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Review Article

Surface Enhanced Raman Scattering Spectroscopy for Pharmaceutical Determination

Abstract

The rapid growth of pharmaceutical industries worldwide demands continuous development of efficient analytical techniques that help not only to detect the presence of the molecules at extremely low concentration levels, but also to detect the structure. Optical spectroscopic techniques are widely used in pharmaceutical development and manufacturing because of their speed and versatility. However, IR and Raman are relatively insensitive. Surface enhanced Raman scattering (SERS) enhances the weak Raman signal, thus, extending the range of available applications. This allows fast, sensitive detection of trace levels of key pharma molecules. However, the use of SERS for analysis requires substrates like silver nanoparticles. In this review, the applications of nano-substrates for SERS will be discussed. The synthesis and fabrication of nanocomposites; such as gold and silver, and nanocomposites will be highlighted. The characterization of the fabricated nanomaterials provide information on structures and properties that could help to improve and control their activity in SERS.

Introduction

One of the main challenges in analytical science and technology is to develop methods that provide unambiguously the chemical nature of the material of interest with the lowest detection limits, no interferences and the shortest acquisition time. Among the promising methods for such purpose is the optical spectroscopy. The most appropriate one is Raman spectroscopy to determine the amount of substances. The Raman Effect occurs when a beam of monochromatic exciting radiation interacts with a sample and scattering occurs. Large portion of this scattered radiation has either the same energy as the incident photons (elastic scattering and known as Rayleigh scattering). A small portion of this scattered radiation (Figure 1) has either higher or lower energy than the incident photons (inelastic scattering) and is known as Raman scattering. Due to light-matter interactions, energy is either gained or lost by the molecule during Raman scattering. This method of characterization can yield narrow, well-resolved vibrational bands which, in essence, provide a "fingerprint" of a given analyte and involve surface processes and interfacial reactions [1,2]. Several methods have been reported for various pharmaceutical compounds analysis [3-9], such as ofloxacin (antibiotic), amlodipine (antihypertensive), chlorpheniramine (antihistamine) and promethazine (antihistamine). However, optical spectroscopic methods attracted more attention over others.

Optical spectroscopy is considered selective technique, both because of the molecularly specific nature of the pattern of peaks obtained and because of the wide variation in the Raman cross section of different analytes. Water gives very weak Raman scattering and organic molecules usually have much larger scattering cross sections thereby enabling Raman scattering to be recorded from organic molecules in aqueous solution and allowing analytes to be identified without the required pretreatment as in some other techniques.

Surface-enhanced Raman scattering (SERS)

SERS is a technique that enhances Raman scattering by

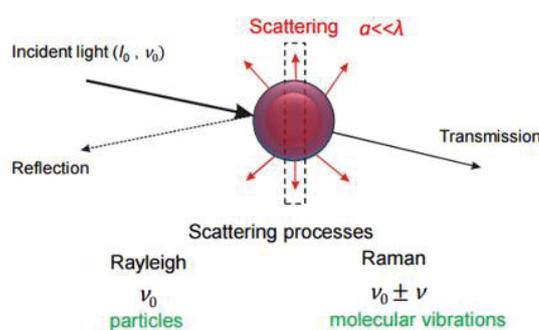


Figure 1: Illustration of scattering processes

molecules adsorbed on rough nanometal surfaces. Surfaces of plasmonic nanostructures are often used of the classic SERS substrates of gold, silver, or copper. The first observation of surface-enhanced Raman scattering (SERS) was reported on the pyridine molecule adsorbed from an aqueous solution onto the silver electrode by oxidation–reduction cycles [10]. The electrode surface was altered to allow for the examination of charge transfer between analyte molecules and substrate metal surface as well as orientation of the molecules.

The amplified signal was explained by increased surface area that enables more pyridine molecules adsorbed on the electrode surface, from the roughened silver electrode [11]. Later, it was reported that the enormously strong surface Raman signal could be caused by another enhancement of Raman scattering efficiency itself in addition to the surface area [12].

Conditions

SERS involves adsorption of molecules onto the substrate surface, Figure 2. Substrates are of a variety of metals, like silver, gold, or copper with differing morphologies [13]. Generally, gold and silver is most often used as SERS substrates because they are air stable materials. All three metals have the excitation of localized surface plasmon resonances (LSPRs) that cover most of the visible and near infrared wavelength range, where most Raman measurements occur, also making them convenient to use, Figure 3 [19]. Delivering molecules to metal structures can be achieved in different ways, as shown in Figure 4. Droplet formation depends on nature of solution, surface materials, and surface nanopatterns. Molecule attachment may be strong or weak depending on molecule affinity to metal and surface chemistry. In general, SERS substrate is any metallic structure (nanostructure) that produces the SERS enhancement. The SERS substrates can be classified as depicted in Figure 5.

The coinage metals of Au, Ag and Cu are usually used since the resonance condition for these metals lies at common laser frequencies for Raman spectroscopy. In addition, at the resonance frequency, the dielectric function for these metals is minor. The simplistic explanation on the basis of the SERS is that the intensity of the Raman scattering is proportional to the induced dipole of the given molecule. The induced dipole is proportional to the polarizability of the molecule and the magnitude of the incident electric field. The main steps proposed in electromagnetic theory containing some fundamentally important aspects of SERS, are as follows:

- (1) An analyte is adsorbed on a surface patterned or roughened so that the chosen excitation frequency will excite a plasmon and create scattering.
- (2) Energy from the plasmon is transferred to the adsorbed molecules and the Raman process occurs on the molecule.
- (3) Energy is transferred back to the plasmon less the

amount transferred to the nuclei and scattered from the surface as wavelength shifted light. These simple steps are the main steps

SERS condition involve:

- i. specific metals, and especially metal nanoparticles such as silver, gold, copper and platinum.
- ii. surfaces with roughness on the nano- or nano-meter scale
- iii. proper wavelength of excitation

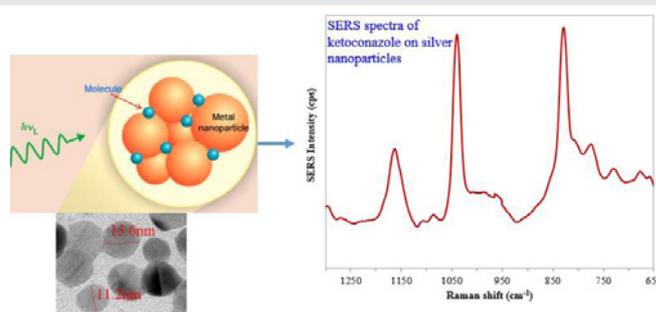


Figure 2: SERS spectra of ketoconazole on silver nanoparticles

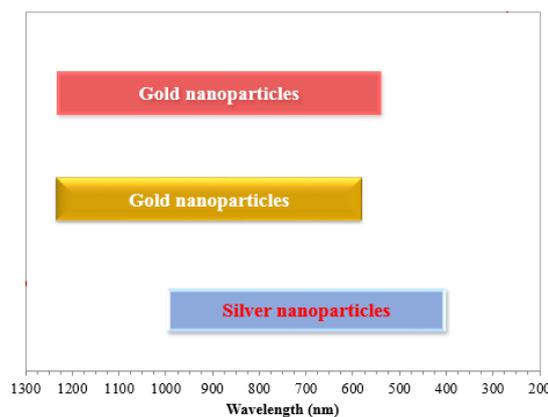


Figure 3: Wavelength ranges where silver, gold, and copper have been characterized and established as supports in SERS.

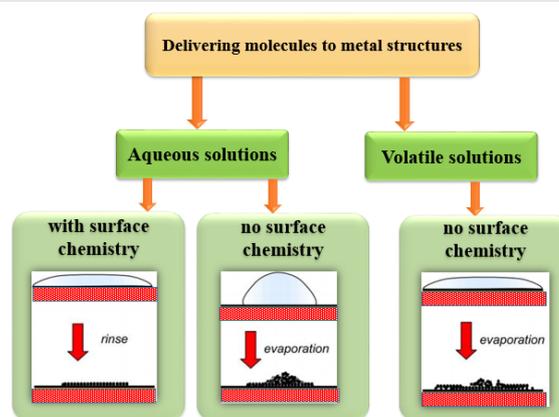


Figure 4: Possible molecules delivering ways to metal structures

Optimization

Several parameters and conditions should be optimized in order to obtain enhanced Raman signal and to ensure maximum signal generation and enhancement. These parameters include the selection of excitation source, the features of the substrate, and the ratio of the sample to the substrate, as shown in Figure 6. It should be noted that the electromagnetic enhancement is strongest where the particles have the highest curvature; thus, the adsorption of the analyte on the long or narrow axis of an ellipsoid or spheroid effects the magnitude enhancement.

Mechanisms

In SERS, there are two main mechanisms of enhancement, an electromagnetic and a chemical enhancement. Chemical mechanism where laser excites (i) new electronic states arising from chemisorption or (ii) shifted or broadened adsorbate electronic states yielding a resonance condition. In this mechanism no roughness requirement. It contributes enhance factor of 10^2 – 10^4 .

In electromagnetic enhancement, localized surface plasmon resonances (LSPRs) induces electromagnetic fields

at roughened metal surface where molecules are adsorbed. It is affected by all factors determining LSPR. It contributes enhance factor of more than 10^4 .

Enhancement factor

SERS enhancement factor can be calculated as:

Analytical enhancement factor (AEF):

$$AEF = \frac{I_{SERS} / C_{SERS}}{I_{RS} / C_{RS}}$$

where I_{SERS} , I_{RS} are intensities of SERS and Raman signals, respectively. C_{SERS} , C_{RS} are molecule concentrations for SERS and Raman, respectively.

SERS substrate enhancement factor (SSEF):

$$SSEF = \frac{I_{SERS} / N_{surf}}{I_{RS} / N_{vol}}$$

where $N_{vol} = C_{RS} V$ – number of molecules in the scattering volume V

Applications of SERS

The SERS methods are widely used for obtaining qualitative and quantitative information of different structures including pharmaceuticals. SERS line-widths are relatively narrow which allows for higher discrimination between samples with similar spectral profiles.

Another substrate commonly used in SERS analysis is vacuum deposited metal island films which include metals on planar surfaces such as glass, quartz, and silicon wafers or nanoparticles embedded surfaces such as silica beads and polystyrene. Metal island films are of high purity and can also be tuned somewhat to appropriate localized surface plasmon resonances by altering parameters such as film thickness and deposition rate, with most thicknesses of metal being between 5–20 nm [19]. SERS substrate of colloidal silver or gold nanoparticles can consistently yield large signal enhancement [20]. Colloids are generally produced by reducing metal salts, often silver nitrate with sodium citrate, which can be done in manner to create cubes, rods, triangles, and other structures [21]. The aggregated clusters of metal colloid can possess hot spot within the aggregate itself that achieve extremely high enhancement [20–25]. There is debate as to the exact reason for the areas of high enhancement and whether it is the aggregates specifically or if a “hot” particle becomes entrapped in the aggregate. Generally, bottom-up and top-down groups of fabrication methods have been used for SERS detection on numerous occasions [26]. The first one focuses on synthetic methods for creating substrates by assembling nanoscale building blocks into specific patterns. The second one involves conventional lithographic techniques where nanoscale structures are created by removing parts of a bulk material, often by some etchant process. It has been used commonly in electronic and photonic industries and is also becoming increasingly more common in the creation of SERS substrates [27–29], but certain limits related to reproducibility have prevented rapid development in these areas.

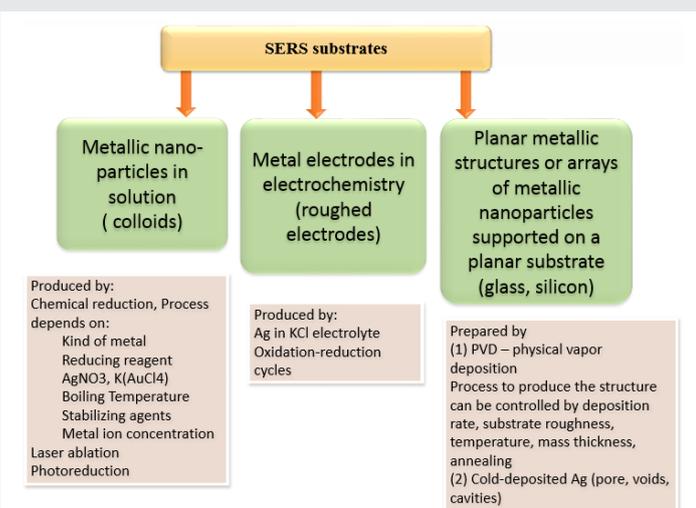


Figure 5: SERS substrates types and their methods of production

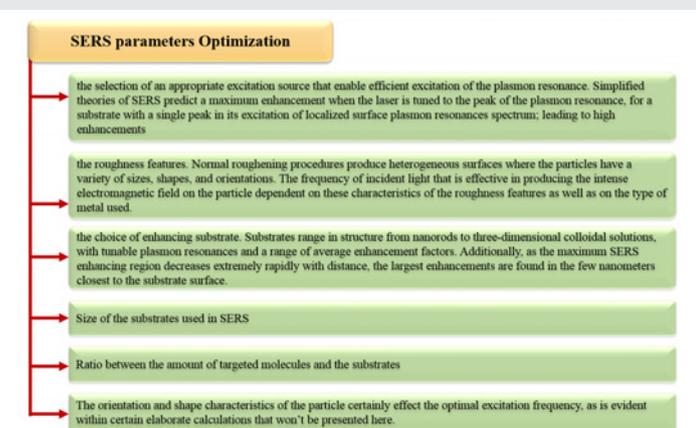


Figure 6: Some of the parameters that should be considered during the SERS method optimization.

Over other techniques, SERS has many advantages for use in a variety of areas. In its simplest form, SERS is comparable to Raman spectroscopy with better sensitivity. As such, SERS still provides specific detail about the “fingerprint” of a given molecule or process. However, since conventional Raman has weak signal intensity, the useful technique has not been applied as universally as other methods. SERS has the ability to not only improve the sensitivity for those applications already used by Raman while also expanding the potential uses of the method to those that would not be possible without the added sensitivity and limits of detection. SERS has the potential to impact the areas of analytical chemistry, biochemistry, forensics, environmental analysis, trace analysis, and many others.

SERS has been reported as a promising technique for quantitative and qualitative identifications of organic and inorganic targets [30–35]. Due to its ultra-sensitivity, SERS was used to detect trace organic and inorganic analytes in different media. For example, some organophosphorus compounds, such as methylparathiol and dimethoate, that exist in pesticides were identified at the nanogram level [36]. Due to the fact that water molecules scatter weakly in Raman experiments made SERS technique an attractive choice to conduct useful characterizations of samples [37]. For example, SERS detection of organic and inorganic compounds in ground water was evaluated and proven to be effective [38]. Moreover, highly active polyhedral Ag nanocrystals SERS substrates have performed very well in low-level arsenate and arsenite sensing in aqueous solutions. Detection at 1 ppb of order of magnitude was achieved [39]. In addition, selected polycyclic aromatic hydrocarbon (PAH) compounds in artificial seawater were detected using SERS [42], and a limit of detection of 10 ppb for naphthalene and pyrene were recorded. For the PAH characterization, gold colloidal monolayer substrates were used [43] and have been shown to enhance Raman signals of PAH very dramatically. Other studies reported the detection of thiocyanine [44] and folic acid [45] in water and human serum using SERS technique. Moreover, trace analysis using SERS has been implemented to detect biomolecular systems prepared in aqueous solutions at low concentrations. For instance, SERS was successfully utilized to detect as low as 10^{-5} M dipeptides on a surface of colloidal silver [46].

One major advantage of SERS is the relative easiness of preparing its samples which are obtained from variety of sources with direct analysis without the need for pretreatment as in some other techniques. Currently, this technique has been implemented successfully for detecting trace amounts of pharmaceuticals [47,48]. It has been used in biochemical fields to help analyze electron transfer reactions in proteins [49] and provide quantitative DNA information [50,51]. It has been implemented in a variety of scientific areas and rivals fluorescence spectroscopy in many ways [52]. SERS technique has used to compare relative intensity shifts and to investigate the adsorption geometry of protoberberine alkaloids on Ag nanoparticles [53]. It has been employed to study the interaction between protoberberine alkaloids and human serum albumin [54]. SERS with gold surface has been used for ultra-trace analysis of latent drug materials [55].

Pros and cons of SERS

SERS has advantages of

- producing spectra which have sharp peaks whereas for example fluorescence spectra are broad and overlapping and less specific for a particular molecule. This enables much higher numbers of analytes to be discriminated.
- It is used for the analysis of materials in different phases
- There is no need to prepare the sample
- SERS is a non-destructive and non-invasive method
- It can be used for in-situ and in-vitro analysis
- It can be used under a wide range of conditions
- It can be coupled with fibre optic cables for remote sensing applications

Importance of pharmaceutical analysis

Pharmaceutical samples are of a complex nature, routinely being composed of several ingredients including active, inactive, and others like coating components. For example, Raman spectroscopy system- a Lab Ram HR Evolution Raman spectrometer- equipped with an internal He-Ne 17mW laser at a 633 nm excitation wavelength was used for detection of methimazole on analysis of substrates of graphene dendrimer loaded with silver nanoparticles. SERS samples were prepared in a small cuvette by using a 4:1 volume ratio of aqueous MTZ solution to G-D-Ag. A 50x objective was used for focusing the laser beam to the solution. The data acquisition time was 20 sec with one accumulation for collection with each SERS spectra. The SERS spectra were obtained in the range from $400-2000$ cm^{-1} as shown in Figure 7. The calibration curve was reported as a plot of the SERS response versus the logarithmical scale of 10^{-6} M to 10^{-11} M of MTZ at 1359 cm^{-1} , showing a good coefficient of determination, $R^2 = 0.9976$ with physical detection limit of 10^{-11} M [32].

In the context of quality assurance:

It is beneficial to analyze pharmaceutical samples to determine both the overall composition of the sample and the actual distribution of the components within the tablet.

The ideal analytical tool for analyzing pharmaceutical samples should be fast, non-destructive, and record chemically specific data to differentiate between the multiple components within a pharmaceutical tablet.

The analytical method should provide specific data or signals that should be a fingerprint of the molecule of interest.

SERS has gained attention in the investigation of various pharmaceutical compounds [12–18], such as ofloxacin (antibiotic), amlodipine (antihypertensive), chlorpheniramine (antihistamine) and promethazine (antihistamine)

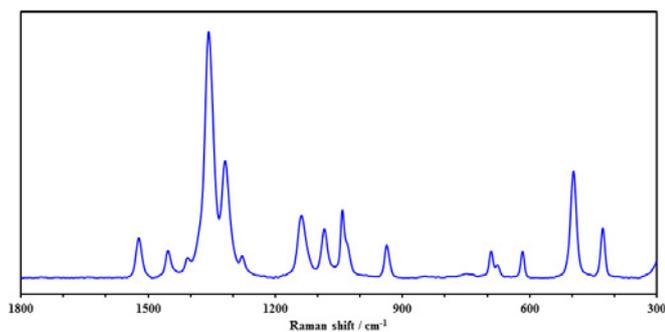


Figure 7: SERS spectrum of methimazole.

Some methods have been developed electrochemical-based methods [56–59] for detection of such pharmaceuticals. However, the achieved detection limits were not satisfactory. As a continuation of our research, we will target these compounds in the project since studying wider range of pharmaceuticals requires several years.

However, the development of SERS is being holdback because of some obstacles. For example, it is still a big challenge to prepare the appropriate SERS-active substrates to meet the requirements such as large enhancement factor, good stability and reproducibility.

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References

- Kahl M, Voges E, Kostrewa S, Viets C, Hill W (1998) Periodically structured metallic substrates for SERS. *Sensors and Actuators B-Chemical*. 51: 285-291. [Link: https://goo.gl/hwxR54](https://goo.gl/hwxR54)
- Raman CV, Krishnan KS (1928) A new type of secondary radiation. *Natur* 121: 501-502. [Link: https://goo.gl/blxBe7](https://goo.gl/blxBe7)
- Saleh TA, Abulkibash AM, Ibrahim AE (2012) Portable system of programmable syringe pump with potentiometer for determination of promethazine in pharmaceutical applications. *Saudi Pharm J* 20: 155-160. [Link: https://goo.gl/LU6NoS](https://goo.gl/LU6NoS)
- Saleh TA (2011) Sensing of chlorpheniramine in pharmaceutical applications by sequential injector coupled with potentiometer. *Journal of Pharmaceutical Analysis* 1: 246-250. [Link: https://goo.gl/SLUHmo](https://goo.gl/SLUHmo)
- Saleh TA (2014) Spectroscopy: Between Modeling, Simulation and Practical Investigation. *Spectral Analysis Review* 2: [Link: https://goo.gl/m8vEPP](https://goo.gl/m8vEPP)
- Saleh TA (2015) Detection: From Electrochemistry to Spectroscopy with Chromatographic Techniques, Recent Trends with Nanotechnology. *Detection* 2: 27. [Link: https://goo.gl/lz6ojN](https://goo.gl/lz6ojN)
- Alshalalfeh M, M Sohail, T Saleh, M Aziz (2016) Electrochemical Investigation of Gold Nanoparticles-Modified Glassy Carbon Electrode and its Application for Ketoconazole Determination, *Australian Journal of Chemistry*. [Link: https://goo.gl/VFnXZa](https://goo.gl/VFnXZa)
- Saleh TA (2016) Nanomaterials for Pharmaceuticals Determination. *Bioenergetics*

- Alaqad K, Saleh TA (2016) Gold and Silver Nanoparticles: Synthesis Methods, Characterization Routes and Applications towards Drugs, *Journal of Environmental & Analytical Toxicology* 6: [Link: https://goo.gl/OLWlZX](https://goo.gl/OLWlZX)
- Das RS, Agrawal YK (2011) Raman spectroscopy: Recent advancements, techniques and applications. *Vib Spectrosc* 57: 163-176. [Link: https://goo.gl/oyal6C](https://goo.gl/oyal6C)
- Fleischmann M, Hendra PJ, McQuilla AJ (1974) Raman spectra of pyridine adsorbed at a silver electrode. *Chemical Physics Letters* 2: 163-166. [Link: https://goo.gl/d7TU3w](https://goo.gl/d7TU3w)
- Jeanmaire DL, Vanduyne RP (1977) Surface Raman spectroelectrochemistry. part I. heterocyclic, aromatic, and aliphatic amines adsorbed on the anodized silver electrode. *Journal of Electroanalytical Chemistry* 84: 1-20. [Link: https://goo.gl/CNwcnj](https://goo.gl/CNwcnj)
- Saleh TA (2013) A strategy for integrating basic concepts of nanotechnology to enhance undergraduate nano-education: Statistical evaluation of an application study, *Journal of Nano Education* 4: 1-7 [Link: https://goo.gl/MhJReO](https://goo.gl/MhJReO)
- Moskovits M (1985) Surface-enhanced spectroscopy. *Reviews of Modern Physics* 57: 783-826. [Link: https://goo.gl/ZR8JYE](https://goo.gl/ZR8JYE)
- Schatz GC (1984) Theoretical studies of surface enhanced Raman scattering. *Acc Chem Res* 17: 370-376. [Link: https://goo.gl/UDaz1H](https://goo.gl/UDaz1H)
- Kambhampati P, Child CM, Foster MC, Campion A (1998) On the chemical mechanism of surface enhanced Raman scattering: experiment and theory. *Journal of Chemical Physics* 108: 5013-5026. [Link: https://goo.gl/qhBQgb](https://goo.gl/qhBQgb)
- Campion A, Kambhampati P (1998) Surface-enhanced Raman scattering. *Chem Society Reviews* 27: 241-250. [Link: https://goo.gl/Pc7jvj](https://goo.gl/Pc7jvj)
- Sharma B, Renee R (2012) *Frontiera*, Anne-Isabelle Henry, Emilie Ringe, and Richard P. Van Duyne, SERS: Materials, applications, and the future. *Materials today* 15: 16-25. [Link: https://goo.gl/MilkNE](https://goo.gl/MilkNE)
- De Jesús MA, Giesfeldt KS, Sepaniak MJ (2004) Factors Affecting the Sorption of Model Environmental Pollutants onto Silver Polydimethylsiloxane Nanocomposite Raman Substrates. *Appl Spectrosc* 58 10: 1157-1164. [Link: https://goo.gl/z6FmBF](https://goo.gl/z6FmBF)
- Reilly TH, Corbman JD, Rowlen KL (2007) *Vapor Deposition Method for Sensitivity Studies on Engineered Surface-Enhanced Raman Scattering-Active Substrates*. *Analytical Chemistry* 79: 5078-5081. [Link: https://goo.gl/3n3Jcz](https://goo.gl/3n3Jcz)
- Kneipp K, Kneipp H, Itzkan I, Dasari RR, Feld MS (1999) Ultrasensitive chemical analysis by Raman spectroscopy. *Chem Rev* 99: 2957-2976. [Link: https://goo.gl/qCEc3W](https://goo.gl/qCEc3W)
- Aroca RF, Alvarez-Puebla RA, Pieczonka N, Sanchez-Cortez S, Garcia-Ramos JV (2005) *Advances in Colloid and Interface Science*. 116: 45-61.
- Nie S, Emory SR (1997) Probing Single Molecules and Single Nanoparticles by Surface-Enhanced Raman Scattering. *Science* 275: 1102-1106. [Link: https://goo.gl/MPA3b9](https://goo.gl/MPA3b9)
- Michaels AM, Nirmal M, Brus LE (1999) Surface Enhanced Raman Spectroscopy of Individual Rhodamine 6G Molecules on Large Ag Nanocrystals. *J Am Chem Soc* 121: 9932-9939. [Link: https://goo.gl/E3gxZW](https://goo.gl/E3gxZW)
- Weiss A, Haran G (2001) Time-Dependent Single-Molecule Raman Scattering as a Probe of Surface Dynamics. *J Phys Chem B* 105: 12348-12354. [Link: https://goo.gl/sKqekX](https://goo.gl/sKqekX)
- Khan I, Cunningham D, Graham D, McComb DW, Smith WE (2005) Identification and Characterization of Active and Inactive Species for Surface-Enhanced Resonance Raman Scattering. *J Phys Chem B* 109: 3454-3459. [Link: https://goo.gl/L3xtRL](https://goo.gl/L3xtRL)

27. Camden JP, Dieringer JA, Wang Y, Masiello DJ, Marks LD, et al. (2008) Probing the structure of single-molecule surface-enhanced Raman scattering hot spots. *J Am Chem Soc* 30: 12616-12617. [Link: https://goo.gl/jpT6ks](https://goo.gl/jpT6ks)
28. Fan M, Andrade GF, Brolo AG (2011) A review on the fabrication of substrates for surface enhanced Raman spectroscopy and their applications in analytical chemistry. *Analytica Chimica Acta* 693: 7-25. [Link: https://goo.gl/z4XK5n](https://goo.gl/z4XK5n)
29. Yang P, Yan R, Fardy M (2010) Semiconductor Nanowire: What's Next? *Nano Letters* 10: 1529-1536. [Link: https://goo.gl/cN3auZ](https://goo.gl/cN3auZ)
30. Hering K, Cialla D, Ackermann K, Dorfer T, Moller R, et al. (2008) SERS: a versatile tool in chemical and biochemical diagnostics. *J Popp Anal Bioanal Chem* 390: 113-124. [Link: https://goo.gl/rcRMSr](https://goo.gl/rcRMSr)
31. Golightly RS, Doering WE, Natan MJ (2009) Surface-enhanced Raman spectroscopy and homeland security: a perfect match? *ACS Nano* 3: 2859-2869. [Link: https://goo.gl/lgwDyV](https://goo.gl/lgwDyV)
32. Saleh TA, MM Al-Shalalfeh, AA Al-Saadi (2016) Graphene Dendrimer-stabilized silver nanoparticles for detection of methimazole using Surface-enhanced Raman scattering with computational assignment. *Scientific Reports* 6: 32185. [Link: https://goo.gl/X4Ttuw](https://goo.gl/X4Ttuw)
33. Al-Shalalfeh, MM, Saleh TA, Al-Saadi AA (2016) Silver colloid and film substrates in surface-enhanced Raman scattering for 2-thiouracil detection. *RSC Advances* 6: 75282-75292 [Link: https://goo.gl/eJpvxY](https://goo.gl/eJpvxY)
34. Haruna K, Saleh TA, AlThagfi J, Al-Saadi AA (2016) Structural properties, vibrational spectra and surface-enhanced Raman scattering of 2, 4, 6-trichloro-and tribromoanilines: A comparative study. *Journal of Molecular Structure* 1121: 7-15 [Link: https://goo.gl/RVxGxb](https://goo.gl/RVxGxb)
35. Alak AM, Vo. Dinh T (1987) Surface-enhanced Raman spectrometry of organo phosphorus chemical agents. *Anal Chem* 59: 2149-2153. [Link: https://goo.gl/g5UTfC](https://goo.gl/g5UTfC)
36. Szymanski HA (1967) *Raman Spectroscopy: Theory and Practice*. Plenum Press, Buffalo, NY. [Link: https://goo.gl/5okNNE](https://goo.gl/5okNNE)
37. Carabba MM, Edmonds RB, Rauk RD (1987) Feasibility studies for the detection of organic surface and subsurface water contaminants by surface-enhanced Raman spectroscopy on silver electrodes. *Anal Chem* 59: 2559-2563. [Link: https://goo.gl/hqt1D9](https://goo.gl/hqt1D9)
38. Mulvihill M, Tao A, Benjauthrit K, Arnold J, Yang P (2008) Surface-Enhanced Raman Spectroscopy for Trace Arsenic Detection in Contaminated Water**. *Chem Int Ed* 47: 6456-6460. [Link: https://goo.gl/L6dmSs](https://goo.gl/L6dmSs)
39. Peron O, Rinnert E, Lehaitre M, Crassous P, Compere C (2009) Detection of polycyclic aromatic hydrocarbon (PAH) compounds in artificial sea-water using surface-enhanced Raman scattering (SERS). *Talanta* 79: 199-204. [Link: https://goo.gl/SYZKcT](https://goo.gl/SYZKcT)
40. Kitahama Y, Tanaka Y, Itoh T, Ozaki Y (2009) Time-resolved Surface-enhanced Resonance Raman Scattering Spectra of Thiocyanine Molecules in Water. *Chem Lett* 38: 54-55. [Link: https://goo.gl/WCNvgy](https://goo.gl/WCNvgy)
41. Stokes RJ, McBride E, Wilson CG, Girkin JM, Smith WE, et al. (2008) Surface-enhanced Raman scattering spectroscopy as a sensitive and selective technique for the detection of folic acid in water and human serum. *App Spectrosc* 62: 371-376. [Link: https://goo.gl/mIVeCr](https://goo.gl/mIVeCr)
42. Piorek BD, Lee SJ, Santiago SJ, Moskovits M, Banerjee S, et al. (2007) *Proc Natl Acad Sci USA* 104: 18901.
43. Wong-ek K, Horprathum M, Eiamchai P, Limnonthakul P, Patthanasettakul V (2011) Portable surface-enhanced Raman spectroscopy for insecticide detection using silver nanorod film fabricated by magnetron sputtering. *Proceedings of the SPIE - The International Society for Optical Engineering* 7911: 791108. [Link: https://goo.gl/3HbSSs](https://goo.gl/3HbSSs)
44. M. Muniz-Miranda, B. Pergolese, A. Bigotto (2008) Surface-Enhanced Raman Scattering and Density Functional Theory Study of 4-Nitrobenzonitrile Adsorbed on Ag and Ag/Pd Nanoparticles. *J Phys Chem C* 112: 6988-6992. [Link: https://goo.gl/Q3Kgnw](https://goo.gl/Q3Kgnw)
45. Hao J, Han MJ, Li J, Meng X (2012) Surface modification of silver nanofilms for improved perchlorate detection by surface-enhanced Raman scattering. *Sci* 377: 51-57. [Link: https://goo.gl/4JvLbI](https://goo.gl/4JvLbI)
46. Han MJ, Hao J, Xu Z, Meng X (2011) Surface-enhanced Raman scattering for arsenate detection on multilayer silver nanofilms. *Anal Chim Acta* 692: 96-102. [Link: https://goo.gl/PjJTIX](https://goo.gl/PjJTIX)
47. Long S, Li L, Guo H, Yang W, Lu F (2012) Preparation of stable core-shell dye adsorbent Ag-coated silica nanospheres as a highly active surfaced-enhanced Raman scattering substrate for detection of Rhodamine 6G. *Dyes Pigments* 95: 473-477. [Link: https://goo.gl/80wxwE](https://goo.gl/80wxwE)
48. Farquharson S, Maksymiuk P (2003) Simultaneous Chemical Separation and Surface-Enhanced Raman Spectral Detection Using Silver-Doped Sol-Gels. *Applied Spectroscopy* 57: 479-482. [Link: https://goo.gl/pGSJwl](https://goo.gl/pGSJwl)
49. Pavel I, Cota S, Cinta-Pinzaru S, Kiefer W (2005) Raman, Surface Enhanced Raman Spectroscopy, and DFT Calculations: A Powerful Approach for the Identification and Characterization of 5-Fluorouracil Anticarcinogenic Drug Species. *J Phys Chem A* 109: 9945-9952. [Link: https://goo.gl/KrTKB6](https://goo.gl/KrTKB6)
50. Kranich A, Naumann H, Molina-Heredia FP, Moore HJ, Lee TR, et al. (2009) Gated electron transfer of cytochrome c6 at biomimetic interfaces: a time-resolved SERR study. *Physical Chemistry Chemical Physics* 11: 7390-7397. [Link: https://goo.gl/Jjo63V](https://goo.gl/Jjo63V)
51. Marras SAE, Gold B, Kramer FR, Smith I, Tyagi S (2004) *Nucleic Acids Research* 32:
52. Wang HN, Vo-Dinh T (2009) *Nanotechnology* 20:
53. Le Ru EC, Etchegoin PG (2009) *Principles of Surface-Enhanced Raman Spectroscopy and Related Plasmonic Effects*. Elsevier. [Link: https://goo.gl/eVtHw0](https://goo.gl/eVtHw0)
54. Zhang W, Zhao Y, Bai X, Wang Y, Zhao D (2011) The orientation of protoberberine alkaloids and their binding activities to human serum albumin by surface-enhanced Raman scattering. *Spectrochimica Acta Part A* 78: 1105-1109. [Link: https://goo.gl/LQQCJF](https://goo.gl/LQQCJF)
55. Fox JD, Waverka KN, Verbeck GF (2012) Gold-plating of Mylar lift films to capitalize on surface enhanced Raman spectroscopy for chemical extraction of drug residues. *Forensic Science International* 216: 141-145. [Link: https://goo.gl/eIVCxd](https://goo.gl/eIVCxd)