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A Nanosensor for Explosives Detection Based on Molecularly Imprinted Polymers (MIPs) and Surfaced-enhanced Raman Scattering (SERS)

by Ellen Holthoff and Dimitra Stratis-Cullum

ARL-TR-5092 **March 2010**

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14. ABSTRACT
Molecularly imprinted polymers (MIPs) can be used as *artificial* recognition elements for target chemical analytes of interest. Molecular imprinting involves arranging polymerizable functional monomers around a template followed by polymerization and template removal. The selectivity for the target analyte is based on the spatial orientation of the binding site and covalent or noncovalent interactions between the functional monomer and the analyte. In a sensor format, the recognition event is monitored with some form of transduction. MIP technology is still in its infancy and limitations such as non-specific binding may be overcome using surface enhanced Raman scattering (SERS) as an integrated transduction method for enhanced sensor performance. Compared to other spectroscopic techniques employed with MIPs, SERS should be less affected by the cross-selectivity resulting from non-specific adsorption to the polymer. This report details the development of a MIP-SERS sensing platform for explosive targets.

15. SUBJECT TERMS
Molecularly imprinted polymer (MIP), surface enhanced Raman scattering (SERS), explosives detection, Xerogel

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1. Objective

The objective of this Director's Research Initiative (DRI) is to investigate, *for the first time*, the feasibility of using molecularly imprinted polymers (MIPs) and surface enhanced Raman scattering (SERS) to develop highly selective and sensitive nanosensors for detecting explosive compounds.

2. Approach

The Army does not have a sensing technology that meets both the chemical selectivity and sensitivity requirements for detection of a wide range of explosive compounds. Our approach aims to address this significant shortfall through the combination of two separate technologies, MIPs and SERS. Although each technology has been separately studied in the literature with limited success, this report is the first successful integration and demonstration of this multi-functional approach for explosives detection to date. In this first-year effort, we have clearly validated the MIP-SERS concept to include the development of an integration strategy and MIP formulation that has excellent adhesion properties, along with a demonstration of integrated SERS detection. Although not planned in the first-year objectives, we have demonstrated a greater selectivity of the imprinted polymer for 2,4,6-trinitrotoluene (TNT) over other nitro-containing compounds. Initially, we chose a commercially available SERS substrate platform to validate the sensing concept; however, we aim to address the required sensitivity through more advanced substrate development and integration approaches as the project continues.

MIPs can be used as artificial recognition elements for target chemical analytes of interest. Essentially, one creates a molecular "memory" within the imprinted polymer matrix. In a sensor format, the recognition event is monitored with some form of transduction (i.e., optical, electrochemical, etc.). MIP technology is still in its infancy and limitations such as non-specific binding may be overcome by using SERS as an integrated transduction method for enhanced sensor performance. The basic MIP-SERS concept is illustrated in figure 1.

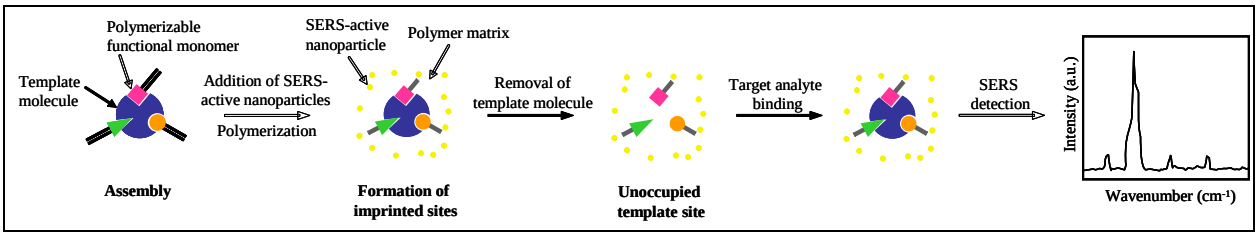

Figure 1. Proposed MIP-SERS concept.

Briefly, MIPs involve arranging polymerizable functional monomers around a template, followed by polymerization and template removal (*1*). Arrangement is generally achieved by non-covalent or reversible covalent interactions. In both types of molecular imprinting, once the template is removed, three-dimensional cavities are generated within the final material that are complementary to the template molecule in size, shape, and functionality. This arrangement allows the preparation of polymers that are selective for the adsorption of the target molecule of interest. Other advantages of this technique include robustness and stability under a wide range of chemical and physical conditions, and an ability to easily design recognition sites for a plethora of target chemicals (e.g., pesticides, energetic materials, pharmaceuticals, and proteins) (*2, 3*). There have been some published work and patents on the development of MIP materials for explosive compounds (*3–5*). However, a MIP alone does not meet the requirements for a sensor. Thus, unless additional selectivity is achieved through some other means, a MIP alone will not be functional for practical application.

The detection capabilities of SERS should make it an excellent transduction method for selective, full compound identification, a capability that is not currently possible with existing MIP sensors. SERS is an extremely sensitive and selective technique that involves enhancements in the Raman scattering intensities of substances adsorbed on a rough metal surface (typically, gold or silver). The enhancements are due to an increase in the electric field surrounding the molecules, which results when the incident light in the experiment strikes the metal surface and excites localized surface plasmons. The enhancement factor can be as great at 10^{14}, which permits single molecule detection (*6*). Compared to other, more conventional spectroscopic techniques employed with MIPs, SERS should be less affected by the cross-selectivity resulting from non-specific adsorption to the polymer. As part of our technique, the MIP will concentrate the target onto the SERS-active surface, thereby making the combined approach more selective than a SERS-only detection platform, which is plagued by background chemical interference.

This integrated MIPs and SERS concept could be a very attractive approach as a chemical sensing platform for the Army, yet only two investigations of this pairing have been reported (*7, 8*). In the first, before the onset of this project, Kostrewa et al. (*7*) prepared MIPs on SERS-active surfaces to directly monitor the uptake and release of either (2S,3S)-(+)-di-O-benzoyl-tartaric acid or N-benzyloxycarbonyl-(L)-apartic acid to a polymer by SERS. Adhesion of the MIPs to the SERS-active substrates was unsatisfactory for practical application as the MIP was not truly integrated with the substrate. In our approach, we have incorporated a specific functional group in the chemical formulation that binds to the metallic under layer support through thiol chemistry. During this year, the Kantarovich group (*8*) used a nano fountain pen to print MIP droplets on SERS-active surfaces and directly monitor the uptake and release of the β-blocking drug propranolol by SERS. In both of these experiments, the MIP was not designed for explosive targets and the SERS-active metallic nanostructures were not integrated into the polymer imprint, which is key to the development of a sensitive and robust nanosensor platform.

We also conducted a literature and patent search using Web of Science and SciFinder. In summary, the survey revealed literature pertaining to MIPs for explosive compounds (*3–5*) or SERS for explosives recognition (*9–12*), but there were no reports on an integrated MIP-SERS nanosensor for explosives detection. Also, it is worth pointing out that there are many groups and companies (e.g., Edmiston, EIC Labs) that are pursuing SERS-only sensing platforms (with no MIP capability) or MIP-based schemes with other transduction methods.

The goal of the current work was to demonstrate that the MIP-SERS combination is an effective and robust chemical nanosensing scheme and the *first-ever* hybrid MIP-SERS sensing platform for explosive targets. The feasibility of the hybrid MIP-SERS nanosensing approach was assessed through polymer optimization for explosive imprinting, enhanced polymer adhesion to the substrate, and integration with SERS through active nanoparticle templating and commercially available SERS substrates.

Polymer optimization involved combining polymers in a precise manner so as to create a variety of usable polymer materials. The polymer materials of interest are sol-gel-derived xerogels, which have been used as a platform for MIP-based sensor development (*13–15*). The sol-gel process is favorable as it allows one to entrap analytes within a readily tunable material (*16*). These materials are also attractive because their physicochemical properties can be adjusted by choice of precursor(s) and the processing protocol. Xerogel hosts may be prepared with (1) a wide range of surface areas, mean pore dimensions, and pore size distributions; (2) good thermal stability; (3) adjustable conductivities; and (4) a reasonably broad optical window that allows the use of modern spectroscopic tools to study dopants within the xerogel. Precursors chosen based on potential interactions with the template molecule (and target analyte), TNT, allow for increased target recognition. For example, MIPs comprised of 3-aminopropyltriethoxysilane, 2-(trimethoxysilylethyl)pyridine or acrylamide have been shown to engage in strong non-covalent interactions with TNT molecules (*17*) via the formation of a charge-transfer complex between the electron-deficient aromatic ring of nitroaromatics and the electron-rich amino or pyridine group of the precursor (*18–20*). This interaction significantly improves polymer selectivity and affinity for TNT (*3*). Adhesion of the polymer to the SERS substrate is also a consideration in precursor selection. For example, chemisorption of the polymer to the metal may be achieved by incorporating a xerogel precursor that contains a thiol or disulfide group, such as 2-(2-pyridylethyl)thiopropyltrimethoxysilane or bis[3-(triethoxysilyl)propyl]disulfide.

Although MIPs have been integrated with other, less selective spectroscopic methods such as fluorescence, integration with surface enhanced Raman is not straightforward and poses a unique set of challenges. One challenge, discussed previously, is successful polymer integration, which we address through thiol precursor chemisorption. However, a major technical challenge is ensuring that the polymer layer is a thin enough film to concentrate the chemical target of interest (in this case, an explosive compound) within the surface plasmon responsible for the Raman enhancement, which drops off exponentially with distance from the nanostructure surface. Therefore, thin-film formulations are necessary (sub micron) with our casting approach.

In order to validate this concept in the first year, our first approach was to use commercially available SERS-active substrates (Klarite^{TM}) and thin-film MIP integration. These substrates offer reproducibility, but lack the required sensitivity. The longer-term approach was to integrate the MIP with more advanced substrate architectures, such as a multi-layer film over nanosphere approach (*21*, *22*) or colloidal encapsulation. Therefore, the sensitivity of the sensor for TNT would be limited by the SERS-active substrate. Although outside the first-year objectives, SERS-active substrates were prepared in-house by embedding metal colloids (silver or gold) in a sol-gel-derived structure (*23*). This approach combined the high activity of colloids with the stability of xerogels. Sol-gel-based molecularly imprinted SERS substrates may be prepared by embedding silver or gold colloids in the MIPs.

3. Results

3.1 TNT-doped Xerogel Preparation

We have developed a procedure for polymer fabrication and formulated a sol-gel-derived xerogel following this process. A TNT stock solution was prepared at 6.05×10^{-3} M in acetonitrile. A high concentration of TNT was needed due to the sensitivity limits of the Klarite substrates. Sol solutions were prepared by mixing methyltriethoxysilane (C1-TriEOS), 3-mercaptopropyltrimethoxysilane (MPTMS), 3-aminopropyltriethoxysilane (APTES), ethanol (EtOH), and hydrochloride (HCl) (1 M). These components were simultaneously combined at room temperature and then stirred for 30 min to ensure a visually homogeneous sol solution. The TNT-doped sol solution was prepared by adding 150 μL of the TNT stock solution to the prehydrolyzed C1-TriEOS/MPTMS/APTES/EtOH/HCl sol solution. This solution was then vigorously mixed for 30 s with a vortex mixer. The strong non-covalent interaction between APTES and TNT resulted in the appearance of a red color. Control xerogel films were prepared to ensure that the observed SERS signal did not arise from artifacts. The controls were prepared by following the exact reaction sequence described above except as noted in section 3.2. Control A was formed by eliminating TNT and control B was formed by eliminating TNT and APTES.

3.2 Controlling Film Thickness

The xerogels were spun cast as thin films onto purchased Klarite SERS substrates using a spin coater. SERS enhancement is known to decrease tenfold with a distance of approximately 2–3 nm. Due to the short range of this phenomenon, the templated sites of the polymer must be kept within the enhancing electromagnetic fields; therefore, the thickness of the MIP films deposited on the substrates for SERS detection must be controlled. In order to determine the optimal thickness, the volume and spin deposition rate of the sol solutions was optimized. Figure 2a presents SERS spectra collected for three volumes (50, 75, and 100 μL) of a TNT-doped xerogel MIP deposited by spin casting (2000 rpm, 30 s) on Klarite substrates. Plainly

apparent in all the samples are the nitrogen dioxide (NO_2) out-of-plane bending modes between 820 and 850 cm^{-1} and the NO_2 stretching modes between 1350 and 1370 cm^{-1} (*24*). These bands can be used as a "fingerprint" for the detection of TNT by its SERS spectrum. Comparison of the spectra for each sample volume suggests there is less polymer background when smaller aliquots of sample are used. Although SERS detection was achieved for all volumes of the TNT-doped MIP, the films ranged in thickness from 7–10 μm, which is outside of the enhancing electromagnetic field. We suspect a high concentration of TNT resulted in a majority of the signal arising from the substrate-film interface.

Figure 2b presents SERS spectra collected for 50 μL of a TNT-doped xerogel MIP deposited by spin casting on Klarite substrates at three spinning speeds (2000, 4000, and 6000 rpm). The TNT fingerprint is apparent in these spectra. Comparison of the spectra at each spinning speed suggests there is less polymer background at faster speeds. Spin casting at 4000 and 6000 rpm yielded films ranging in thickness from 2–5 μm. Based on the results from the volume and speed studies, we determined the optimal parameters for sample preparation to be 50 μL of sample, spun cast at 4000 rpm.

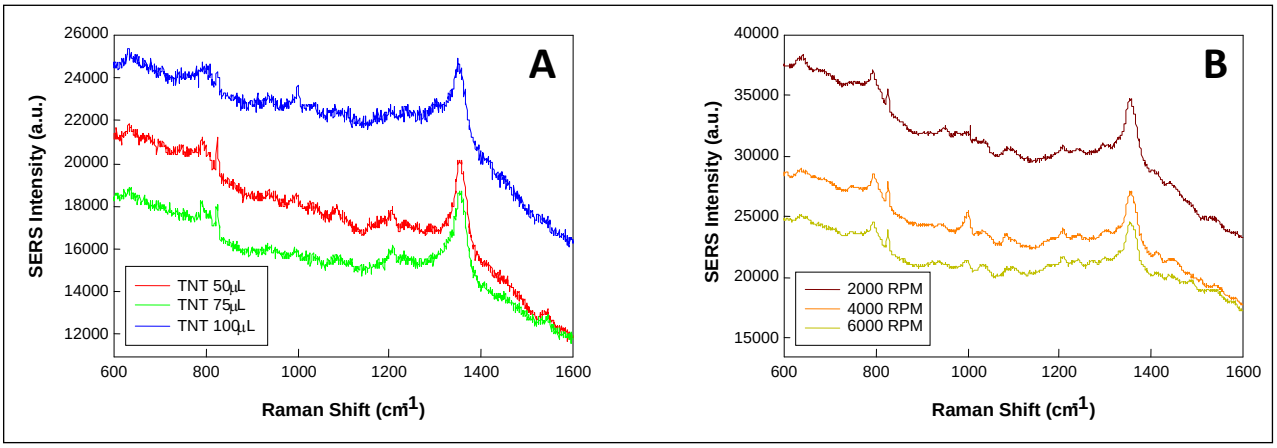

Figure 2. SERS spectra of a TNT-doped xerogel MIP deposited on Klarite substrates at different (a) volumes and (b) spinning speeds.

3.3 MIP Performance

Figure 3a presents the SERS spectra for both a TNT-doped xerogel thin film and control (A and B) xerogel thin films. The TNT fingerprint is apparent in the spectra of the doped samples. The control spectra are similar and have only a broad peak between 1300 and 1340 cm^{-1}. This peak is also partially apparent in the doped samples. This is attributed to the glass to which the Klarite active area is mounted. A glass spectrum is provided in figure 3a for comparison. Figure 3b presents the SERS spectra for a TNT-doped xerogel thin film with the control spectra subtracted. The broad glass background peak is no longer evident and the TNT fingerprint peaks are more defined.

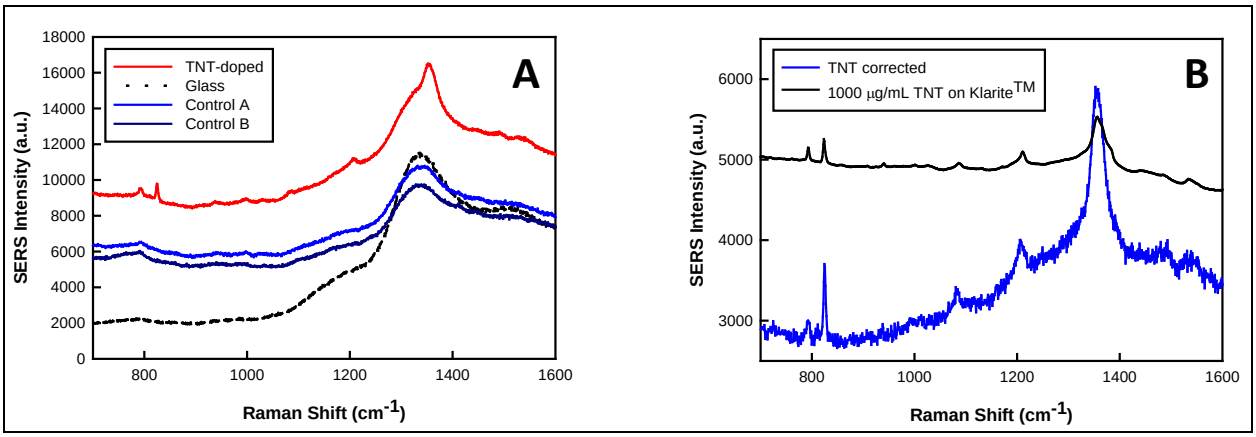

Figure 3. SERS spectra of (a) TNT-doped and control xerogel thin films and (b) a control subtracted TNT-doped xerogel thin film.

Xerogel thin films were treated with an EtOH/acetonitrile/acetic acid (v/v/v 8:2:1) solution at room temperature. The xerogels were allowed to react with the EtOH/acetonitrile/acetic acid solution overnight (18 h). Figure 4 presents the SERS spectra for a TNT-doped xerogel thin film before and after treatment with the EtOH/acetonitrile/acetic acid solution. The results of this experiment suggest that 85% of the TNT is removed by the wash step.

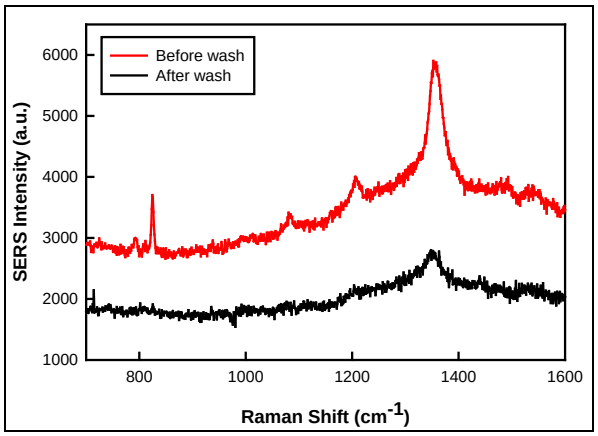

Figure 4. SERS spectra from a TNT-doped xerogel thin film recorded before and after the TNT was removed with the wash solution.

A TNT stock solution was prepared at 0.4 mM in acetonitrile. MIP and control thin films were incubated in this stock solution at room temperature. The xerogels were allowed to react with the TNT for 1.5 h. Figure 5 presents the SERS spectra for a MIP xerogel thin film and controls A and B after treatment with the TNT solution. The TNT fingerprint is apparent in all of the spectra. The results of this experiment suggest that TNT remains on the surface of the xerogel thin films. The MIP and controls were rinsed with 2 mL of acetonitrile in order to remove the TNT from the film surface. Figure 6a presents the SERs spectra for a MIP xerogel thin film and controls A and B after the acetonitrile rinse. There was no longer a TNT fingerprint present in

the SERS spectrum collected for control B. The control B SERS spectrum was subtracted from the SERS spectra for a MIP xerogel thin film and control A. These spectra are shown in figure 6b. The results of this experiment suggest that the MIP binds 67% more TNT than control A and 100% more TNT than control B. It was expected that some of the TNT would react with control A due to the presence of APTES.

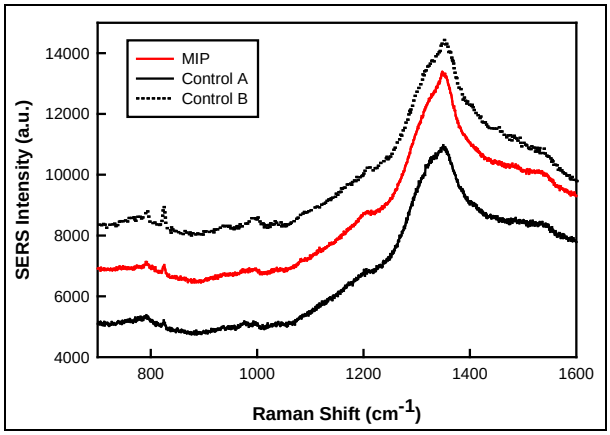

Figure 5. SERS spectra recorded after a MIP and controls A and B were incubated in a TNT solution; 85% of the TNT is removed by the wash step.

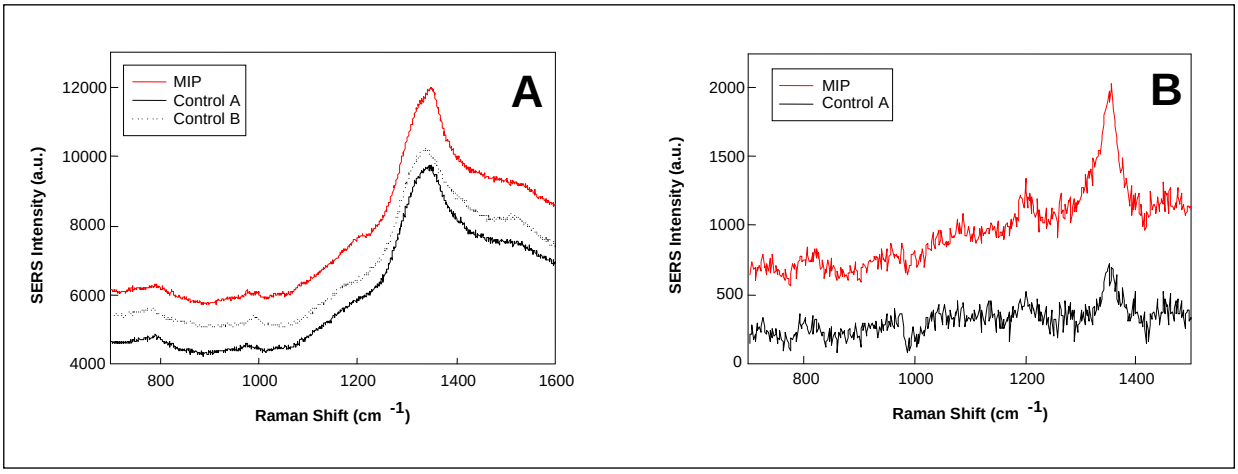

Figure 6. SERS spectra (a) recorded after a MIP and controls A and B were incubated in a TNT solution and then rinsed with acetonitrile and (b) for a MIP and control A after control B subtraction.

3.4 MIP Selectivity

The MIP was challenged by two structurally similar analogues to TNT. A 2,4-dinitrotoluene (DNT) stock solution was prepared at 0.4 mM in acetonitrile. MIP and control A thin films were incubated in this stock solution at room temperature. The xerogels were allowed to react with the DNT for 1.5 h. Figure 7 presents the SERS spectra for a MIP xerogel thin film and control A after treatment with the DNT solution and rinsing with 2 mL acetonitrile. Similar to TNT, DNT also exhibits NO_2 out-of-plane bending modes between 820 and 850 cm^{-1} and the NO_2 stretching

modes between 1350 and 1370 cm^{-1} (*11*). DNT also exhibits the aromatic ring breathing mode around 1000 cm^{-1}. The results of this experiment suggest that the MIP and control A bind similar amounts of DNT. The MIP binds only 6% more DNT than control A. Based on the presence of APTES, it was expected that some of the DNT would react with the MIP and control A. Because DNT is a precursor and a manufacturing impurity of TNT, it is possible that DNT was the template molecule for some of the imprinted sites in the MIP, which explains the minimal binding. Also, due to the size and shape of the templated sites in relation to DNT, it is possible that some of the DNT was bound in these sites.

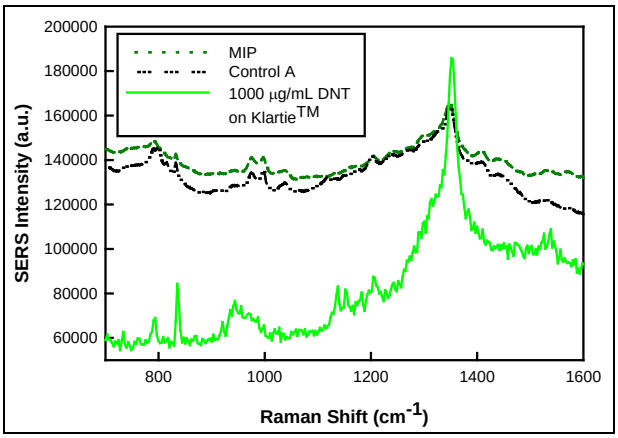

Figure 7. SERS spectra recorded after a MIP and were incubated in a DNT solution and then rinsed with acetonitrile.

A 2-nitrotoluene (NT) stock solution was prepared at 0.4 mM in acetonitrile. MIP and control A thin films were incubated in this stock solution at room temperature. The xerogels were allowed to react with the NT for 1.5 h. Figure 8 presents the SERS spectra for a MIP xerogel thin film and control A after treatment with the NT solution and rinsing with 2 mL acetonitrile. Similar to TNT and DNT, NT also exhibits the NO_2 stretching mode between 1350 and 1370 cm^{-1}, although it is not as pronounced. The aromatic ring breathing mode around 1000 cm^{-1} is also present. The results of this experiment suggest that the MIP and control A bind minimal amounts of NT and the MIP binds 5% more NT than control A. Again, based on the presence of APTES, it was expected that some of the NT would react with the MIP and control A. Due to the size and shape of the templated sites in relation to NT, it is possible that some of the NT was bound in these sites, which explains the minimal binding.

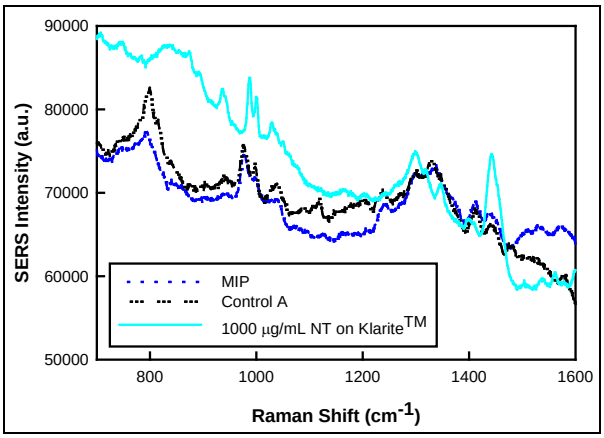

Figure 8. SERS spectra recorded after a MIP and control A were incubated in a NT solution and then rinsed with acetonitrile.

Figure 9 presents a bar graph comparing the percentage of TNT, DNT, and NT binding to the MIP in comparison to control A. The percentage of MIP binding is significantly greater for TNT and suggests a successful preliminary demonstration of a MIP-SERS sensing platform for this explosive target.

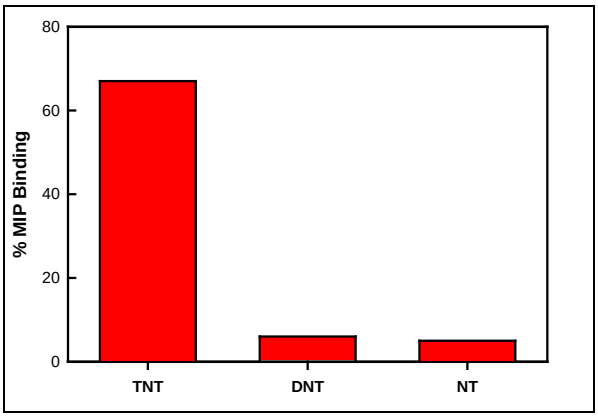

Figure 9. Assessment of TNT, DNT, and NT binding to the MIP in comparison to control A.

3.5 MIP Stability

During our effort, we overcame the technical barriers to MIP adhesion. This was achieved by incorporating the xerogel precursor, MPTMS, in the xerogel formulation used to prepare the MIP. The thiol group in this precursor chemisorbs onto the metal surface of the Klarite substrate. Adhesion was assessed by soaking the xerogel-coated substrate in various aqueous environments, including water (H_2O), 6 M HCl, 0.1 M pH 7.4 phosphate buffer, and the ethanol/acetonitrile/acetic acid wash solution. The polymer showed excellent adhesion and stability, with no apparent degradation, which is necessary for practical field use.

3.6 Colloid-embedded Xerogel SERS-active Substrates

We also developed a procedure for coating silver nanoparticles with a xerogel. Preparation of silver nanoparticle suspensions has been reported elsewhere (*25*). To coat the particles, 1 mL of the stock silver suspension was first diluted with 200 mL 2-propanol with stirring. To this solution we added 10.5 mL ammonium hydroxide (NH_4OH) and 18.0 mL distilled H_2O. This mixture was stirred at 600 rpm at 40 ºC. After the temperature was stabilized, a mixture of xerogel precursors, tetraethoxysilane (TEOS), 0.101 mL, and 1,4-bis(trimethoxysilylethyl)benzene (BTEB) , 0.0394 mL, were rapidly injected and the reaction continued for 2 h. The xerogel shell thickness varies depending on the amount of precursor and the reaction time. Specific conditions have been reported elsewhere (*26*). Control nanoparticles were prepared by eliminating the silver nanoparticle suspension.

Figure 10a presents a transmission electron micrograph (TEM) of silver nanoparticles coated with xerogel. The dark silver centers can be seen encapsulated with approximately 50 nm of material. Figure 10b is the energy dispersive x-ray (EDX) analysis of the nanoparticles. A prominent silver peak is observed, verifying the presence of silver.

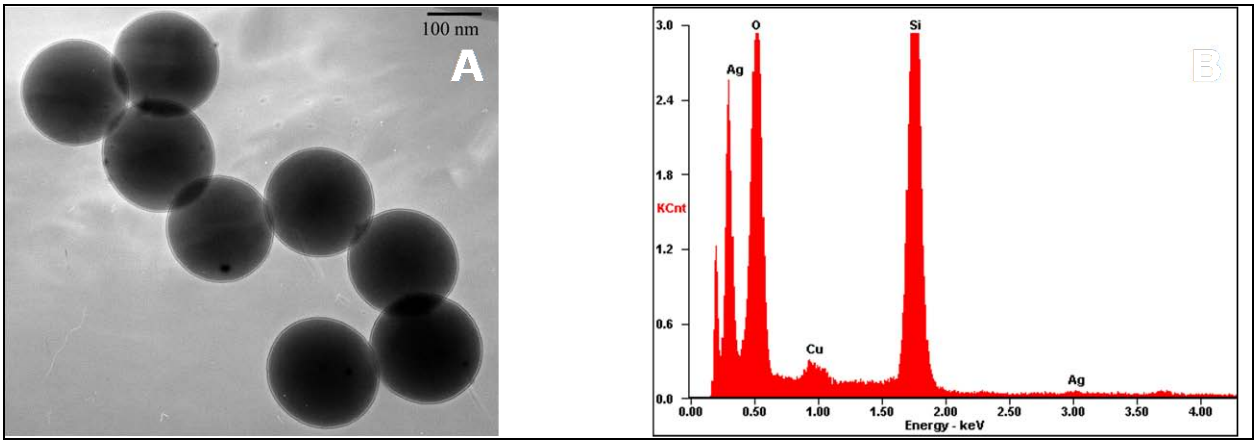

Figure 10. (a) TEM of silver nanoparticles coated with xerogel and (b) EDX analysis verifying the presence of silver.

Figure 11 presents the SERS spectra for xerogel-coated silver nanoparticle and control nanoparticles. The spectrum for BTEB on a Klarite substrate is also shown for reference. In the reference spectrum, there are two prominent peaks. The peaks around 700 and 1100 cm^{-1} can be used as a fingerprint for BTEB. This BTEB fingerprint is visible in the spectrum for the BTEB-coated silver nanoparticles. The results of this experiment suggest that SERS-active substrates were successfully prepared by embedding metal colloids in a xerogel structure. It is expected that controlling shell thickness will provide increased SERS enhancement.

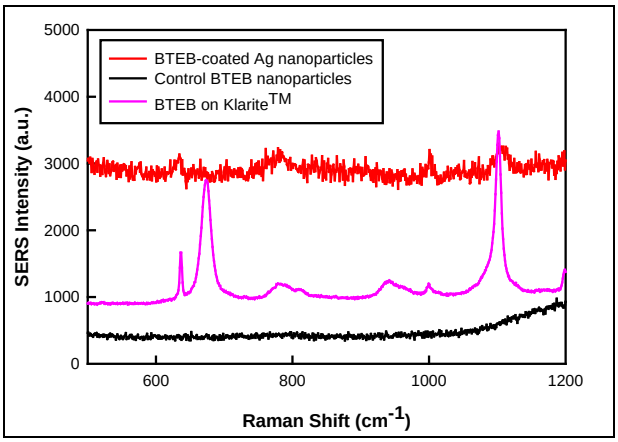

Figure 11. SERS spectra for BTEB-coated silver and BTEB control nanoparticles.

4. Conclusions

The work reported here validates the hybrid MIP and SERS sensing concept and demonstrates the feasibility of this nanosensor concept for the detection of explosive compounds. To date, this is the *only* demonstration of a MIP-SERS sensing platform for these targets. Although preliminary, the data suggests that the MIP-SERS combination is an effective and robust chemical nanosensing scheme. Although high-risk, the successful development of a MIP-SERS sensing platform for direct target analyte detection would be high impact as it could provide the Army with an adaptable chemical nanosensing platform for rapid and robust detection of a variety of threat and target species.

Further investigations should focus on refinement of both the MIP (i.e., xerogel formulation) for improved selectivity and the SERS substrate for enhanced sensitivity. Also, the MIP-SERS sensor platform evaluation should be expanded to include other explosives and chemical warfare agents of interest to the Army. This research could provide a base for an effort at the U.S. Army Research Laboratory (ARL) to develop MIPs suitable for the detection of a variety of chemical and biological agents. A successful MIP-SERS sensing format could reduce sensor cost and size, while maintaining the high sensitivity, selectivity, and portability needed for military applications.

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6. Transitions

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List of Symbols, Abbreviations, and Acronyms

APTES	3-aminopropyltriethoxysilane
ARL	U.S. Army Research Laboratory
BTEB	1,4-bis(trimethoxysilylethyl)benzene
C1-TriEOS	methyltriethoxysilane
DNT	2,4-dinitrotoluene
DRI	Director's Research Initiative
EDX	energy dispersive x-ray
EtOH	ethanol
H_2O	water
HCl	hydrochloride
MIPs	molecularly imprinted polymers
MPTMS	3-mercaptopropyltrimethoxysilane
NH_4OH	ammonium hydroxide
NO_2	nitrogen dioxide
NT	2-nitrotoluene
SERS	surface enhanced Raman scattering
TEM	transmission electron micrograph
TEOS	tetraethoxysilane
TNT	2,4,6-trinitrotoluene

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