



Research Paper

Composite MF@Ag-NPs microspheres for label-free quantitative detection of uric acid



Xu Dong, Ruimin Li, Christian G. Schäfer, Fang Wang*

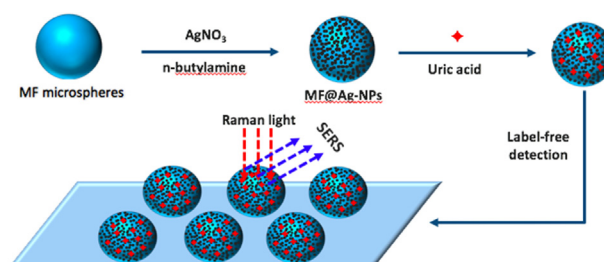
State Key Laboratory of Molecular Engineering of Polymers, and Department of Macromolecular Science, Laboratory of Advanced Materials, Fudan University, Shanghai 200433, China

HIGHLIGHTS

- A convenient and easy-scalable synthetic strategy to achieve highly sensitive SERS substrates for single particle detection.
- Individual MF@Ag-NPs microspheres were screened under a microscope and were used to examine their single particle SERS properties by using four different probe molecules.
- The experimental results demonstrated the as-prepared SERS substrates possess a very high SERS activity and sensitivity for trace analysis of targeting molecules.
- The quantitative trace detection of uric acid (UA) as biomarker based on the label-free strategy has been successfully conducted.

GRAPHICAL ABSTRACT

Monodisperse composite MF@Ag-NPs microspheres of variable sizes have been successfully synthesized, which were used for the quantitative trace detection of uric acid as biomarker based on the label-free strategy.



ARTICLE INFO

Article history:

Received 16 January 2017
 Received in revised form 14 March 2017
 Accepted 21 March 2017
 Available online 23 March 2017

Keywords:

Composite MF@Ag-NPs microspheres
 SERS
 Single particle detection
 Trace analysis
 Label free

ABSTRACT

A convenient and easy-scalable synthetic strategy to achieve ultrasensitive surface enhanced Raman spectroscopy (SERS) substrates for single particle detection of targeting molecules is reported. Melamine-formaldehyde (MF) microspheres with variable sizes were synthesized and decorated with Ag nanoparticles (NPs) through an in-situ chemical deposition to obtain composite MF@Ag-NPs microspheres. Individual MF@Ag-NPs microspheres were screened under a microscope and used to examine their single particle SERS properties by using four different probe molecules. The experimental results demonstrated that as-prepared SERS substrates displayed a dramatically enhanced SERS activity and sensitivity as well as an extraordinary stability and reproducibility of the SERS signal. Moreover, we also showed a first example of single MF@Ag-NPs microsphere for quantitative trace detection of uric acid (UA) as biomarker based on the label-free strategy, making them a promising candidate as an ideal substrate for applications in fields of biosensor, trace analysis and biomedical diagnostics.

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1. Introduction

Surface enhanced Raman spectroscopy (SERS) is an ultrasensitive spectroscopic technique, which is currently the only way capable of simultaneously detecting a single molecule and provid-

* Corresponding author.

E-mail address: wangf@fudan.edu.cn (F. Wang).

ing its fingerprint chemical information [1]. SERS spectra combined with its label-free molecular specificity promise to be employed as high level quantitative analysis technique with the remarkable advantages of robust stability and ultrasensitivity towards analytes, which holds a great potential for next-generation convert security labels and biomarker trace detections [2–4].

Surface plasmons associated with noble metal nanoparticles can generate significant enhancement of local electromagnetic fields, which leads to intense SERS signals from Raman probe molecules in the vicinity of nanostructured substrates [5–9]. Notably, the enhancement factor and the stability of the SERS signal are strongly dependent on the respective SERS substrate. Such so-called SERS substrate with well-controlled “hot spot”, large area, and excellent spatial reproducibility would be desirable for SERS enhancement [10,11]. Moreover, the intensity of SERS signal could be highly affected by the surface physical state of the SERS substrates including the degree of aggregation, shape and size of gold or silver nanoparticles, as well as by the position and power of the focused laser beam, which may make it difficult to obtain quantitative SERS signals from the targeting molecules.

At present, there are many methods such as vacuum deposition [12,13], chemical reduction [14,15], chemical assembly [16], lithography [17] and nano-lithography [18] used for the preparation of high-performance SERS substrates. More recently, many new type of noble metal nanoparticles were developed for this purpose, such as core-shell structured nanoparticles [19–22], nanostructures [23] and bimetallic nanostructures [24,25], nano-arrays [26], nanochains [27,28], nanowires [29] and so on. Although the nanostructure design is very sophisticated, it is still difficult to position the laser beam precisely in order to distinguish the specific unit or group. Usually, Raman spatial resolution is about 1 μm , which means that the laser is usually focused on many particles and the Raman signal of different particles is simultaneously measured. However, the localized disordered stacking and alignment of the nanostructured SERS substrates will inevitably result in uneven distribution of the “hot spots”, and the reproducibility and stability of the Raman signal will be greatly reduced [30]. Thus, the use of nanoparticles as SERS substrate for the quantitative detection of probe molecules remain challenging and the practical application will be subject to many restrictions. Therefore, there is growing interest in the preparation of highly stable and uniform SERS substrate with simple, cost-effective and highly efficient methods with regard to practical applications of SERS quantitative detection.

To improve the accuracy of SERS quantitative detection, an internal standard method is often used [31–33]. In this case, a constant amount of a model substance is added to the sample and used for calibration of the analyte signal compared to the internal standard signal. According to the formula, the peak height or peak area, the relative correction factor, and the concentration of the sample can be obtained. To a certain extent, although the internal standard method eliminates the operating conditions caused by changes in the error, it is very difficult to find an appropriate internal standard substance in complex detection system, and moreover, the sample preparation is also very complicated. Therefore, the utilization of well-defined microspheres with metal nanoscale surface as SERS substrates would have clear advantages: (1) possess uniform structure and micron size to generate highly sensitive and reproducible SERS signal; (2) can be probed under an optical microscope to achieve single microsphere SERS detection.

Herein, we introduce a new class of single particle SERS detection of different probe molecules by using Ag nanoparticles decorated MF microspheres (MF@Ag-NPs microspheres) as highly efficient SERS substrates. MF microspheres with precisely adjustable sizes were synthesized through an easily controllable condensation polymerization technique (Fig. S1). The MF microspheres were subsequently decorated with Ag-NPs by using an

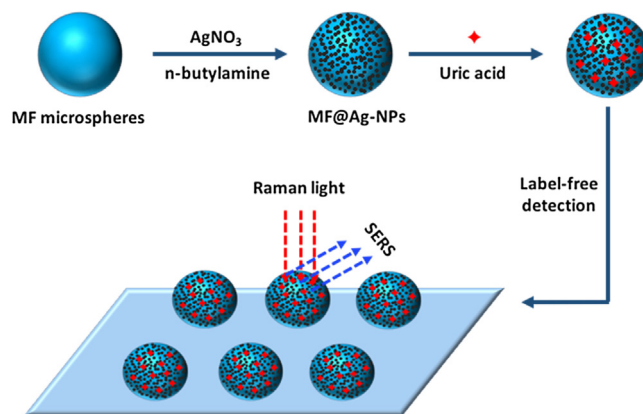


Fig. 1. Schematic illustration of operation mechanism of composite MF@Ag-NPs microspheres for label-free quantitative SERS detection of uric acid.

in-situ chemical deposition method. The composite MF@Ag-NPs microspheres were thoroughly characterized by FESEM, XRD and TGA measurements. Moreover, due to the unique large diameters in the micron range as SERS substrates, herein prepared particles could be directly employed for SERS applications without transferring procedures and be easily distinguished and manipulated under a microscope, providing access to highly sensitive single particle SERS detection of different probe molecules, combined with a remarkable Raman signal enhancement effect, extremely high sensitivity as well as an extraordinary stability and reproducibility of the SERS signal. Furthermore, we demonstrated that this single MF@Ag-NPs microsphere has utility in label-free, quantitative trace detection of uric acid, illustrating their broad potential applications in areas of biological sensing and immunoassays (Fig. 1).

2. Experimental Sections

2.1. Materials

Melamine ($\text{C}_3\text{H}_6\text{N}_6$, AR), silver nitrate (AgNO_3 , $\geq 99.8\%$), *n*-butylamine ($\text{CH}_3(\text{CH}_2)_3\text{NH}_2$, AR), 4-aminothiophenol ($\text{C}_6\text{H}_8\text{NS}$, ATP, AR), 4-methoxy- α -toluenethiol ($\text{CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{SH}$, MATT, AR), 4-chlorothiophenol ($\text{C}_6\text{H}_5\text{ClS}$, CTP, AR) and 3,5-bis(trifluoromethyl)benzenethiol ($\text{C}_8\text{H}_4\text{F}_6\text{S}$, FMBT, AR) were all purchased from Aladdin and used as received. Formaldehyde (HCHO , 37% in water), formic acid (HCOOH , AR), uric acid (UA, 99%) and ethanol ($\text{CH}_3\text{CH}_2\text{OH}$, 73.0–75.0 in water) were obtained from Sinopharm Chemical Reagent Co., Ltd. Deionized water was used in all experiments.

2.2. Synthesis of melamine resin (MF) microspheres

MF microspheres were synthesized using condensation polymerization. 0.32 g of $\text{C}_3\text{H}_6\text{N}_6$ and 0.45 g of HCHO (molar ratio = 1:6 mol/mol) were added under stirring to 60 mL of deionized water at 70 °C. After 30 min, a certain amount of HCOOH was added. After polymerization at 70 °C for 1 h, the obtained dispersion was allowed to cool to room temperature. The dispersion was purified by centrifugation at 11000 rpm for 5 min, and the precipitated MF microspheres were re-dispersed in deionized water. A series of MF microspheres with different sizes were synthesized by changing the amount of HCOOH .

2.3. Preparation of composite MF@Ag-NPs microspheres

MF@Ag-NPs microspheres were synthesized using an in-situ deposition method. A typical procedure for the deposition of Ag

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