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Swellable polymer films containing Au nanoparticles for point-of-care therapeutic drug monitoring using surface-enhanced Raman spectroscopy

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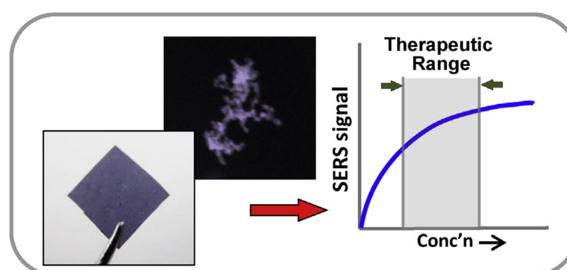
HIGHLIGHTS

- SERS active nanoparticle aggregates have been stabilised in dry hydroxyethylcellulose films.
- Cl^- ions interfere with the detection of the anticonvulsant drug phenytoin using Ag particle films.
- Au particle films can be used to monitor the concentration of phenytoin even in the presence of Cl^- ions.
- Phenytoin was detected at 1.8 mg L^{-1}, the therapeutic target range is 10–20 mg L^{-1}.

GRAPHICAL ABSTRACT



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ABSTRACT

Large (10 × 10 cm) sheets of surface-enhanced Raman spectroscopy (SERS) active polymer have been prepared by stabilising metal nanoparticle aggregates within dry hydroxyethylcellulose (HEC) films. In these films the aggregates are protected by the polymer matrix during storage but in use they are released when aqueous analyte droplets cause the films to swell to their gel form. The fact that these "Poly-SERS" films can be prepared in bulk but then cut to size and stored in air before use means that they provide a cost effective and convenient method for routine SERS analysis. Here we have tested both Ag and Au Poly-SERS films for use in point-of-care monitoring of therapeutic drugs, using phenytoin as the test compound. Phenytoin in water could readily be detected using Ag Poly-SERS films but dissolving the compound in phosphate buffered saline (PBS) to mimic body fluid samples caused loss of the drug signal due to competition for metal surface sites from Cl^- ions in the buffer solution. However, with Au Poly-SERS films there was no detectable interference from Cl^- and these materials allowed phenytoin to be detected at 1.8 mg L^{-1}, even in PBS. The target range of detection of phenytoin in therapeutic drug monitoring is 10–20 mg L^{-1}. With the Au Poly-SERS films, the absolute signal generated by a given concentration of phenytoin was lower for the films than for the parent colloid but the SERS signals were still high enough to be used for therapeutic monitoring, so the cost in sensitivity for moving from simple aqueous colloids to films is not so large that it outweighs the advantages which the films bring for practical applications, in particular their ease of use and long shelf life.

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1. Introduction

For most therapeutic drugs using a standard dose regime gives sufficient control over the level of drug in each patient. However, in some cases the toxicity of the drug and/or a narrow therapeutic window means that it is necessary to measure the drug level at regular intervals. Currently this is typically done through time consuming, laboratory-based analysis of blood samples with HPLC [1] [2] although numerous methods for therapeutic drug monitoring which exploit bead technologies, enzymes, antibodies and magnetic separation in various combinations have been developed over the years [3].

The ability to carry out therapeutic drug monitoring at the patient's bedside could potentially reduce delays associated with laboratory–based analysis and reduce costs. SERS is attractive for bedside drug monitoring since it is expected to have the required sensitivity [4–6] and can be combined with hand-held instruments for signal readout within a matter of a few minutes. However, for such applications simple aqueous metal colloids are unsuitable as the enhancing media due to their limited shelf life and the need to have liquid sample handling steps in the analysis. Previous work [7–9] has demonstrated that SERS could be used for the point-of-care monitoring of drugs based on tubing which could be used both to collect the sample and to detect the targets using integrated SERS enhancing components based on Ag nanodomes. This method was impressive, however the devices were complex and expensive to fabricate. Here we explore a much lower cost approach based on SERS-enhancing nanoparticle aggregates which are stabilised by encapsulation within dry swellable polymer matrices but are released on application of the analyte. Previous attempts to prepare Ag nanoparticles in polymer hosts have included the photoreduction of matrix-stabilised Ag halides [10] and chemical reduction of agarose gels containing Ag nitrate with borohydride [11]. Au nanoparticles have also been isolated within a thiolated-polystyrene matrix [12]. These methods each have their own disadvantages, so none have been widely adopted.

We have recently reported that large, thin (50 μm) dry polymer sheets containing numerous SERS active Ag nanoparticle aggregates can be prepared by drying aqueous mixtures of hydroxyethylcelloulose (HEC) and pre-aggregated Ag colloid [13] which was an improvement of our earlier method which used polycarbophil as dried films or gels [14,15]. Although conventional aqueous colloids are known to give the highest SERS enhancements and are inexpensive to prepare, they are unstable systems, need to be stored at 4 °C and should not be stored for long periods. In the dry “Poly-SERS” films the particle aggregates are stabilised in the polymer matrix. The films can be stored at RT, are portable and are easy to handle, for example, they can be cut to size with scissors meaning they are highly appropriate for regular or intermittent bed-side SERS analysis if used alongside a portable Raman spectrometer [13].

The Poly-SERS films are made of highly swellable HEC polymer and so upon activation with aqueous analyte, the films can rapidly absorb the analyte whilst simultaneously releasing the Ag nanoparticle aggregates to interact and generate SERS. The ability of the polymer to swell quickly means that a SERS signal can be obtained almost immediately once analyte is deposited onto the surface of the film. Furthermore, if the analyte is allowed to preconcentrate onto the film there is an increase in signal intensity with time where maximum SERS signals are given when all of the solvent evaporates. For droplets of analyte dissolved in 25% ethanol in water, optimum SERS signals can be obtained at approximately 60 min after depositing onto the film, *i.e.* when the solvent has fully evaporated.

Here we explore the use of such films for the detection of phenytoin, an anticonvulsant which is commonly used as an anti-epileptic drug, dissolved in PBS as a model for interstitial fluid. Phenytoin must be routinely monitored in patients due to the adverse side effects which occur at concentrations above the target therapeutic range of 10–20 mg L^{-1}, where effects include depression of the central nervous system, which can give symptoms ranging from mild sedation to coma [16].

2. Materials and methods

2.1. Reagents and materials

Gold (III) chloride hydrate, magnesium sulphate, trisodium citrate, phenytoin and phosphate buffered saline (PBS) tablets were purchased from Sigma Aldrich. Natrosol hydroxyethylcellulose (HEC) 250 pharm HX was purchased from Ashland Inc.

2.2. Preparation of Ag Poly-SERS films

The Ag Poly-SERS films were prepared as described previously [13]. In brief, citrate reduced Ag colloids (CRSC) were prepared and had λ_{max} = 405 nm. The colloid was then pre-aggregated using $MgSO_4$ mixed with HEC powder and dried to a film. The UV–vis spectrum of an Ag Poly-SERS film showed a broad extinction from 300 to 1000 nm (see Supplementary Data, Fig. S1), which was due to a combination of light scattering by the semi-opaque film and absorption by the aggregated particles.

2.3. Preparation of Au Poly-SERS films

Colloidal Au nanoparticles (*ca.* 50 nm diameter) were prepared by citrate reduction of gold chloride hydrate [17], and had λ_{max} = 545 nm. The Au Poly-SERS films where then prepared by pre-aggregating the as-prepared colloid (54.2 mL) with 10.8 mL $MgSO_4$ at 0.1 mol dm^{-3} and mixing with HEC powder (1.2% w/v polymer) at 400 rpm using a mechanical stirrer until a smooth, glossy gel was obtained, which typically took approx. 50 min. The resulting gel was then poured into a 10 × 10 × 0.5 cm casting mould and left to dry in air (relative humidity ≤50%).

2.4. SERS analysis with Poly-SERS films

The Ag and Au Poly-SERS films were both used in the same way; small (5 × 5 mm) squares of the films were placed onto glass slides covered in aluminium foil before they were rehydrated by applying a 15 μL aqueous droplet of analyte directly on top. The aqueous analyte was then allowed to dry before a spectrum was collected by directing the probe laser from a PerkinElmer RamanMicro 200 Raman microscope using a 4× objective lens at 55% laser power onto it. The microscope uses a 785 nm cavity diode laser (80 mW) with a Czerny-Turner spectrometer with a spectral range of 95–3200 cm^{-1}. It is composed of an Olympus microscope (BX51 reflected illumination frame) which is connected to a spectrometer through fibre optic cables, this gives a spot diameter of 230 μm. In all cases, SERS spectra were collected with accumulation times of 30 s.

Phenytoin stock solution was initially prepared in ethanol and serial dilutions were then carried out using DDI water or PBS solution.

2.5. SERS analysis with aqueous Au colloid

Aqueous samples were held in 96 well polyethylene microlitre plates analysed using a 785 nm Avalon RamanStation. The system has a 785 nm laser source (*ca.* 160 mW at sample) with a spot

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