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Research Paper

Rapid identification and quantification of illicit drugs on nanodendritic surface-enhanced Raman scattering substrates

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ABSTRACT

In this paper, we demonstrate rapid, sensitive and specific detection of illicit drugs in both aqueous samples and saliva using surface-enhanced Raman scattering (SERS) substrates with a unique, dendritic architecture. The substrates are prepared on a reusable microelectrode platform by electrokinetically assembling colloidal silver nanoparticles from a droplet. Identification and quantification of illicit drugs is accomplished on these substrates with the aid of Principal Component Analysis (PCA) coupled with a Support Vector Machine (SVM). We demonstrate 100% accuracy in the detection of four different illicit drugs (cocaine, heroin, THC, and oxycodone), and 98.3% accuracy in the quantification of cocaine across four orders of magnitude. Finally, we demonstrate a simple method, with limited sample processing, for the ultrasensitive detection of cocaine in saliva to a limit of detection of 100 ppb.

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1. Introduction

The increasing abuse of illicit or recreational drugs represents a major public health and safety risk, identifying a crucial need for an effective technique to detect these chemicals in roadside, workplace, or emergency room applications. Worldwide, it is estimated that a quarter of a billion people abuse at least one illicit drug annually, leading to 207,400 drug-related deaths [1]. Ideally, a drug detection technology should be: (1) sensitive, such that drugs can be detected at relevant concentrations; (2) specific, such that false negatives and resulting further investigations are avoided; (3) rapid and portable, enabling point-of-use detection in a wide variety of environments; (4) inexpensive, and (5) user friendly – that is, simple and intuitive for a non-technical user (e.g. a police officer). To date, the commercial detection mechanisms used for sensing illicit drugs or their metabolites in blood, urine, saliva or seized material samples predominantly use immunoassay methods (e.g. ELISA) for screening, followed by liquid/gas chromatography combined with mass spectrometry (LC–MS or GC–MS), for confirmation [2–4]. These methods, although sensitive and specific, require dedicated laboratory facilities, expensive equipment, and trained personnel, all of which significantly limit the potential for widespread point-of-use analysis [4,5]. Furthermore, this inherently two-tiered system requires that the sample (and potentially the individual) be transferred, adding to the time required to obtain results and imposing potential legal complications.

Surface-enhanced Raman scattering (SERS) is an emerging technology that provides a specific spectral fingerprint of an analyte via inelastic light scattering from the sample. Through plasmonic effects on nanostructured metallic surfaces, SERS achieves necessary signal intensities to detect molecules at ultralow concentrations [6]. SERS finds strong applications in medical diagnostics, therapeutic monitoring, food safety analysis, forensics, and potentially, if integrated into a microcapsule, as ingestible sensors for gut health analysis or therapeutic monitoring [7,8]. Several groups have applied SERS for the detection of drugs in aqueous solution; these methods are well summarized in a review by Ryder [9]. SERS is generally applied through one of two methods: (1) by using a microfluidic chip in which the analyte interacts with nanoparticles in solution, promoting colloidal aggregation in the laser detection site; or (2) by using a chip with a fixed metal nanostructure, which functions as a sensing surface. The former method often suffers from poor reproducibility and a transiency of SERS-active sites [10], while the principal challenge in the latter method arises in the fabrication of the sensing surfaces. Generally, in order to reproducibly fabricate a nanostructured metallic surface, highly specialized equipment, a dedicated cleanroom facility and trained personnel are required [11,12]. An alternative is the cheaper method (which has been used by several producers of commercial SERS substrates) of dropcasting silver nanoparticles on a

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paper-based/cellulose substrate, and allowing for their aggregation to form randomly distributed hot spots. This method, although convenient and inexpensive, suffers from poor reproducibility in signal enhancement. Additionally, paper renders the substrate single-use [13]. Emerging methods employ wet-chemistry techniques for the production of nanostructured substrates [14]. These methods typically involve the electrochemical growth of nanostructured material onto solid supports through replacement reactions, starting with metal salt (e.g. $AuCl_4$, $AgNO_3$) in solution [15,16].

Here, we present the application of a novel SERS sensor, produced through an electric field-guided assembly process of colloidal silver nanoparticles into ultrasensitive 'nanodendrites' upon a silicon surface. These SERS surfaces form quickly (within 12 min), and are washable with a simple soap solution, enabling reusability, thus increasing cost-effectiveness. We demonstrate that through the application of chemometric methods we are able to achieve accurate identification of four illicit drugs: cocaine, heroin, tetrahydrocannabinol (THC, the active component in marijuana), and oxycodone, in aqueous solutions. Additionally, we demonstrate the capacity for order of magnitude quantitative detection of cocaine. Finally, we demonstrate real-world applicability through sensing of cocaine in saliva at relevant concentrations.

2. Experimental

2.1. Materials

Cocaine (1 mg/mL in acetonitrile), heroin (1 mg/mL in acetonitrile), tetrahydrocannabinol (1 mg/mL in methanol), oxycodone (1 mg/mL in methanol), and acetonitrile were obtained from Sigma-Aldrich (Oakville, ON). Silver nanoparticles of 50 nm in diameter, stabilized in 2 mM citrate were obtained from Cytodiagnostics Inc. (Burlington, ON). Polished silicon wafers (4″ diameter) with a thermally grown SiO_2 layer (0.5 μm) were purchased from University Wafer (South Boston, MA, USA). Millipore® water (18.2 MΩ cm) was used for all drug dilutions.

2.2. Microchip fabrication

The microfabrication of electrodes was carried out at Nanofabrication Kingston (NFK, Innovation Park, Kingston, Ontario) through maskless photolithography on silicon wafers, followed by electron beam metal film evaporation and liftoff. The negative photoresist SU-8 (MicroChem Corp, Westborough, MA) was used with the IMP maskless photolithography system to transfer the microelectrode pattern to the silicon substrate. A 5 nm layer of chrome was used to improve the adhesion of the deposited Au layer (100 nm thickness) to the silicon substrate.

2.3. SERS substrate preparation

The nanoparticles were concentrated prior to use through centrifugation at 3800*g* for 20 min, followed by removal of the supernatant to reach a final concentration of 2.9×10^{11} particles/mL. Samples were sonicated post-concentration. A Zetasizer Nano ZS (Malvern, Inc.) was used to measure the hydrodynamic radius (67.7 nm) of the nanoparticle suspensions, to ensure that a unimodal, non-aggregated, stable dispersion was consistently used in the experiments. For nanoparticle deposition, a 10 μL sample of concentrated NP solution was placed over the microelectrode center using a micropipette (Fig. 1a). The collection was run for 12 min at an AC frequency of 10 Hz, and a peak-to-peak voltage of 2.9 V, with a 0.5 V DC bias. Following NP deposition, the chip was washed with water and dried in a stream of air.

2.4. Raman measurements

For each experiment, a 5 μL analyte solution was deposited on the dendrite-modified microelectrodes using a micropipette and left to evaporate. A HORIBA/Jobin Yvon Raman Spectrometer (Model: LabRAM) with a 632.8 nm He/Ne laser (17 mW), 1800 1/nm grating and an Olympus BX-41 microscope system were used. The collection of spectra was performed in the backscattered mode under the following conditions: x100 microscope objective, 500 μm pinhole, 500 μm slit width, attenuation filter 10x, for a sampling time of 10 s with 10 repeats. Following SERS measurements, the surface was cleaned by gentle brushing with a cotton swab and a solution of dish soap with water. This regenerated the clean silicon microelectrode for future nanoparticle deposition and SERS measurements.

2.5. Saliva processing

Saliva samples were self-collected by healthy donors, and used immediately after collection. Cocaine solution was added to saliva to a final concentration of 100 ppb. The following method was employed to crash out the proteins from the saliva: (1) acetonitrile was added at a ratio of 1:1, (2) the solution was centrifuged at 2700*g* for 20 min, (3) the supernatant was removed for analysis. Only small sample volumes are required for analysis, approximately 5 μL.

2.6. Multivariate analysis

Spectral processing and multivariate analysis (MVA) was performed using Matlab (R2017a). Spectra were filtered using a Savitzky-Golay filter before being corrected using a derivative function (derivative function used for MVA). The built in Matlab function 'pca' was used to perform PCA and calculate the PCs. The principal components were standardized before the Classification Learning App was used to calculate a linear SVM model for discrimination between different sample classes. Baseline correction and Hotelling T^2 test were performed using functions available on Mathworks [17,18].

3. Results and discussion

Here, we present the results of our recently established technology, through which synthesis of SERS substrates is accomplished by means of an electric field-guided assembly process of colloidal silver nanoparticles. These substrates can be formed on the surface of reusable microelectrode chips energized by an alternating current (AC) signal [19]. The interaction between the electric field and the colloidal droplet brings about a host of electrokinetic phenomena (dielectrophoresis, electrophoresis, mutual dielectrophoresis) that cause Ag nanoparticles to collect along the electrodes and follow an assembly process in the microelectrode gap. Under the proper conditions (AC voltage and field frequency) it can be seen that the Ag nanoparticle assembly produces an ultrasensitive branched layer, consisting of a dendritic structure with a high density of SERS hot spots (shown by optical microscopy, scanning electron microscopy (SEM), and transmission electron microscopy images (TEM) in Fig. 1 [19]). The assembly, detection, and regeneration steps are shown schematically in Fig. 2. The first step involves *in situ* assembly of the sensor: an Ag nanoparticle suspension is placed upon the microelectrode surface, and the microelectrodes are activated at 10 Hz, 2.9 V peak-to-peak, with a 0.5 V DC bias for 12 min. At this frequency, electrohydrodynamic flows are minimized and the nanoparticles form branched structures through a mass-limited growth process. The DC bias functions as a protective electrostatic barrier, preventing shorting of the electrodes, and also improves the dendritic surface coverage [19]. Next, the nanoparticle droplet

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