseln, Switzerland). All chemicals if not otherwise specified were purchased from Sigma Aldrich (St. Louis, USA). Solutions were prepared in ultrapure water (Millipore Corporation, Billerica, USA).

Flow rate measurements. To determine the flow rate, 200 μ L blue ink (Staedtler, Nürnberg, Germany) dissolved in distilled water (1:1000), was added in the loading chamber. The channel was primed by spinning the disc with a frequency of 12 Hz for 2 sec. Subsequently, the metering chamber was filled up with fluid by spinning with a lower frequency (5 Hz). When the metering chamber was completely filled the spinning motor was turned on and images were recorded using a program (PCO Camware 64, PCO AG) as described previously⁵⁴. The obtained raw image data were analyzed using Matlab (R2017a, MathWorks, Natick, USA).

Fabrication and loading of microcontainers. The epoxy-based photoresist SU-8 (SU-8 2075 / SU-8, Microresist Technology GmbH, Berlin, Germany) was used to fabricate the microcontainers with two-steps of photolithography. The microcontainers with an inner diameter of 234.5 μ m and a depth of 211.0 μ m, were fabricated on top of a Teflon coated silicon wafer (4-in. b100N n-type, Okmetic, Finland)^{55,56}. After fabrication, the wafers were cut into chips (12.8 x 12.8 mm²), with 625 microcontainers/chip, using laser microstructuring tool (microSTRUCT vario, 3D Microac AG, Germany). The FiC was loaded in the microcontainers by powder embossing. The excess FiC in between the microcontainers was removed with pressurized air.

Release monitoring from microcontainers. Initially, the microchannel was primed (12 Hz for 2 sec) with 100 μ L PBS, followed by filling up (5-6 Hz) of the metering chamber with 50 μ L PBS for precise volume control. The microcontainers filled with FiC were scraped off the Teflon/silicon wafers and $\frac{1}{4}$ of the chip (approximately 156 microcontainers) inserted in the access hole with spatula, followed by the addition of 150 μ L PBS in the loading chamber. The electrochemical detection was carried out during priming in the absence of electrochemically active compound (FiC) (for baseline) with PBS, and during rotation in the presence of loaded microcontainers, at 1.5 Hz.

Data acquisition software and data analysis. During the experiment with PoD, the generated data was transmitted via Bluetooth to a Windows PC. The data was plotted live and

displayed in the custom made LabVIEW (National Instruments, Austin, USA) program. After experiments, the data file was saved in text format automatically with a time stamp and technique name. The obtained raw data from the developed potentiostat was treated using Savitzky-Golay method with 30 points averaging. Origin 2018b (OriginLab Corp., Northampton, USA) was used to analyze and display the data. For the calibration curves the peak heights (SWV) and current changes (amperometry) were obtained either using the CHI data analysis software or Origin 2018b (PoD).

RESULTS AND DISCUSSION

Design of the PoD unit. The PoD was designed to be versatile for centrifugal microfluidics-based application. The modular structure of the device enables direct, effortless, and robust interfacing with the electrodes optical observation of the reaction chamber and provides the possibility for further instrumental development, with compatible functional units.

As depicted in Figure 1A, the PoD detection unit is composed of three main functional parts: (i) a 5V-250 kHz Qi-based wireless power supply, (ii) a core circuit (platform) and (iii) a module (shield). The device works in stream processing and can be controlled by any external device such as a smartphone (Android studio) and a PC (LabVIEW) through Bluetooth communication. At every iteration, a DAC output signal is generated and an ADC sample is collected.

The core circuit, called platform (Figure 1B) houses the main potentiostat features. It is composed of a single channel 14-bits DAC, which controls the potential of the WE vs. RE as well as a 14-bits SAR ADC for high speed/high resolution data sample. The function of the ATmega 2560 microcontroller is to operate the device, while the serial interface enables to programming of the microcontroller. In addition, a HC-05 Bluetooth module is used for wireless data communication and a 16-pin header interface facilitates the connection of the platform to the specific module (shield).

The shield was mounted above the microfluidic disc and has been designed such that it permits the imaging of the LoD device during rotation, with minimal obstruction of the fluidics view. This part of the PoD can be configured when adding complementary features (e.g. multiplexing) to the detection unit, and contains a three-electrode potentiostat circuit in the three operational amplifier/buffered reference configuration with 24 spring-loaded connectors for direct short path connection between the potentiostat and the electrodes (Figure S1A). The 24 spring loaded pins enables connection to a maximum of 8 electrode arrays, each array composed of three electrodes (WE, RE and CE). As indicated in Figure 1C, the shield is equipped with a switch to select the current range of the measurement. Additionally, a multi-channel application specific shield (Figure S1B) was also developed to enable four electrochemical measurements at the same time.

Evaluation of the performance of the PoD. The potentiostat has been designed to perform commonly used electrochemical detection techniques, such as CV, SWV and chronoamperometry. However, other electrochemical techniques can be easily programmed via a custom made LabVIEW program when required. The experimental set-up is presented in Figure 2A. During experiment the PoD was placed on stage and connected to a spindle motor controlled by custom-made software in a LabVIEW environment. The assembly of the system and the concept of the modular design is depicted in Figure 2B, showing the four main functional parts: a power source, a platform, a fluidic disc with integrated electrodes and a shield.

The performance of the PoD was evaluated as described in details in the Material and methods section. The PoD, with power rating of 850 mW, enables the generation of DC voltage range between

$\pm 1\text{V}$ at a resolution of $200 \pm 40 \mu\text{V}$ having the possibility to manually choose the transimpedance gain (10 k Ω , 100 k Ω , 1 M Ω , 10 M Ω).

Figure 3. (A) Representative CVs of 1 mM Fc with PoD and commercial potentiostat, Au WE area: 50 mm², applied potential vs. pseudo Au-RE, Au-CE. The CVs were performed at a scan rate of 50 mV/sec; (B) Oxidation and reduction peak currents as a function of the square root of the scan rate; (C) SWVs of 10 mM ascorbic acid, (Carbon WE area: 50 mm², applied potential vs. Ag-RE, carbon CE). The SWVs were recorded with a potential step 0.004 V, frequency 10 Hz, amplitude 0.025 V; (D) Calibration plot recorded for different concentrations of ascorbic acid; (E) Calibration curve of paracetamol obtained with PoD and commercial potentiostat, using Au WE (area: 50 mm²), Au-CE and Au-RE. Applied potential +0.4 V vs. pseudo Au-RE; (F) CVs were recorded at various rotation speeds at 100 mV/sec scan rate in 1 mM Fc, Au WE area: 0.69 mm², applied potential vs. pseudo Au-RE, Au-CE. All measurements were performed in PBS as supporting electrolyte, pH 7.4 and standard deviations were calculated based on triplicates (n=3).

The measurable current range can vary from $\pm 400 \text{ nA}$ to $\pm 400 \mu\text{A}$ depending on the used gain, with a measured current resolution of 200 pA at 10 M Ω gain setting (Table S1).

We found that the standard deviation of the measured current was 0.075 % (of the range) for 10 M Ω and 0.03% (of the range) for 10 k Ω , 100 k Ω and 1 M Ω gain. Due to the sampling rate of 25 ms the maximum scan rate for CV was $\Delta V \cdot 1000 / 25\text{V/s}$ and the maximum frequency for SWV was 20 Hz. ΔV is the parameter (voltage resolution) defined by the user in the program which in turn controls the voltage step of the DAC, ΔV does not necessarily coincides with the minimum. While the time (sec) is defined by the sum of time taken for the transfer of a single

sample data between the computer to PoD via Bluetooth, signal propagation time through the PoD and the time for conversion and plotting in real-time.

The electrochemical performance of the potentiostat was evaluated both in static and flow condition. All static measurements were performed in open vial LoD systems (Figure S2). An open vial LoD system can be used for electrochemical characterization as well as for calibration⁵⁴.

SWV is a well-accepted voltammetric technique for quantitative measurements⁵⁷. Ascorbic acid (vitamin C) is an antioxidant, commonly used in the food industry, since addition of ascorbic acid averts undesired changes in flavor and color. Therefore, monitoring ascorbic acid for quality control is very important^{58,59}. SWVs were recorded with commercially available carbon electrodes in the open vial LoD-3 (Figure S2C), using different concentrations of ascorbic acid from 500 μ M to 10 mM. The SWVs presented in Figure 3C, are the signals from 10 mM ascorbic acid recorded with commercial potentiostat and PoD. Figure 3D presents the comparison of the data collected with both potentiostats and shows that the signal recorded with PoD was comparable with the data obtained with the commercial system.

In addition we performed amperometric measurements with paracetamol, an electrochemically active drug, commonly used for pain and fever relief⁶⁰ and is commonly detected using electrochemical techniques^{61,62}. Due to its continuous use in large scale, paracetamol has become one of the most prominent contaminants in water bodies and it has been shown that excessive intake of this compound can cause hepatotoxicity^{63,64}. The experiment was performed in a static condition by successive addition of paracetamol in the reservoir of the open vial LoD-2 (Figure S2B). We found a good comparison between the values obtained from the PoD and commercial potentiostat as seen in Figure 3E.

The light weight design of the PoD is especially important when performing measurement during rotation, since the weight of the device can greatly affect the inertia during spinning⁵². The modular nature of the PoD helps in distributing the weight by combining the platform (108 g) and the disk holder (26 g), thus displacing the center of gravity more towards the spindle motor. The shield weighing 19 g, is the only weight placed on top of the LoD device.

We evaluated the performance of the PoD during rotation and compared the baseline noise, with the data recorded using the commercial potentiostat, in PBS at applied potential of + 0.4 V vs. pseudo-Au-RE. The connection of the electrodes to the commercial potentiostat was achieved with a slip ring (SRS110073, Penlink, Sweden) as shown in Figure S3, a method commonly used when connecting electrochemical sensors in centrifugal microfluidics^{31,35,39}. Both the PoD interfaced with the electrodes in the LoD and the commercial potentiostat connected through a slip ring were rotated at 1, 2, 3, 5, 8 and 10 Hz. The raw signal, as recorded with the PoD, without any internal filtering is shown in Figure 4, in comparison with the data obtained from the software of the commercial potentiostat. We observed that at lower rotation speeds (1 and 2 Hz) the baseline current is comparable in both instruments. Despite using raw data, the acceleration and deceleration of PoD causes low noise ($\approx 3 - 6$ nA). At higher rotation speeds we recorded higher peaks in the signal with the PoD, than with the commercial potentiostat. The electrochemical baseline noise, recorded as peaks are due to the movement of PBS over the electrode surface as a result of inertia when changing the speed of rotation. The lack of peaks at 3 and 5 Hz and the lower peaks in the baseline recorded with the commercial potentiostat is probably due to the internal noise filtering while converting analog signals to digital (ADC) during data acquisition. Based on our experiments, the observed noise during acceleration and deceleration recorded with both instruments is mostly electrochemical and not instrumental.

The presented data in the manuscript was treated using the Savitzky-Golay method as described in the 'Data acquisition software and data analysis' section and there was no need for any fast Fourier transform data treatment as reported by Bauer et al.⁵²

Figure 4. Baseline noise measured during rotation in fluidics using PBS at applied potential of + 0.4 V vs. pseudo-Au-RE recorded with PoD and commercial potentiostat using the Au electrodes (WE area: 0.69 mm², pseudo-Au-RE, Au CE) patterned on PMMA.

Considering that the maximum baseline noise recorded in PBS was 6 nA, the theoretical lowest measurable signal at limit of detection, would be 18 nA ($S/N=3$). In our experiments the lowest measured signal for an analyte was 45 nA in static (Figure 3E) and 100 nA in flow (Figure 5A). However, as it can be seen in Figure 5A, measuring lower electrochemical signal than 45 nA is feasible.

CVs were also recorded at different rotational frequencies (Figure 3F) using electrodes integrated in the fluidic system (Figure 6). We observed that at 0 and 1 Hz the reaction is diffusion limited, while at rotation speeds at and above 2 Hz the curve is reaction limited due to mass transfer as has also been reported previously⁵².

So far, in the case of LoD systems multiple electrochemical measurements during rotation, were only feasible when connecting the electrodes in the fluidic system to a multichannel potentiostat through a slip ring³⁷. In the presented PoD, multichannel detection capability was also implemented using the multichannel shield (Figure S1B). The amperometric detection presented in Figure 5A was performed with four electrodes at the same time during rotation.

Previously in an electrochemical LoD device, it has been shown that an increase in flow rate results in increased current response³⁹. We evaluated the effect of rotational frequency on amperometric measurements. As it can be seen in Figure 5A and 5B the current arising from the electrochemical reduction of FiC increased when increasing the flow rate. We recorded the same behavior when working with paracetamol (Figure S5). This effect was proposed and used for increasing the sensitivity of electrochemical detection^{39,52}.

Real-time release from drug delivery microdevices. Dissolution and release of drugs are of high importance in the development phase of new oral drug formulations and delivery systems^{65,66}. For a drug to be absorbed after oral administration, it needs to be dissolved before it can pass the intestinal membrane and be absorbed into the bloodstream. For being able to deliver more drugs by the oral route, novel oral drug delivery systems are needed. One such system is the polymeric microcontainers which

serve to protect the drug through the stomach followed by a drug release in the intestine^{67–69}. Such devices are increasingly utilized for drug delivery^{67,70,71}, and it is essential to characterize them

(e.g. release studies).

Figure 5. (A) Multichannel amperometric measurement in the LoD platform of 500 μM FiC in PBS, pH 7.4 as supporting electrolyte at an applied potential of -0.4 V vs. pseudo-Au RE, using on PMMA patterned Au electrodes (WE area: 0.69 mm², pseudo Au-RE, Au CE) under 1, 1.5 and 2 Hz; (B). Calibration plot, showing the normalized current changes, recorded for different concentrations of FiC during rotation at 1, 1.5 and 2 Hz, ($n=3$).

Most of the current setups for studying drug release from micro devices such as microcontainers are not appropriate, as the volumes are very large compared to the quantity of drug in the devices. Therefore, it is essential to exploit new ways to investigate drug release in much smaller volumes and thereby, also more relevant compared to the *in vivo* situation^{67,72}. The microfluidic disc developed for monitoring drug release from microdevices is composed of four PMMA layers (Figure 6A, layer 1, 3, 5 and 7) of which the bottom PMMA layer (layer 7) contains the patterned Au electrode arrays. The three layers of PSA (Figure 6A, layer 2, 4 and 6) are used for assembling the PMMA layers. The fully assembled LoD device with eight measurement units is shown in Figure 6B. Each unit has three main functional parts: (i) loading chamber with embedded filters and access holes used for the addition of liquids and microdevices; (ii) microchannel connecting the loading and the metering chamber, with integrated Au electrode array (WE, CE,

RE); and (iii) metering and waste chamber (Figure 6C). The dimension of the microchannel along with the spinning speed defines the flow rate, while the embedded filter with pores of 160 μm ϕ , with 0.5 mm spacing, and physically prevents the microdevices from entering the microchannel during release studies. The metering chamber is designed to hold a volume of 50 μL . The metering chamber is useful to collect the fluids during priming which usually requires a high burst frequency (12 Hz). After the overflow of 50 μL in the metering chamber, a uniform flow rate can be established at lower flow rates ($1 - 2$ Hz).

Figure 6. (A) Exploded view of the microfluidic disc; (B) View of the assembled microfluidic disc, with a highlighted measurement unit; (C) A cartoon showing one measurement unit with its functional parts.

In order to use the LoD system for drug release studies, the flow rate in the microfluidic channel needs to be evaluated. Given that the working volumes in the fluidic system are in the range of a few 100 μL , the assay needs to be performed at relatively low rotation frequencies to enable real-time detection of drug release for longer durations. The flow rates were evaluated optically using a MATLAB program and the results were compared with theoretically calculated values (Supplementary information).

One of the main challenges when developing the LoD device was to obtain a reliable and controllable flow at low (below 10 $\mu\text{L}/\text{min}$) flow rate in order to be able to perform real-time release studies, using small amounts of microdevices in a relatively low volume (approx. 100 μL). Figure 7A shows, the correlation between flow rate and rotational frequency, comparing experimental and theoretical values. We found that in the developed LoD we can achieve flow rates in the range of 1 - 10 $\mu\text{L}/\text{min}$ enabling a total assay time from 10 up to 100 min, considering 100 μL volume in the loading chamber.

We observed that the thickness of the used PSA layer is crucial when aiming for precise control of the flow rate. There were substantial differences between measured and theoretically calculated higher hydraulic resistance due to the PSA being pressed in the microchannels during the assembly process (calculations provided in Supplementary material).

The real-time release was evaluated from the microcontainers (50 microcontainers) loaded with FiC. The porous feature i.e., filters on PMMA, in the bottom of the chamber (layer 5, Figure 6A), physically prevented the microcontainers from blocking the channels leading to the detection chamber during spin. At -0.4 V (vs. Au pseudo Au-RE) FiC is reduced and the resultant

electrochemical signal was recorded. After the fluidic system was primed, a baseline was recorded in a static condition for 30 sec in PBS, before the rotational frequency was set to 2 Hz. In a similar manner, we followed the dissolution of 50 μL FiC solution (10 mM) respectively. Figure 7B shows the stable baseline recorded with PBS as well as the dissolution and release curves as current vs. time. The release of FiC from microcontainers (blue curve) results in an initial high current indicating burst release as

Figure 7. (A) Optical measurements of flow rate vs. rotation frequency ($n=3$), for LoD platforms with microchannels in 86 μm thick PSA; (B) Amperometric release and dissolution of FiC in PBS, pH 7.4 as supporting electrolyte, at a potential of +0.4 V vs. Au pseudo-RE. PMMA patterned fabricated gold Au electrodes (WE area: 0.69 mm^2 , pseudo Au-RE, Au CE).

previously reported⁶⁹. When measuring release from microcontainers, in one of the curves, a small current fluctuation is seen for about 8 seconds. This may be due to a momentary re-orientation of microcontainers during release.

From the stabilized current at 400 sec, we can estimate the amount of released FiC to be 1.25 mM, based on the calibration curve presented in Figure 5B. In addition, the current profile measured from the FiC solution (green curve) is different, as burst release is not seen, which is expected considering the mixing of the FiC with PBS in the loading chamber. The concentration in this case calculated based on the calibration curve in flow (Figure 5B) is 2.5 mM as anticipated considering the dilution in the loading chamber. The release of FiC from the microcontainers mimics the situation of drug delivery from these devices, while the dissolution of solution is a simplified case of free drug. This application as an example demonstrates the ability to measure on-line and in-flow during spinning.

CONCLUSION

We present for the first time, a modular, lightweight, wirelessly powered potentiostat-on-a-disc for centrifugal microfluidic applications. The developed device provides a practical solution to one of the trivial interfacing challenges during spinning. The presented results demonstrates the performance of the developed device on par with a commercial potentiostat. Considering the shield design which enables visibility of the fluidics during spinning opens up the possibility for real-time optical detection in the future. The flexibility and modularity of the system provides room for implementation of additional electrochemical techniques (e.g. linear sweep voltammetry, differential pulse voltammetry, impedance spectroscopy).

The developed potentiostat in combination with the microfluidic systems, designed for drug dissolution and release studies, opens new avenues for drug delivery studies from drug delivery microdevices. The PoD in combination with the presented microfluidic disc could be used for the investigation of drug release profiles from microdevices with various polymer coatings (e.g. pH-sensitive polymers). In addition, the portability of the PoD coupled with custom designed LoD unit can be applied for on-site detection (e.g. environmental analysis) or point of care application in diagnostics.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Complementary information about the shield modularity and details about the multi-channel shield, table summarizing the PoD performance, photos of the used open vial LoD systems, experimental setup for noise measurement with commonly used slip ring system. Calculation of the theoretical flow rate and show the comparison of calculated and measured flow rate values using 140 μm pressure sensitive adhesive film and electrochemical detection of paracetamol in the LoD platform during rotation (PDF).

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Notes

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