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Synthesis of SERS-encoded nanotags: From single nanoparticles to highly brilliant complex core-satellite structures

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Abstract. In this work, we report novel methods to produce SERS encoded nanoparticles (SEPs). Either as single nanoparticles (NPs) or as more complex core-satellites structures. Single NPs are produced in an easy and fast one-pot approach which, are further use as building blocks to produce the core-satellite SEPs. The presented protocols are very versatile allowing the NPs SERS codification with an extensive variety of Raman codes. Moreover, this protocol can be applied to different NPs materials and shapes. Furthermore, the core-satellite SEPs are designed to exhibit minimal interparticle distances (<2–3 nm) with maximum satellite loading (i.e., maximum number of hot spots per assembly), while positioning the encoding agents at the gaps to achieve a very high optical efficiency. In addition to such versatility, these fabrication methods are simple, cheap, scalable and robust, yielding stable SPEs in high yields.

1. Introduction

Nowadays, the use of SERS encoded nanoparticles (SEPs) is becoming a powerful method to solve analytical problems in complex media such as biological fluids^[1-5] due to their high-throughput screening, multiplexing capabilities, and large surface area for bioconjugation.^[6,7] In general, SEPs are composed of three main elements: 1) a plasmonic core, responsible for the generation of the electric field necessary for the Raman amplification; 2) a SERS encoding agent, responsible for the unique vibrational fingerprint of the encoded particle; 3) a protective layer which allows the attachment of biorecognition elements meanwhile preventing SPEs degradation.^[8,9] In this work, we propose an easy and fast one-pot approach to produce SEPs. This versatile strategy relies in the use of plasmonic NPs (gold or silver nanoparticles) and the controlled co-absorption of mercaptoundecanoic acid (MUA) and a Raman active molecule on the metallic surface followed by their coating with a silica shell. This procedure allows for the SERS codification of particles with wide variety of Raman active molecules, for instance, more than 31 different encoded particles were produced using the same standard procedure. However, although these SEPs composed of single plasmonic particles are desirable because of their homogeneous SERS signals.^[8] Their efficiency is limited because they cannot form electromagnetic hot spots. Thus, hindering their applicability to other more demanding applications in which acquisition time or spatial resolution are of paramount importance. To solve this problem, we present a synthetic approach to produce SERS encoded core-satellites structures with maximum particle loading and



minimal interparticle gaps ($< 2\text{-}3\text{ nm}$) where the encoding agent is positioned. The presented procedure remarkably improves the SERS efficiency of the SEPs and, exhibit consistent and homogeneous SERS intensities from assembly to assembly. Additionally, they also keep an appropriate size ca. 100 nm for biological applications.^[10] The presented encoded core-satellites structures present an outstanding optical performance with homogeneous enhancement factors over 4 orders of magnitude as compared with classical SERS encoded particles because they have a dense collection of symmetrically arranged hot-spots in a small volume. Moreover, cores of different materials (Au and Ag) and different shapes can be also produced.

2. Results and discussion

2.1. Synthesis of SERS encoded Nanoparticles

The successful production of SEPs, requires the simultaneous control of different experimental parameters which can be divided in four main different steps: 1) Synthesis of plasmonic NPs; 2) MUA functionalization; 3) SERS codification; and 4) Silica coating. **Figure 1** shows a schematic representation of the proposed process.

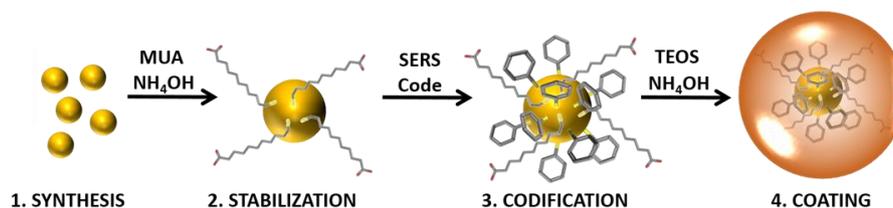


Figure 1. Schematic representation of the MUA assisted encoded process.

Due to the low stability of aqueous colloidal solutions upon functionalization with SERS active molecules, a pre-stabilization step is required. Therefore, a molecule that binds covalently to the gold surface while providing particle stability (steric and electrostatic repulsion due to a long aliphatic chain and a terminal carboxylic group) was chosen. Additionally, the selected molecule should also present a negligible Raman cross-section to avoid undesired SERS signals. To this end, mercaptoundecanoic acid (MUA) was used in a first step to functionalize the NPs.^[8,10,11] Another crucial issue is that MUA should be added in an adequate proportion to avoid the formation of a compact monolayer that could passivate the metallic surface, preventing the retention of the SERS codes, and should also be homogeneously distributed on the NPs surface to avoid heterogeneous adsorption of the Ramon code. Consequently, after the NPs synthesis, MUA was rapidly added under vigorous stirring at basic pH to functionalize the plasmonic nanoparticles with $0.8\text{ MUA molecules nm}^{-2}$ which, is the minimal amount required to provide colloidal stability to the NPs.^[9,10] After that, the SERS code can be added without inducing NPs aggregation. Finally, to ensure the SEPs stability for long periods and to provide them with an easy functionalizable external surface, the nanoparticles were encapsulated in a silica matrix. To this end, the well-known Stöber method^[12] was used by exploiting the ability of ligands with terminal carboxylic acid groups, such as MUA, to induce silica growth.^[13,14] **Figure 2** shows representative example of the produced NPs.

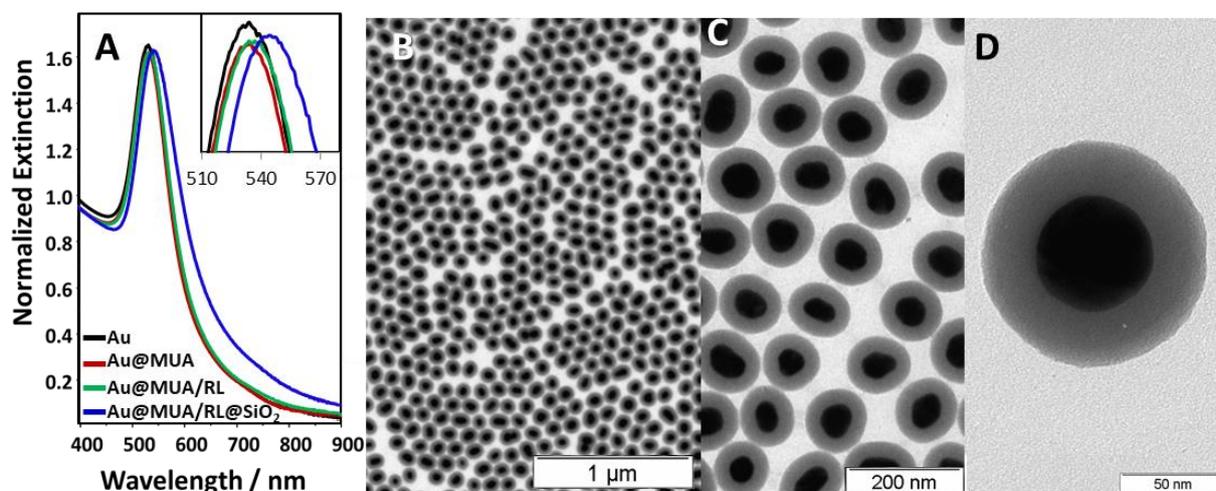


Figure 2. (A) Extinction spectra of Au particles after each step of the presented protocol. (B–D) Representative TEM images at different magnifications of the produced SEPs.

2.2. Synthesis of Core-Satellites SEPs

The assembling strategy for the fabrication of silica-coated SERS-encoded core–satellites is showed in **Figure 3A**. In this scheme, the plasmonic SEPs using the previously described MUA-mediated protocol were used as cores.^[8,10] To produce core-satellites, the negatively charged SEPs were then wrapped with a single layer of positively charged polyelectrolyte (branched polyethyleneimine (PEI)) to yield the corresponding positively charged NPs. These core units were subsequently exposed to a large excess of negatively charged small plasmonic NPs, which, via electrostatic interactions, saturates the core particles yielding the plasmonic assemblies. Finally, silica encapsulation was performed using a modification of the Stöber method.^[12] This directly procedure for silica coating allows an efficient separation of the light satellites from the clustered particles via post-centrifugation cycling with no risks of perturbing the aggregation state of the assemblies. Since nanomaterials below 100 nm are required for most biomedical applications,^[13] the core and satellite building blocks were selected of ca. 60–65 nm and ca. 12 nm respectively. **Figure 3B** shows three different encoded core-satellite structures with cores of different materials (Au and Ag) and shapes (spheres, rods, and stars).

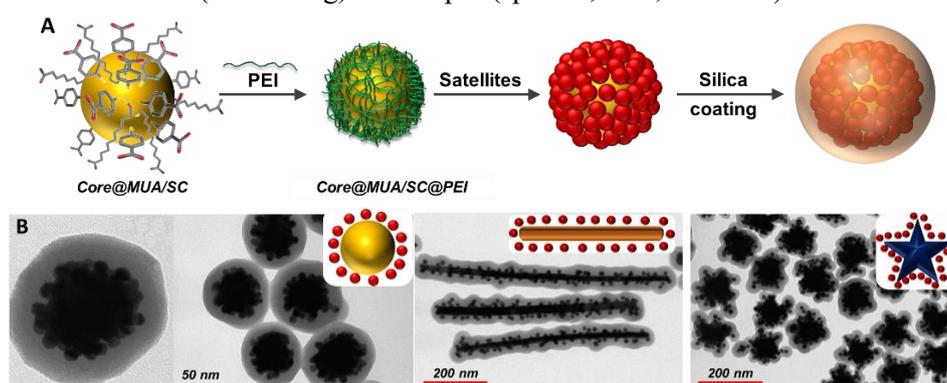


Figure 3. (A) Schematic representation of the process. (B) Core-satellites structures with different core shapes.

2.3. SEPs optical enhancing properties

To test their optical enhancing properties and their usability for single particle detection, diluted SEPs solutions were spin-coated on silicon slides to reach concentrations below 0.2 particle per μm^2 . Then, the samples were imaged on a Raman microscope with 532, 633 and 785 nm laser lines. The obtained results reveal that all the core-satellite structures yielded strong SERS signals for all lasers in the single

particle regime. However, for the case of individual silver and gold nanoparticles, more concentrated substrates were required to provide a measurable signal, specifically, 18 and 5 particles per μm^2 for gold and silver cores, and 45 particles per μm^2 for the small gold satellites. In fact, the enhancement factors for the core-satellites were 4 orders of magnitude higher than those of the individual gold or silver SEPs.

Figure 4 shows the SERS intensity comparison between all components of the core-satellite structures.

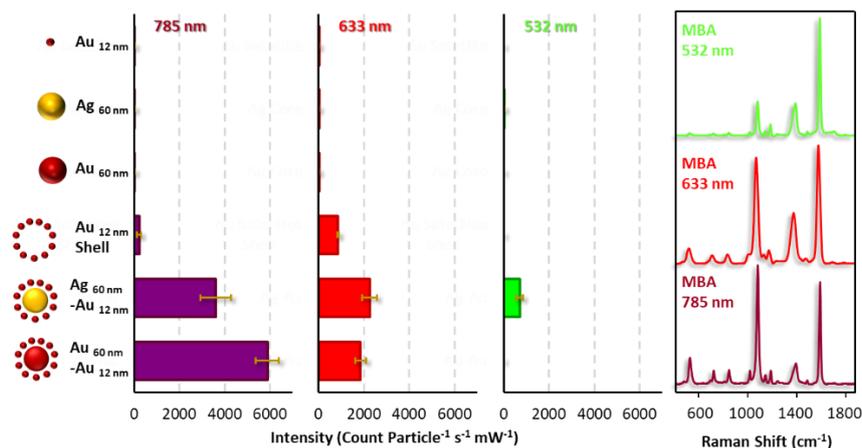


Figure 4. SERS intensity, normalized for a single particle, provided by each material at three laser lines: 785, 633 and 532 nm.

3. Conclusion

In summary, we have developed an innovative and easy approach to produce SERS encoded nanoparticles which allows the use of a wide variety of Raman active molecules. This versatile strategy relies in the use of plasmonic NPs that are first stabilized with MUA for the further codification process. This approach allows for the further use of these nanoparticles as building blocks to produce core-satellites encoded structures. The obtained structures are highly brilliant SERS tags that allows for single particle detection.

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