Plasmon-Enhanced Optical Probes for Sensing of Drug Metabolite

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Jennifer Boryczka

Thesis submitted to the Statler College of Engineering at West Virginia University in partial fulfillment of the requirements for the degree of Master's in Material Science and Engineering.

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ABSTRACT

Plasmon-Enhanced Optical probes for Sensing of Drug Metabolite

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An Au@SiO$_2$ core-shell nanostar structure was synthesized along with CuInS$_2$ quantum dots. The quantum dots display near-infrared fluorescence. In this work, the nanostar structure was functionalized with antibodies and then was utilized as a SERS probe for drug metabolite detection. Drugs are an illicit substance that police, medics, and hospitals need to know if an individual is under the influence of but that individual will not always be willing or able to provide that information. A sensor based on this new probe has been developed for detection of drug metabolites in buffer.
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# Table of contents

**Abstract** ii

**Acknowledgements** iii

**Chapter 1: Introduction** 1
  1.1 Significance 1
  1.2 Objective 1
  1.3 Approach 2
  1.4 Outline of Thesis 2

**Chapter 2: Literature Review** 3
  1.1 Background 3
  1.2 Resonance Enhancement 4
  1.3 Effect of Shape 6
  1.4 References 8

**Chapter 3: Material Synthesis and Characterization** 10
  3.1 Introduction 10
  3.2 Experimental 11
    3.2.1 Gold Nanostars Synthesis 11
    3.2.2 Silica coating of the Gold Nanostars 12
    3.2.3 CulnS$_2$ Quantum Dot Synthesis 12
    3.2.4 Characterization 13
  3.3 Results and Discussion 13
    3.3.1 Gold@silica core-shell 13
    3.3.2 Quantum dots 15
  3.4 Conclusions 17
  3.5 References 17

**Chapter 4: Cocaine metabolite paper test strip** 19
  4.1 Introduction 19
  4.2 Experimental 20
    4.2.1 SERS Probe Preparation 20
    4.2.2 Test Strip Preparation and SERS Measurements 21
  4.3 Results and Discussion 22
  4.4 Conclusions 25
  4.5 References 25

**Chapter 5: Conclusions and Future Studies** 27
  5.1 Conclusions 27
  5.2 Future Studies 27
Chapter 1: Introduction

1.1 Significance

Illicit drugs are a problem for medical professionals and police officers to detect the exact type and amount of the illicit drug the individual had used. This is a problem when medical professionals are trying to treat these individuals for an overdose or if police officers are trying to determine if the individual they are in contact with is safe to drive. The individuals that have used the illicit substance often do not want to undergo the urine test for fear of the outcome causing more charges, making the jobs of the medical professionals and police officers more complicated. Many of the tests that are used to detect these illicit drugs must be done in the hospital. Illicit drug screening is also used to screen possible job candidates before hiring and ensure that athletes are not under the influence of these illicit drugs to ensure fair play. This test strip aims to provide a point of care device that can quickly and inexpensively determine the level of cocaine.

1.2 Objective

The goal of this presented study was to synthesize both a gold@silica core-shell nanostar structure and CuInS$_2$ quantum dots for comparison and then the use of the core-shell structure as an effective probe for the development of a paper-based lateral flow test strip that is used for the detection of a cocaine metabolite.
1.3 Approach

The work was approached by starting with the synthesis of the gold@silica nanostars structure as well as the CuInS$_2$ quantum dots. The structures were then characterized and compared. The gold@silica was then chosen for use in the lateral flow paper test strip. The gold@silica was functionalized to detect a cocaine metabolize and the paper strip was constructed. Limit of detection tests were carried out and the results were compared with the commercial test strips.

1.4 Outline of Thesis

The following chapter includes an introduction to lateral flow test strips, SERS, and a brief review of previous work for lateral flow test stripes for the detection of drug metabolites. Chapter 3 details the synthesis of two materials, gold nanostars coated with silica and CuInS$_2$ quantum dots, and the selection of the synthesized material for use in the test strip. Chapter 4 describes the functionalization use of the selected nanostar core-shell structure as a probe for a cocaine metabolite. Finally, chapter 5 concludes the study with a summary of the study and future studies for this project.
Chapter 2: Literature Review

2.1 Background

Metallic Nanomaterials and quantum dots have been widely used in SERS applications and fluorescence imaging, respectively. Quantum dots are nanospheres that are sized below 10 nm. CuInS\textsubscript{2} quantum dots have been used as sensors for biomaterials for example, they have been used to detect low ug concentrations of heparinase in fetal bovine serum \cite{1} or dopamine in human serum samples \cite{2}. These quantum dots are generally synthesized in organic solvents that result in a hydrophobic surface which limit their uses \cite{3}. The transfer from the organic solvent to an aqueous solvent generally greatly decreases the intensity of the fluorescence. This decrease in fluorescence is typically solved by adding a layer of ZnS to the quantum dot \cite{3}.

Surface-enhanced Raman scattering (SERS) utilizes the fingerprint capabilities of Raman and enhances the signal by plasmonic effects to increase the sensitivity of this method. SERS is used to detect many different chemicals such as chemical warfare agents, pollutants, and illicit drugs \cite{4}. Gold nanostructures functionalized with antibodies have been utilized for the detection of biomarkers within human samples \cite{5}. SERS has an advantage over the quantum dot fluorescence due to the plasmonic enhancement. This enhancement by SERS allows for a higher sensitivity in comparison to the fluorescence by the CuInS\textsubscript{2} quantum dots.
People who use illicit drugs often encounter police officers and medical professionals as a result of their illicit drug use. These encounters are often frustrating for all individuals involved, the police officers and medical professionals are trying to do their jobs and the individuals that use the illicit drugs are trying to hide that they use from the professionals to avoid any other drug related charges.

The methods that are currently used to detect illicit drugs such as cocaine have a few drawbacks such as high cost and large equipment that must be run in a laboratory by a professional. These methods include mass spectrometry, Raman spectrometry, thin-layer chromatography, color/spot tests, immunoassays, and microcrystalline tests [6] with mass spectrometry being the gold standard. A point of care device would cut the costs of the current tests and allow for the need for a laboratory to be removed. Another group published a SERS method using gold and silver doped sol-gels that was able to consistently detect 50 ppb of cocaine in saliva [7]. A cocaine metabolite, benzoylcegonine, was utilized instead of the illicit drug, cocaine itself.

2.2 Resonance Enhancement

Surface plasmons are an oscillation of the free electrons on metallic nanoparticles that are excited by light. The wavelength of light that causes the plasmon is the same wavelength as the peak of the plasmon itself viewed using UV-Vis spectrometry, which induces the resonance wave of free electrons. The resonance generated by the oscillating electrons increases the electric field creating strong optical absorption or scattering with strong electromagnetic fields [8].
This resonance of the electron cloud can be used to enhance Raman signals. Raman signals are usually weak, and the enhancement of these signals (SERS) can be used to increase the sensitivity and lower background interference. The plasmon resonance is sensitive to the absorption of molecules on the material surface allowing for sensing applications [8].

The first observation of the SERS effect was done by Martin Fleischmann, Patrick J. Hendra and A. James McQuillan at the Department of Chemistry at the University of Southampton, UK in 1973. This initial publication involved pyridine adsorbed on a roughened silver electrode [10, 11]. The 1980s was when the development of underlying key concepts of SERS such as, the electromagnetic effect and the predicted existence of the surface plasmon [11]. After the description of the phenomenon, the interaction between the electromagnetic resonance between two materials was explored by P.K Aravind, et al. They showed the sharp decrease in the enhancement effect as the distance increased as well as SERS “hot spots”. These “hot spots” are points of interaction between two plasmonic materials that have an even greater enhancement of the electromagnetic field due to the additive resonance of the plasmon present on each of the surfaces [11]. Though this greater enhancement is extremely dependent on the shape, size, and distance between the particles. From there SERS is all about placing the analyte in these hot spots and appropriately designing the substrates [11].

In 1996, Shuming Nie and Katrin Kneipp individually reported single molecule SERS, renewing the interest in the area. Since then further experiments showed that the individual particles claimed in Nie’s paper were aggregates [11]. Current uses of SERS is for point-of-care lateral flow immunoassays. These immunoassays are used to detect
anything from toxic molecules, proteins in the body, pesticide in runoff water, pollutants, etc.

2.3 Effect of Shape

The plasmonic properties of the nanoparticles are tunable based on the size and shape. When the size of the nanoparticle is small the resonance is mostly absorption and when the size is large the resonance is mostly scattering. The shape affects the local electromagnetic field surrounding the nanoparticles when the plasmon was induced. Nanospheres have a dipole induced by the plasmon that is spread across the surface. A nanorod’s dipole is concentrated in the ends of the rod increasing the electromagnetic field there and increasing the enhancement of the SERS signal. Further, a nanostar’s dipole is concentrated on the tips of the star points further localizing the electromagnetic field and enhancing the possible SERS signal, like the lightning rod. The electromagnetic field distributions are shown below in figure 1.
Figure 1: Simulated electromagnetic field distributions of gold in the shapes of sphere, rod, and star [9].

The concentration of the dipole and the localization of the electromagnetic field increase the enhancement factor and thus increases the sensitivity of the measurement.
2.4 References


Chapter 3: Material Synthesis and Characterization

3.1 Introduction

Metallic Nanomaterials and quantum dots have been widely used in SERS applications and fluorescence imaging, respectively. Quantum dots are nanospheres that are sized below 10 nm. CuInS$_2$ quantum dots have been used as sensors for biomaterials for example, they have been used to detect low ug concentrations of heparinase in fetal bovine serum [1] or dopamine in human serum samples [2]. These quantum dots are generally synthesized in organic solvents that result in a hydrophobic surface which limit their uses [3]. The transfer from the organic solvent to an aqueous solvent generally greatly decreases the intensity of the fluorescence. This decrease in fluorescence is typically solved by adding a layer of ZnS to the quantum dot [3].

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3.2 Experimental

3.2.1 Gold Nanostars Synthesis:

The gold nanostar was synthesized using a method from work done in Dr. Nianqiang Wu’s group previously \[^6\]. The method consisted of growing a gold seed, functionalizing the gold seed, and then finally the growth of the functionalized seed into a nanostar.

The seed was grown by adding 20mM HAuCl\(_4\), and 38.8mM trisodium citrate to DI water. Then 0.075% wt of sodium borohydride in trisodium citrate was added slowly to the stirring solution. This was allowed to stir over night. After the seed was formed it was functionalized with polyvinylpyrrolidone (PVP) by mixing 10mM of the PVP seed with 50 ml of the gold seed and stirred overnight.

Once the seed was functionalized, the gold nanostar could be grown. PVP was completely dissolved in dimethylformamide (DMF) before 20 mM of the HAuCl\(_4\) was added. This was allowed to stir for 5 minutes before the PVP functionalized gold seed was added to the stirring solution. The amount of the seed that was added controls the size of the resulting star and therefor the wavelength that the plasmon peak absorbs at, more seed blue shifts the plasmon peak. The star growth solution was left stirring overnight and then the product was cleaned and suspended in water or ethanol. All of the reactions were done at room temperature.
3.2.2 Silica coating of the Gold Nanostars:

The silica coating method also came from a previously publish paper from this group \cite{6}. The gold nanostar with an optical density of 1.7 was diluted by a volume ratio of 1:4 with DI water. These diluted stars has (3-mercaptoproply) trimethoxysilane (MPTMS) slowly added and stirred to functionalize the gold nanostars. Once the gold nanostars were functionalized, sodium silicate was added as the silica source and sodium hydroxide was added to reduce silica onto the gold nanostar. This reaction was heated overnight and then cleaned and stored in ethanol, just the same as the uncoated gold nanostars.

3.2.3 CuInS$_2$ Quantum Dot Synthesis:

The quantum dot synthesis was slightly modified from the method published by Dr. Yueqing Gu's group \cite{3}. Indium acetate, copper acetate, 1-dodecanthiol (DDT), 1-octadecene (ODE), and oleic acid was all mixed together in a 3-necked round bottom flask. This solution was heated at 100 °C with stirring under an argon atmosphere until all the solids dissolved to form a clear solution. Once all the solids were dissolved the temperature was raised to 230 °C and this caused a color change from clear, to yellow, then red, and finally to black over a period of 90 minutes. After the color change finished the transition, indicating the formation of the CuInS$_2$ quantum dots, the reaction was cooled to 50 °C and then an equal volume of hexane was added to complete the reaction.
3.2.4 Characterization:

The materials synthesized were characterized by UV-Vis absorption (Hitachi), JEOL JEM-2100 Transmission Electron Microscope (TEM), and EDX using the JEOL JEM-2100 TEM.

3.3 Results and Discussion

3.3.1 Gold@silica core-shell:

The gold nanostar and the gold@silica nanostar share their shape and there is only a slight change in size, ~3 nm, due to the silica being added. Figure 2 shows that this additional layer red-shifts the absorbance due to the increase in size but does not change the overall shape of the absorbance.

Figure 2: UV-Vis of both the gold nanostar and the gold nanostar coated with silica.
Figure 3 shows a TEM image of gold nanostars and figure 3 shows gold nanostars coated with silica. The gold nanostars in figure 2 are ~60 nm from tip to tip. Figure 4 shows that the gold nanostars have a halo of sorts and that is the silica layer. Figures 2 and 4 show different batches of the gold nanostars for the purpose of example and are not necessarily the same size. The size of the nanostars that were utilized in the future chapter was ~60 nm and the plasmon absorbs at 785 nm.

![Figure 3: TEM of Gold Nanostars.](image)
The gold@silica core-shell nanostars were selected for further use in later chapters. This was done to take advantage of the plasmon enhancement that this structure provides as a SERS probe.

3.3.2 CuInS$_2$ Quantum dots:

Figure 5 shows a TEM image of the CuInS$_2$ quantum dots that were synthesized. These quantum dots are ~4 nm in size and have been confirmed to be CuInS$_2$ quantum dots by EDX as seen in figure 6. The peaks of gold and silica that are seen in the EDX spectra are caused by the gold@silica core-shell nanostructure. These were in the same sample due to an attempt of decorating the nanostar structure with the quantum dots to have plasmon induced fluorescence. The decoration of the nanostars, however, was unsuccessful.
Figure 5: TEM image of CuInS2 quantum dots.

Figure 6: EDX taken of the CuInS2 quantum dots mixed with the gold@silica quantum dots, taken in an area of quantum dots similar to figure 4.
The CuInS$_2$ quantum dots were not chosen to be used for the further studies because the fluorescence of the quantum dots after moving to the aqueous phase was visually extremely diminished. The plasmon enhancement of the gold@silica SERS probe will outperform the lack of strong fluorescence shown by the aqueous CuInS$_2$ quantum dots. Along with this difference in performance, the CuInS$_2$ quantum dot synthesis was not consistent or reliable for each individual batch where the gold@silica SERS probe synthesis is both consistent and reliable.

### 3.4 Conclusions

This chapter focused on the synthesis and characterization of the gold@silica core-shell nanostar and the CuInS$_2$ quantum dots, as well as selecting which material would further be used for the cocaine metabolite probe. Both structures were successfully synthesized utilizing chemical methods. The gold@silica core shell structure was then chosen for the production into SERS probes because of the plasmonic enhancement the material provides and consistency in the synthesis.

### 3.5 References


Chapter 4: Cocaine metabolite paper test strip

4.1 Introduction

The methods that are currently used to detect illicit drugs such as cocaine have a few drawbacks such as high cost and large equipment that must be run in a laboratory by a professional. These methods include mass spectrometry, Raman spectrometry, thin-layer chromatography, color/spot tests, immunoassays, and microcrystalline tests \cite{1} with mass spectrometry being the gold standard. A point of care device would cut the costs of the current tests and allow for the need for a laboratory to be removed. Another group published a SERS method using gold and silver doped sol-gels that was able to consistently detect 50 ppb of cocaine in saliva \cite{2}. In this chapter a cocaine metabolite, benzoylecgonine, was utilized instead of the illicit drug, cocaine itself. The difference between cocaine and its metabolite is the ester in cocaine is a carboxylic acid as seen in figure 7. This difference does not affect the overall function of the test strip or antibody binding.

![Figure 7: The chemical structure of cocaine compared to its metabolite, benzoylecgonine.]
4.2 Experimental

4.2.1 SERS Probe Preparation

The SERS probe preparation was done utilizing a previously published method by Dr. Wu’s group [4]. This started by functionalizing the gold@silica nanostars with the Raman active molecule and then protecting that with another layer of silica. The gold@silica nanostars were mixed with 4-mercaptobenzoic acid and this Raman active molecule was given time to adsorb onto the surface of the nanostars. Once the Raman molecule was in place, the gold@silica nanostars were coated with another layer of silica to improve their stability. This was performed by adding tetraethyl orthosilicate (TEOS) to the solution and allowing that to equilibrate and finally adding ammonium hydroxide as a reducing agent to the solution. This reaction was allowed to stir for a full day.

Once the Raman active molecule was added to the SERS probe, it then needed to be functionalized with the antibody. The resulting gold@silica nanostars were washed and 3-(Triethoxysilyl) Propylsuccinic Anhydride (TEPSA) was added and allowed to stand for a full day. The functionalized nanostars were then washed in ethanol followed by washing in 0.3% Tween 20 diluted with PBS buffer. Once the nanostars were washed, NHS EDC was added to prepare the nanostars for binding with the antibody. The antibody was then added to the solution allowed to sit for a full day. These final SERS probes were washed with a NHS EDC solution and then stored in BSA in PBS buffer for future use.
4.2.2 Test Strip Preparation and SERS Measurements

The test strip preparation and measurements were previously published in the paper in the above subsection [2]. The test strip has 4 sections, the sample pad, conjugation pad, nitrocellulose (NC) membrane, and the flow pad. Each of these sections overlapped to ensure that there would be a continuous flow across the entire strip. The paper sample pad was soaked in a salt solution and dried before application onto the strip. The NC membrane had two line of antibodies printed onto them as test and control lines. These lines were printed at 2 ul/sec twice before allowing to dry. The test line would bind to the cocaine metabolite and the control line would bind to the antibody that binds to the cocaine metabolite. Once all the pieces were prepared the pieces were assembled. With the lateral flow paper test strip was assembled, the SERS probe (8 ul) was added to the conjugation pad and allowed to dry. Once completely dry the test strip was ready to be utilized for measurements.

The measurements were conducted with a portable Raman while utilizing various concentrations of the cocaine metabolite in PBS buffer. The samples (100 ul) were dispensed onto the sample pad and allowed to run, once the sample pad started to dry some running buffer, 0.7% Tween 20 in PBS buffer, was added to ensure the sample conjugated with the SERS probe will move down the test strip. The sample and SERS probe was allowed to run down the test strip for 20 minutes. The measurements were taken in triplicate on the test lines for each of the selected concentrations utilizing the portable Raman.
4.3 Results and Discussion

The functionalization of the gold@silica nanostar for use as a SERS probe was successfully performed. Figure 6 shows the FTIR spectrum of the gold@silica nanostars as they are synthesized in the previous chapter. Figure 7 shows FTIR of the gold@silica nanostars after the antibody was bound to the surface. The differences between the two spectra is appearance of the peak at 1600 cm$^{-1}$. This peak is preset in figure 8 and not in figure 7 because the 1600 cm$^{-1}$ peak is attributed to the amide that is formed when the antibody is bound to the silica surface of the gold@MBA@silica surface, this indicates a successful functionalization of the SERS probe for use in the lateral flow test strip.

![Gold@Silica Core-shell Nanostar](image)

*Figure 8: FTIR spectra of the gold@silica nanostar.*
Once the SERS probe was successfully synthesized, it was utilized in the lateral flow test strip. Once the spectra was collected, the peak at 1078 cm$^{-1}$ was utilized as the signature peak of the MBA based SERS probe. The intensities of this peak were recorded and plotted against the log of the concentration of the cocaine metabolite, creating the calibration curve in figure 9. This calibration curve shows a line of best fit with the formula of

$$Y = 82.312x + 239.764,$$

With an R$^2$ value of 0.99856 indicating a good fit. The concentrations used were 1 ng/ml, 10 ng/ml, 50 ng/ml, and 100 ng/ml. With this information, the limit of detection was calculated using three times the standard deviation divided by the slope of the calibration curve. The limit of detection calculated was 0.38 ng/ml.
Figure 10: Calibration curve for the cocaine metabolite taken from the intensity of the 1078 cm\(^{-1}\) Raman shift peak of the SERS spectra.

When compared to the commercial market, this test is much more sensitive. The commercial test utilizes urine to test for multiple illicit drugs at once such as THC, cocaine, opiates, amphetamines, and ecstasy. The commercial limit of detection for cocaine is 300 ng/ml\(^5\). This is 1000x times higher than the SERS probe strip. The difference between the strips is that the commercial test strips are colorimetric, tests urine where the SERS probe strip was tested using buffer, and that the commercial tests are utilized for multiple different types of illicit drugs. The SERS probe strip is a good starting point to improve the sensitivity and utilize the saliva for all these illicit drugs that the commercial test strip includes.
4.4 Conclusions

This chapter focused on the utilization of the previously synthesized gold@silica core-shell nanostars as a SERS probe for a cocaine metabolite. The gold@silica nanostars were successfully functionalized into a SERS probe. The linear range of the metabolite detection encompassed all the concentration values detected and this provided a limit of detection of 0.38 ng/ml. This probe was successful in detecting the cocaine metabolite at levels much lower than the commercial test. The SERS probe is a starting point to decrease the limit of detection for illicit drugs for use in policework, pre-job screening, athletic testing, etc.

4.5 References


Chapter 5: Conclusions and Future Studies

5.1 Conclusions

This study carried out synthesis of materials and then the subsequent use of the selected nanostar core-shell structure for use in a paper-based lateral flow test strip for the detection of a cocaine metabolite. In summary, the presented results show that the nanostar core-shell SERS probe was effective for the detection of and a cocaine metabolite.

5.2 Future Studies

The results presented in this thesis are the beginning of the work needed for a point of care device for the use in hospitals and in the field with police. Future work would include further optimization of the test strip and for the detection of the cocaine metabolite in both saliva and blood plasma. Another avenue would be to include multiple lines for different illicit drugs on a single test strip. More future work would be to successfully decorate the gold@silica core-shell nanostar structure and then explore the properties of this material.