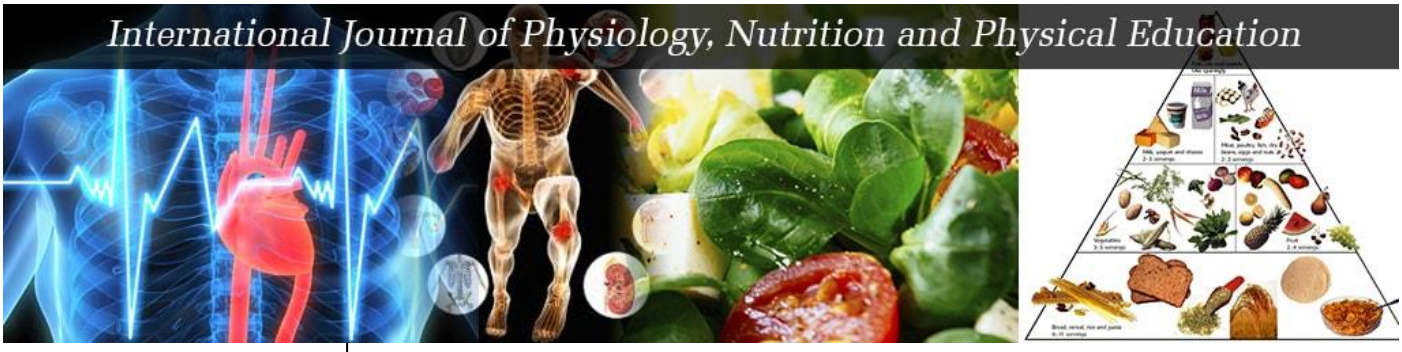

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Surface enhanced Raman scattering: Mechanism and suitable Nanomaterials for detection of trace molecules

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Abstract
SERS is becoming an important tool for detection of molecules in ultra-trace level. In this review, an overview of SERS and different types of SERS active substances are presented. The excessive use of metal and/or metal supported nanostructured materials have been used for making the SERS active substances. Along with pure metal nanoparticles, core-shell or hybrid nanoparticles also made their way as SERS active platform. Notably, unusual shapes such as nanostars or nanoplates have used for such purposes. Further, SERS were used for intracellular detection of biomolecules in different types of cells. It is believed that this review would be useful to further development of advanced SERS platform for various applications especially physiological detection of trace molecules.

Keywords: SERS, mechanism, Nanomaterials, intracellular, trace molecule

1. Introduction
Surface enhanced Raman spectroscopy (SERS) is a powerful vibrational spectroscopy technique that allows for highly sensitive structural detection of low concentration analytes through the amplification of electromagnetic fields generated by the excitation of localized surface plasmons [1]. SERS has progressed from studies of model systems on roughened electrodes to highly sophisticated studies, such as single molecule spectroscopy. We summarize the current state of knowledge concerning the mechanism of SERS and new substrate materials. We highlight recent applications of SERS including sensing, spectro-electrochemistry, single molecule SERS, and real-world applications. We also discuss contributions to the field from the Van Duyne group. This review concludes with a discussion of future directions for this field including biological probing with UV-SERS, tip-enhanced Raman spectroscopy, and ultrafast SERS [2]. A single metal nanoparticle typically offers SERS signal enhancements on the order of 10^2–10^6 [3]. However, when two nanoparticles are in close proximity, their dipoles can couple, leading to stronger overall field enhancements, reported to be as high as 10^{10}–10^{14} [4]. As such, nanoparticle aggregates are often considered an optimum SERS substrate, even though they lack well-defined structure [5]. For intracellular SERS imaging, these nano- particles must self-assemble into aggregates within the cell, since the aggregates are often too large to penetrate the external membrane or wall of the cell. As we shall see, the cells inherently promote this aggregation due to their primary mechanism of nanoparticle uptake; however, this can limit the access that the nanoparticles have to specific regions of the intracellular matrix.

In recent years, purposeful SERS applications have been performed by functionalizing the nanoparticles with antibodies or other bio molecules that have a special receptor [6]. The functionalized nanoparticles that also can be described as SERS targeting nanoprobes always contain Raman reporter molecules to highlight the positions of themselves by their high spectral specificity. More recently, this method has been successfully used in tumor detection on living animals [7]. However, the Raman reporter modified targeting nanoprobe provides only the signature of the reporters and tends to be an imaging instrument rather than a detection probe, like the role of a fluorescent reagent or quantum dot; the application of the latter in targeting research is already proving to be excellent. In fact, delivering molecular structural information from the target analyte is the most important characteristic or advantage of SERS, which until now has not been possible by any other technique.

The cell nucleus is a desirable target because the genetic information of the cell and transcription machinery resides there. Although many methods have succeeded in the nuclear targeted studies using gold nanoparticles, SERS has not been involved, because the functionalization might have blocked the metallic surface or imposed influence on the SERS spectra.

SERS is also applied to bacteria. For example, species-specific bacteria detection based on immunoassay and SERS performed recently enables the *in situ* quantification of microorganisms in aqueous environments [8]. Generally, bacterial cells are much smaller than mammalian cells, and it is difficult to introduce a nanometer-sized colloidal metal particle into this tiny environment. Therefore, the study of bacteria by SERS has to been focused almost exclusively on the extracellular analysis. Jarvis *et al*. reported the formation of gold nanoparticles inside the bacterial cells, which enabled SERS detection from the interior.

2. Mechanism of SERS activity

The exact mechanism of the enhancement effect of SERS is still a matter of debate in the literature. There are two primary theories and while their mechanisms differ substantially, distinguishing them experimentally has not been straightforward. The electromagnetic theory proposes the excitation of localized surface plasmons, while the chemical theory proposes the formation of charge-transfer complexes. The chemical theory applies only for species that have formed a chemical bond with the surface, so it cannot explain the observed signal enhancement in all cases, whereas the electromagnetic theory can apply even in those cases where the specimen is physisorbed only to the surface. It has been shown recently that SERS enhancement can occur even when an excited molecule is relatively far apart from the surface which hosts metallic nanoparticles enabling surface Plasmon phenomena [9]. This observation provides a strong support for the electromagnetic theory of SERS. Research in 2015 on a more powerful extension of the SERS technique called SLIPSERS (Slippery Liquid-Infused Porous SERS) has further supported the EM theory.

3. Suitable Functionalizations of SERS activity

In order to achieve suitable functionality for production of SERS platform, various nanoparticles and nanostructured materials have been used.

3.1 Silver (Ag) -based SERS platform

SERS from pyridine adsorbed on electrochemically roughened silver was first observed by Martin Fleischmann, Patrick J. Hendra and A. James McQuillan at the Department of Chemistry at the University of Southampton, Southampton, UK in 1973. This initial publication has been cited over 4000 times. The 40th Anniversary of the first observation of the SERS effect has been marked by the Royal Society of Chemistry by the award of a National Chemical Landmark plaque to the University of Southampton. In 1977, two groups independently noted that the concentration of scattering species could not account for the enhanced signal and each proposed a mechanism for the observed enhancement. Their theories are still accepted as explaining the SERS effect [10]. Jeanmaire and Van Duynl proposed an electromagnetic effect, while Albrecht and Creighton proposed a charge-transfer effect. Rufus Ritchie, of Oak Ridge National Laboratory's Health Sciences Research Division, predicted the existence of the surface Plasmon.

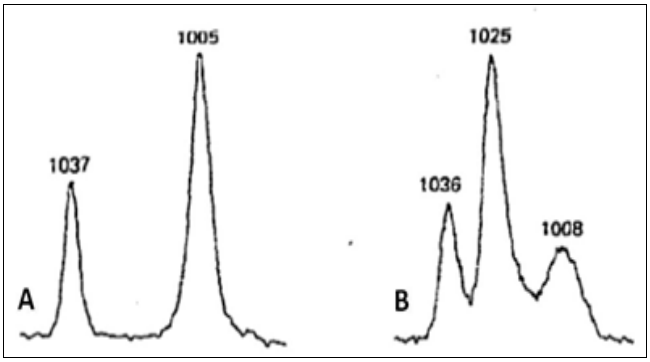

Fig 1: Raman spectra of pyridine in solution (A) and at the silver electrode (B) [11].

From Fig. 1 the Raman spectrum changes considerably when pyridine is examined close to the surface for a silver electrode. The pure pyridine showed Raman band at 1037 and 1005 cm^{-1}. There is a strong new band at 1025 cm^{-1} which decreases in intensity with shift of the potential of the electrode in the cathodic direction [11]. The evidence and the behaviour of the 1025 cm^{-1} band with electrode potential suggest that this band is associated with pyridine coordinated to the metal through the nitrogen atom. The intensities of the Raman bands, which occurs at 1008 and 1036 cm^{-1} also changed.

3.2 Gold (Au) -based SERS platform

Gold island films were also used for this kind of investigation with a different excitation wavelength at 632.8 nm [12]. The Au nanoparticles were deposited on a glass surface at various concentrations of Au colloidal suspension with an immersion time of 6 h [13]. The AFM images for glass surfaces prepared in concentrations of 0.22, 0.31, and 0.40 nm are depicted in Fig. 2. The Au nanoparticles were immobilized on the glass surfaces with a monolayer format, as confirmed using AFM images. For instance, surface densities of Au nanoparticles were obtained respectively as 32.6, 54.9, and 84.9 particles/mm^2 for images in panels (a), (b) and (c) of Fig. 2.

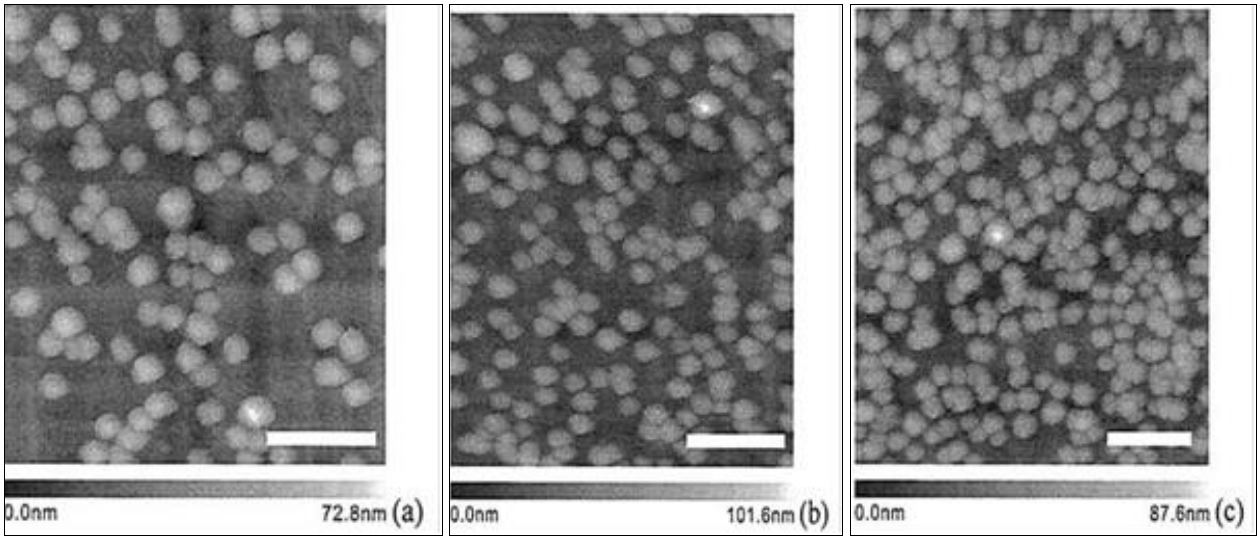

Fig 2: AFM images for glass substrate surfaces with deposited Au nanoparticles. Glass slides (a), (b), and (c) were prepared respectively with concentrations of 0.22, 0.31, and 0.40 nm Au nanoparticle suspensions. Scan areas for each image were 1.7 mm x 1.7 mm for (a) and (b), and 2.1 mm x 2.1 mm for (c). The white bar on images represents the length of 500 nm [13].

Chang *et al.* reported synthesis of SERS active Au/SiO_2 nanocomposites using sonoelectrochemical pulse deposition methods [14]. Here, a simple synthesis route based on sonoelectrochemical pulse deposition (SEPD) methods has been developed to synthesize effectively SERS-active Au/SiO2 nanocomposites (NCs) with an enhancement factor of 5.4×10^8. Experimental results indicate that pH value of solution and addition of SiO_2 NPs before and after oxidation-reduction cycles (ORCs) can significantly influence the corresponding SERS activities (Fig. 3).

3.3 Platinum (Pt) -based SERS platform

Surface-enhanced Raman scattering (SERS) activity and water wettability are important characteristic properties of nanostructured surfaces with respect to their practical applications. The tree-like Pt nanostructures exhibited reproducible SERS activity, and they also showed super hydrophobic nature after n-dodecanethiol modification. The growth process of Pt nanostructures as a function of deposition charge was monitored using a scanning electron microscope, from which the correlation between the structural variation of the Pt nanostructures and the SERS activity and wettability was investigated. The SERS activity was dependent on the presence of sharp edge sites, whereas the wettability was dependent on the apex structures. Well-defined Pt tree nanostructures exhibited high, reproducible, and electrochemically stable SERS activity. The straightforward fabrication of multi-functional Pt nanostructures presented in this work would allow new opportunities for the application of nanostructured metal surfaces.

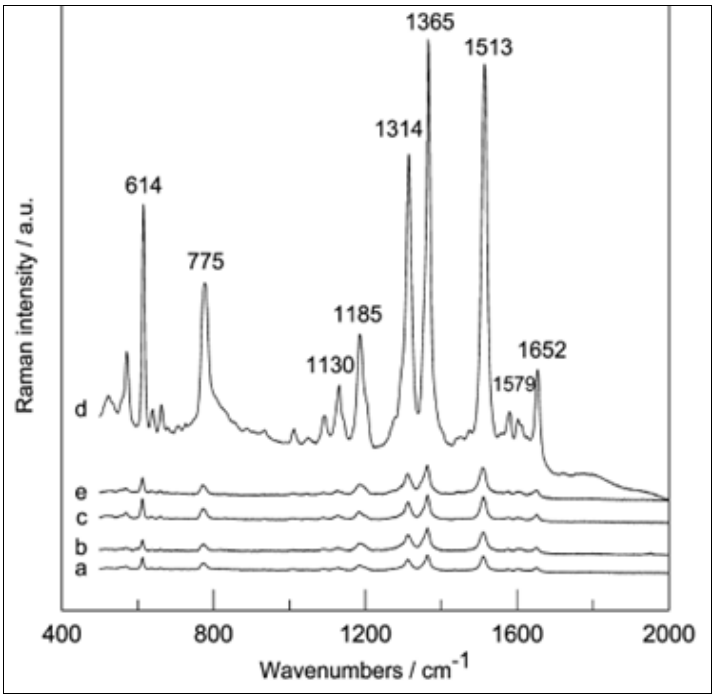

Fig 3: SERS spectra of 2 x 10^{-6} M R6G adsorbed on different Au NPs-deposited Pt substrates prepared by using the same SEPD methods in different solutions: (a) in 0.1 M HCl; (b) in 0.1 M HCl containing 1 mM SiO_2 NPs (addition before ORCs); (c) in 0.1 M KCl; (d) in 0.1 M KCl containing 1 mM SiO_2 NPs (addition before ORCs); (e) in 0.1 M KCl containing 1 mM SiO_2 NPs (addition after ORCs) [14].

3.4 Core/shell materials SERS platform

There have been reports for core/shell materials as well as SERS active substances. Fig. 4 shows the core-shell TEM images of FePt@SiO_2. It revealed the successful sol-gel reaction of the shell of silica (SiO_2) (25–30 nm) for encapsulation of the core of Fe-Pt nanoparticles. Most of the SiO_2 spheres encapsulated one Fe-Pt nanoparticle, and a small portion of the particles contains either zero or two Fe-Pt nanoparticles. The different contrast between the core and shell region is due to the different electron penetration on metallic Fe-Pt nanoparticles and SiO_2 nanoparticle (**15).** Moreover, FePt@SiO_2 nanoparticles could easily dispersed in water system. Surface modification of FePt@SiO_2 was developed through the reaction with N-[3-(trimethoxysilyl) propyl] ethylenediamine (EDS), called as FePt@SiO_2-N. The structure and morphology of FePt@SiO_2-N were also developed in the spherical structure. Figure 3b shows the zeta potential of amine functionalized FePt@SiO_2 (FePt@SiO_2-N). Zeta potential measurement revealed that the surface charge of the FePt@SiO_2 nanoparticles, which would increase with the addition of EDS concentration increase, due to the positive charge (amine group) of EDS. After surface modification, the FePt@SiO_2-N nanoparticles are overall positively charged with the average zeta potential range from +40 until +60 mV Furthermore, we have successfully fabricate Au-NPs through well-established citrate reduction method, and TEM images of gold nanoparticles revealed the spherical morphology in the diameter of ~17 nm.

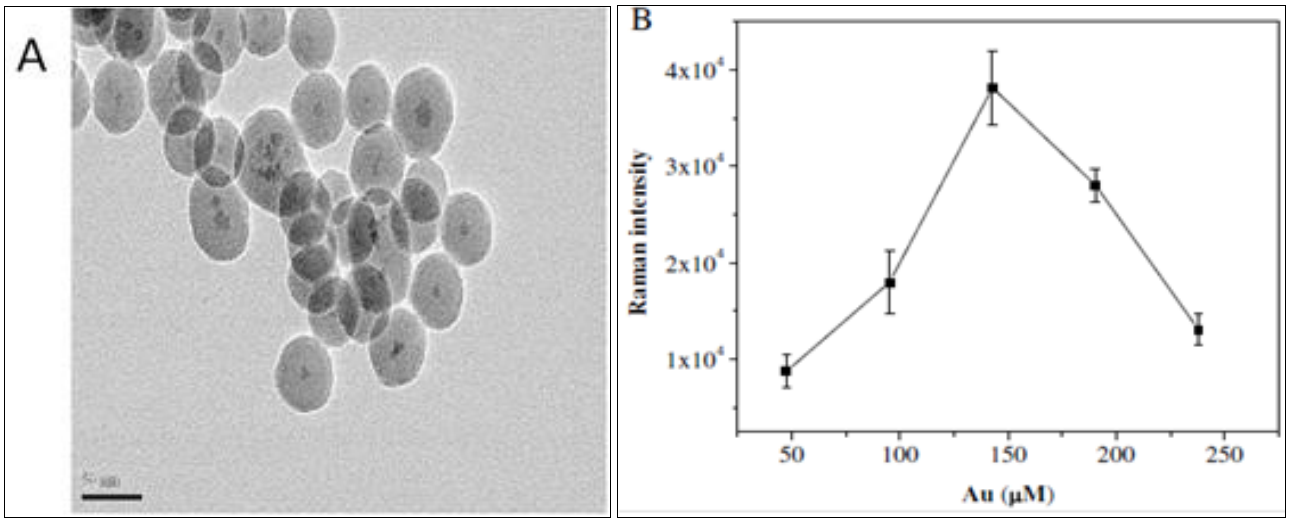

Fig 4: (A) TEM images of FePt@SiO_2 and (B) integrated intensity (733 cm^{-1}) of SERS spectra in the Au-FePt@SiO_2-N (0.3 M of EDS) with various Au nanoparticles concentrations (47.6–238 μM) [15].

4. NPs Size and shape characteristics on detection

There are many reports of SERS active substances with unusual size and shape of the metal nanoparticles [16, 17]. In fact, the abnormal shapes of the metal nanoparticles give the hot-spots enabling the materials as super-active for SERS. For example, Transmission electron microscopy (TEM) images verified star-shaped nanostructures with an average size of *ca* 140 nm (Fig. 5). These NPs have three-dimensional structures with various numbers of tips growing out of the NP core. Analysis of over 100 NPs via TEM revealed that more than 90% of them have at least one tip or more [16]. The corresponding SERS effect of the nanostars for 2-Mercaptopyridine is shown in Fig. 5.

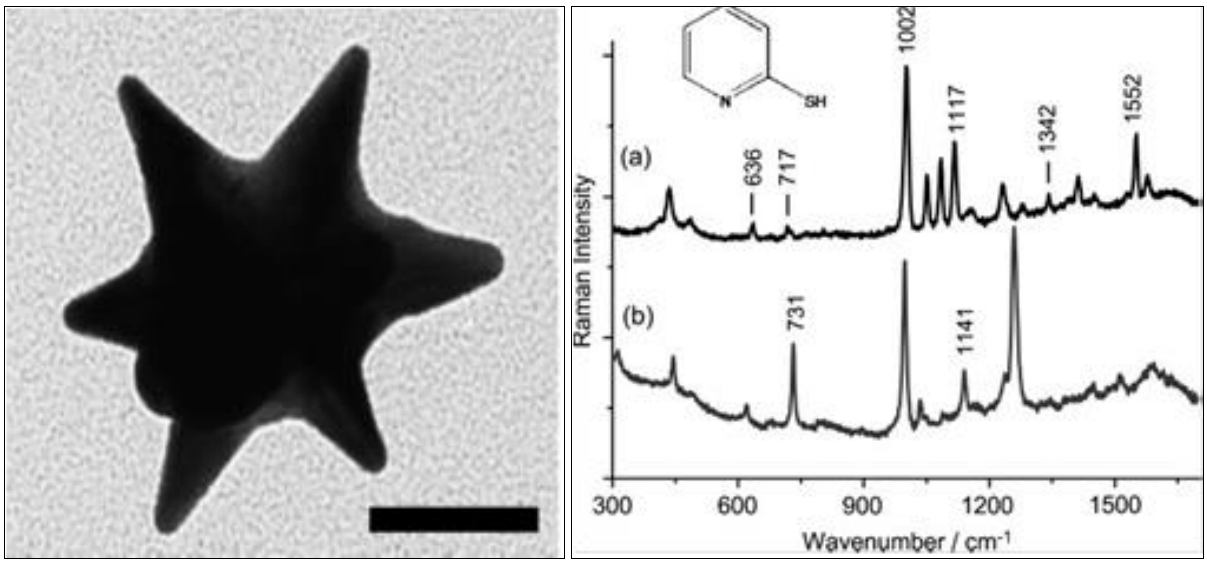

Fig 5: TEM images of star-shaped gold nanoparticles. The scale bars are 50 nm. The corresponding SERS spectra of (a) 1 μM 2-MPy on Au nanostars and (b) Raman spectra of 0.1 M 2-MPy. Inset shows chemical structure of 2-MPy molecule [16].

Sonia *et al.* synthesized triangular nano-plates and studied their SERS effect on 4-nitrobenzenethiol (4-NBT) (Fig. 6) [17].

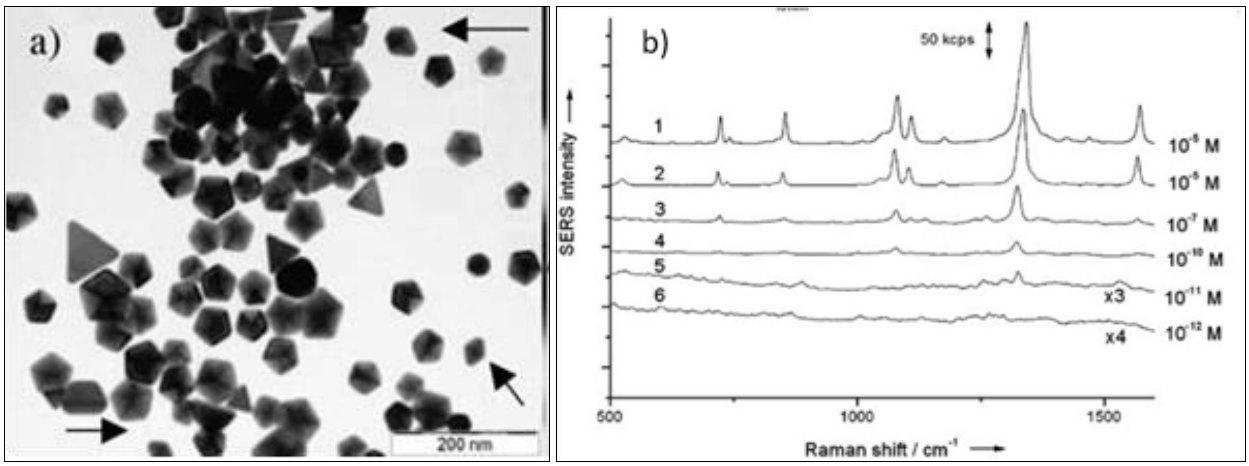

Fig 6: (a) TEM images of Au decahedra synthesized at 80 ºC in the presence of 0.8 mM T904, 30 mM citric acid 0.5 mM $HAuCl_4$ and 1 mM HCl. (b) SERS spectra obtained at different concentrations of 4-NBT in the presence of Au triangular nanoplates (1, 3–6) and Au decahedra (2) upon excitation with a 785 nm laser line [17].

5. Intra-cellular detection

There have been reports for intracellular studies using SERS activity [18, 19]. This study reports on the intracellular detection of cell constituents in mouse fibroblast cells using gold nanoshells. Gold nanoshells were acquired from Nanospectra Biosciences that are based on a silica dielectric core and an outer gold shell layer. They have the unique property of a tenable surface plasmon resonance wavelength from the visible through the near infrared which allows control of the electromagnetic field strength on its surface. Hence gold nanoshells can serve as SERS substrates with plasmonic properties that are not aggregation dependent and thus can be expected to overcome the reproducibility problem that is generally associated with aggregation based colloidal metal nanoparticles. These results represent the first steps in the development of a nano shell-based SERS probe to detect cell organelles and/or intracellular biochemicals with the goal of ultimately improving the ability to monitor intracellular biological processes in real time.

6. Conclusions

In this review, an overview of SERS and different types of SERS active substances are presented. The excessive use of metal and/or metal supported nanostructured materials have been used for making the SERS active substances. Notably, unusual shapes such as nanostars or nanoplates have used for such purposes. Further, SERS were used for intracellular detection of biomolecules in different types of cells. This review will make its use for further development of suitably functionalized SERS materials for detection of physiological trace molecules.

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