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Micro and nanocapsules as supports for Surface-Enhanced Raman Spectroscopy (SERS)

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1 Introduction

Raman spectroscopy (RS) is a relatively weak optical process that provides information about the unique vibrational modes of molecules. This technique is effective and essential, e.g. for solid materials or analysis in solution, however its sensitivity is poor. As a result of many attempts at improving the sensitivity of Raman spectroscopy, a successful solution was a combination of surface enhancement scattering and RS, which proved a highly selective and sensitive method referred to as surface-enhanced Raman scattering/spectroscopy (SERS). SERS is an extremely effective qualitative technique, which works on standard equipment. Moreover, this method permits the analyses of small amounts of samples, e.g. a drastically diluted solution (even 10^{-16} mol/dm^3). Enhancement in SERS is about 100 times that of standard Raman scattering. The most important point is that SERS signals are effective for a wide range of molecules and could be applied for detection, e.g. of cancer, anthrax [1, 2], chemical warfare-stimulants [3], explosive-agents [4, 5]; for environmental monitoring [6] or for the monitoring of heterogeneous catalytic reactions [7] as well as *in vitro* [8–10] and *in vivo* [11] glucose sensing. The best SERS-active materials are nanoparticles of silver and gold, but other metals such as copper are also effective. It is worth highlighting that the enhancement in resolution depends not only on the kind of material but particularly on the shape of the nanoparticles. The most common nanoparticles are colloids of the metals. In recent years, thousands of papers have been published about SERS, which illustrates the fast development of this method and its powerful possibilities.

2 History

Inelastic scattering of light was first presented by an Austrian theoretical physicist, Adolf Smekal in 1923 [12]. This type of scattering was observed by Indian physicists Chandrasekhara Venkata Raman and his student Kariamanikkam Srinivasa Krishnan on the 28 February 1928. A week earlier, Russian physicists Grigory Samuilovich Landsberg and Leonid Mandelstam discovered the same effect as Raman and Krishnan. Chandrasekhara Raman published his results before Landsberg, in an article entitled "A New Type of Secondary Radiation", and that is why the effect carries his name. In Russia this effect is still called "combinatorial scattering of light" [13–16]. In 1930, Sir Ch. V. Raman won the Nobel Prize in Physics "for his work on the scattering of light and for the discovery of the effect named in his honor". The limitation of Raman spectroscopy in the early years was correlated with the preparation of samples (concentration above 1 mol/L and volumes of a minimum 5 mL). The milestone for simplified Raman spectrometers and improved sensitivity of this technique [17] was the use of the laser beam. The first functioning laser was constructed by Theodore H. Maiman in 1960 (a ruby crystal used to produced a red light laser of 694 nm wavelength) and later in 1960 the first gas laser was discovered by Ali Javan, William Bennett and Donald Herriott (helium and neon were used to produce a red light laser of 632.8 nm wavelength).

In 1973, Martin Fleischmann, Patrick J. Hendra and A. James McQuillan observed a much-enhanced Raman signal of pyridine adsorbed on a roughened silver surface [18]. After that, a lot of independent scientists confirmed this extraordinary effect, and a mechanism for the observed enhancement was proposed. Theoretical fundamentals of the SERS were laid in 1977 by two independent groups of scientists. The first research group headed by David L. Jeanmaire and Richard P. Van Duyne proposed the electromagnetic effect as a fundamental of SERS, while the second group of scientists, Albrecht M. Grant and Alan J. Creighton, proposed

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the charge-transfer effect to play this role [19, 20]. In 1997, a milestone was the recording of a SERS spectrum of a single-molecule, which made the grounds for elimination of the limitations of RS. It has resulted in the appearance of a new research field and development of SERS as an effective analytical technique [5, 21, 22].

3 Fundamentals

Classical RS is a technique used to detect vibrational and rotational oscillations of a molecule upon incidence of monochromatic light, as they are functions of frequency of the scattered light. The scattering of light can be elastic (Rayleigh scattering, the frequency of scattered light is the same as that of the initial photon $h\nu_0 = h\nu_0$) or inelastic (Raman scattering). Inelastic scattering can be divided into Stokes and anti-Stokes scattering. The laser light interacts with a molecule to endow it with higher energy and move it to a higher or lower level ($h\nu_0 = h\nu_0 - h\nu_m$ or $h\nu_0 = h\nu_0 + h\nu_m$) (Figure 1).

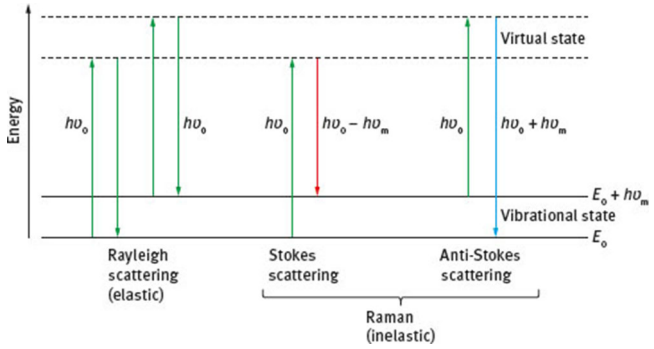

Figure 1: Different forms of scattering.

Stokes and anti-Stokes scattering are relatively weak and their emission intensities are up to several orders of magnitude lower when compared to those of elastic scattering bands, which could be overlapped by Rayleigh bands. Rayleigh and Stokes processes are more important in Raman spectroscopy than the weakest anti-Stokes (Figure 2), but the recording of these signals is essential for higher sensitivity detection. The SERS becomes an extremely effective technique as it permits enhancement of the Raman signal intensities by several orders of magnitude.

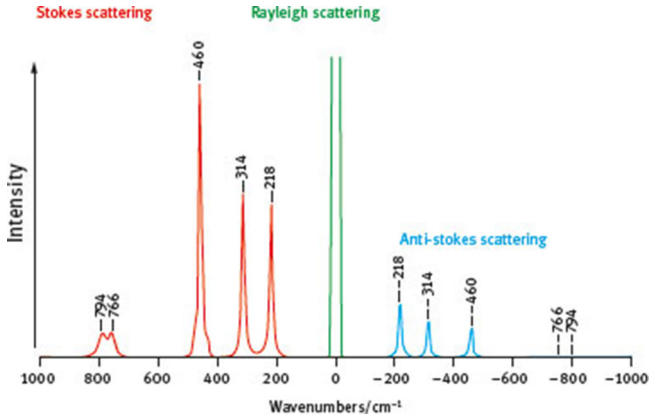

Figure 2: Raman spectra of CCl_4 recorded using a laser line of 488 nm.

The surface enhancement factor of Raman signal $EF_{SERS} = 10^6$ or more could be explained as a result of two contributing effects: (i) the electromagnetic enhancement (EM) [23] and (ii) chemical (charge-transfer) enhancement (EC) [24, 25]. High levels of enhancement are always related to specific morphologies of nanostructures [26–30]. The molecule analyzed must be adsorbed on a SERS-active surface and irradiated by monochromatic radiation, usually from a laser and detected via a Raman spectrometer (Figure 3).

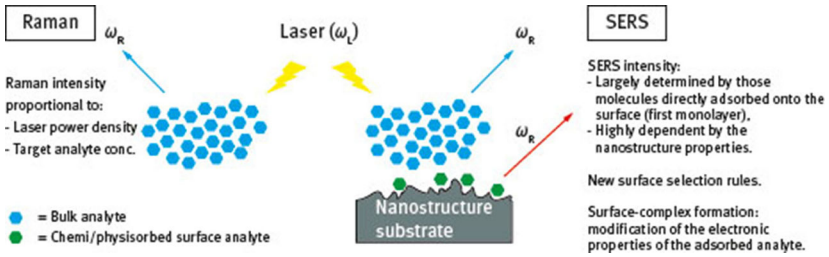

Figure 3: Schematic comparative visualization of the Raman and SERS phenomena [31].

4 The electromagnetic enhancement (EM)

Electromagnetic enhancement (EM) involves interactions between surface plasmon of the metallic nanosized cluster of Ag, Au or Cu and the molecule located near the plasmon surface [32, 33]. Conversely, EM is related to resonances of the optical fields with surface plasmons [34]. Plasmon is a collective excitation of the electron cloud, while surface plasmons is an excitation confined to the nearest surface region (Figure 4).

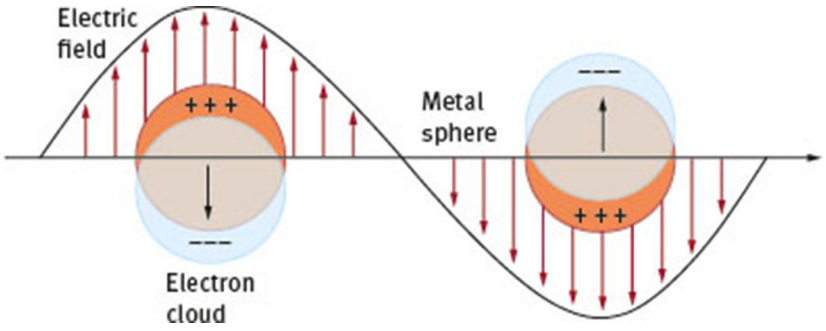

Figure 4: Illustration of the localized surface plasmon resonance effect.

Moreover, nanostructures can be considered as nanoantennae for transmission and enhancement of Raman scattered light. EM depends on the resonance process between the plasmons, excitations and scattered fields. The enhancement is strong when excitation and scattered fields are in resonance with the surface plasmons. The shifts in frequencies between excitation and scattered light are small when compared to the width of the plasmon resonance [35].

5 The chemical enhancement

Chemical (charge-transfer) enhancement (CE) is a result of bonding between the analyzed molecule and metal nanoparticles surface [32, 33]. The exciting radiation interacts with the metal to form an electron-hole pair. The energy is transferred to the analyte through metal to the bonds of the molecule. The charge-transfer complex formed considerably increases the molecular polarizability of the molecule due to interaction with the metal electrons, which generates new, shifted or broadened Raman bands [28, 36–41]. The Raman process occurs on the analyte, and the energy is transferred back into the metal to be scattered [42]. The charge-transfer occurs between the conduction electrons of the metal and the lowest unoccupied orbital of the molecule chemisorbed to its surface. CE occurs only from the molecules directly attached to the surface and increases only up to monolayer coverage. It is possible that electromagnetic and/or chemical effects could enhance a Raman signal by up to $\times 10^{14}$. For the systems in which both mechanisms are simultaneously operative, the effects are multiplied. It has been almost impossible to separate these two effects [24]. Moreover, it has been proved that the electromagnetic enhancement based on plasmon resonances gives larger effects than charge-transfer enhancement [43] (Figure 5).

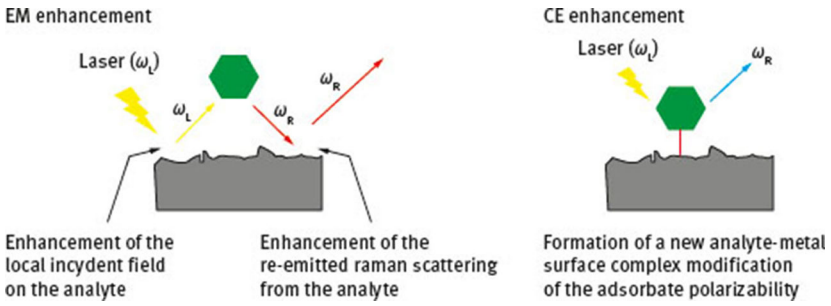

Figure 5: Schematic outline of the electromagnetic and chemical enhancements in SERS [31].

5.1 Effective SERS materials

As mentioned above, Raman scattering is a relatively weak optical phenomenon. SERS is the method allowing enhancement of the weak signal it gives on specially prepared materials. Current efforts in SERS probe development are aimed at reproducible preparation of highly sensitive SERS-active nanostructures with a narrow distribution of their enhancement factor (EF) values [44]. SERS-active substrates, providing nanoscale and atomic-scale roughness, include evaporated island films [45]. The best active materials are based on gold, silver or copper particles. The most common types of SERS-active substrates are clusters of colloidal silver or gold particles in the 10–100 nm size range, used in colloidal solution or "dry" on a surface. These nanoparticles are made by chemical reduction processes using, for example, citric acid, sodium borohydride or glucose [46–49]. Despite considerable success in synthesizing silver nanoparticles with different particle size distributions, many of the reported methods have certain limitations in terms of their control over shape, size and stability in the dispersion system [50, 51] (Figure 6 and Figure 7).

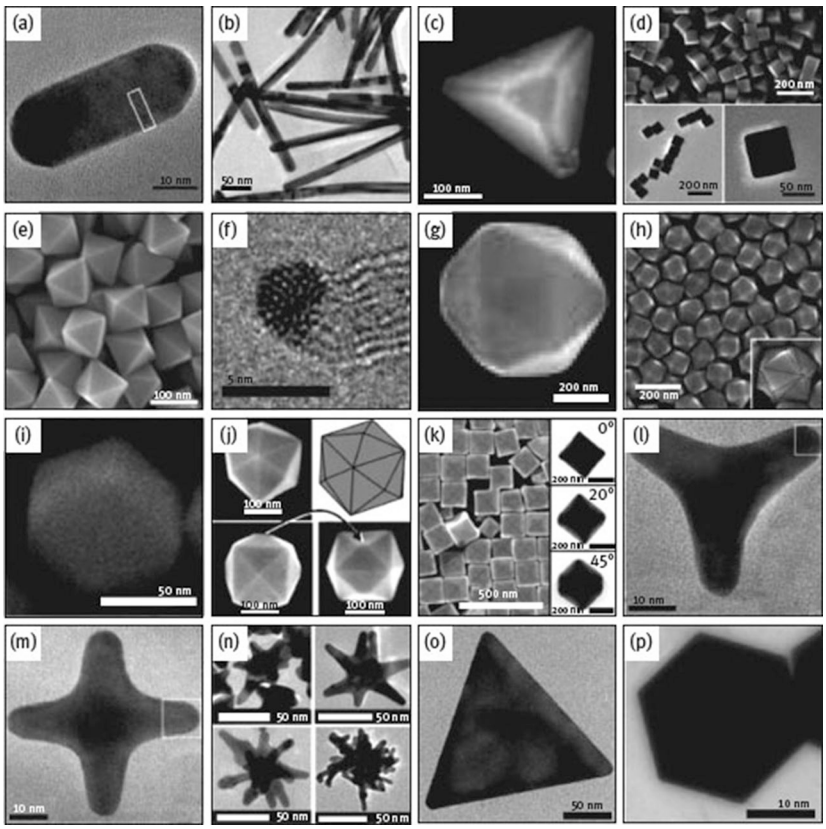

Figure 6: The major classes of noble metal nanoparticle shapes seen through transmission electron microscopy (TEM) and/or scanning electron microscope (SEM): (a) Au octagonal single-crystal rod, (b) Au pentagonally twinned rods, (c) Au tetrahedron NP, (d) Pd hexahedron (i.e. cube) NPs, (e) Au octahedron NPs, (f) decahedron, (g) Au icosahedron NP, (h) Au trisoctahedron NPs, (i) Au rhombic dodecahedron NP, (j) Pt tetrahexahedron NPs, (k) Au concave hexahedron NPs, (l) Au tripod NP, (m) Au tetrapod NP, (n) Au star NPs, (o) Au triangular plate/prism NP, and (p) Au hexagonal plate/prism NP [60].

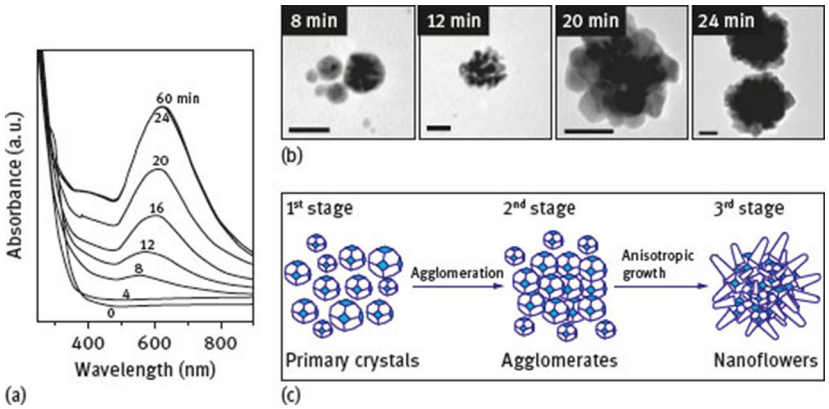

Figure 7: (a) UV-vis spectra as a function of time of reaction between aqueous $AuCl_4^-$ solution (0.5 mM) and HEPES (10mM). (b) Representative transmission electron microscopy (TEM) images of the products harvested at 8, 12, 20 and 24 min into the reaction. All scale bars are 20nm. (c) Schematic illustration of the proposed mechanism for Au nanoflower formation in HEPES solution [52].

Achieving nanoparticles below 10 nm with high monodispersity and stability [52–55] is not easy, but the use of an excess of a strong reducing agent, for example sodium borohydride, permits a synthesis of monodisperse small uniform-sized nanoparticles. Moreover, it is difficult to obtain larger-sized nanoparticles via chemical reduction [47, 56, 57].

On the other hand, aggregated nanoparticles increase the intensity of Raman signals much more than separated particles, because of the enhanced field around the near-field coupling species [58, 59]. Confinement of nanoparticles in a limited space creates the so-called "hot spots", which increase even more the intensity of RS of molecules located in this area. Many reports have been published on different attempts to produce active hot spots to achieve high SERS signal by assembly of nanoparticles on the surface of various supports, such as polystyrene [61], silica [62] or agarose [63] microbeads, but also by use of agarose gels [64] or films of poly(diallyldimethylammonium chloride) and poly(acrylic acid) [65]. The most commonly used preparation method is the LbL assembly technique [63, 65]. Moreover, encapsulation of ready-to-use hot spots is the best method of obtaining active and long-life time materials.

Capsules in general are spherical membranes that separate their inside from the outside environment. They can have different morphology, depending on the material used to their preparation. Furthermore, the preparation technique has a huge impact on the final outcome [66]. "Microcapsule" may be defined as a circular cross-section shaped particle with certain free volume inside, where a core material can be allocated. Their diameter size varies in the range 1–1000 μm (nanocapsules below 1 μm and macrocapsules above 1000 μm) [67, 68]. Depending on their structure they can be characterized as a continuous core/shell microcapsule, polycore capsule, continuous core capsule with more than one layer of shell material and matrix type, where the encapsulated agent is incorporated within the shell material [69].

An example of microcapsulation is a thiolated block copolymer consisting of a pH-responsive PMAA ploymethacrylic acid segment and an amphiphilic polyethylene glycol PEG segment for encapsulating gold nanocrystals. In materials of this type, SERS signals can be switched on and off by molecular conformational changes (Figure 8). It has been shown that neutralized PMAA molecules are able to interact with amphiphilic PEG chains, leading to highly compact and intermingled copolymer structures on the surface of nanoparticles. This type of molecular conformational change provides a new strategy for controling the distances and plasmonic interactions between two or more gold nanoparticles. This opens a possibility of using SERS nanoparticle tags for biomolecular binding and enzymatic cleavage studies [70].

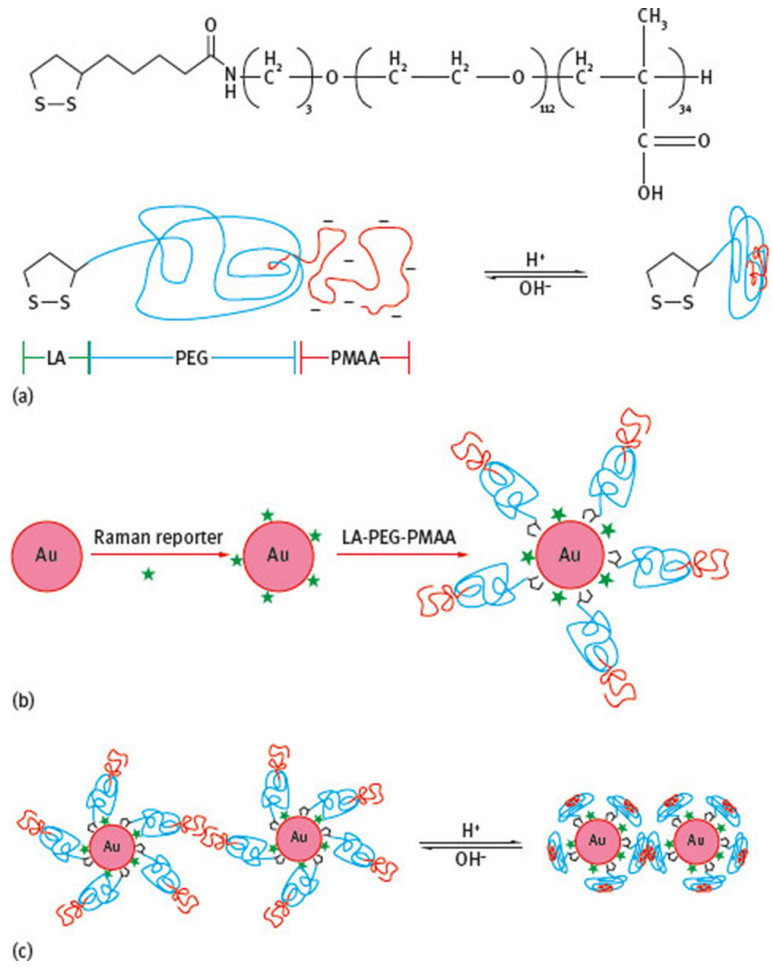

Figure 8: Smart SERS nanoparticles. (a) structure of pH-induced conformational changes in a thiolated block copolymer consisting of a pH-responsive ploymethacrylic acid (PMAA), an amphiphilic polyethylene glycol (PEG), and a terminal lipoic acid. (b) Preparation of dye-encoded gold nanoparticle. (c) Nanoparticle aggregation induced by polymer conformational changes [71].

The development of biocompatible nanoparticles for *in vivo* molecular imaging and targeted therapy is an area of considerable current interest across a number of science, engineering and biomedical disciplines [72–80]. Nanomaterials conjugated with bioligands such as monoclonal antibodies, peptides or small molecules can be used to target malignant tumors with high specificity and affinity [81–84]. Another advantage of nanoparticles is their large surface areas available for conjugation to multiple diagnostic (e.g. optical, radioisotopic or magnetic) and therapeutic (e.g. anticancer) agents. Recent advances have led to the development of biodegradable nontoxic nanostructures for drug delivery *in vivo*, for tumor targeting and spectroscopic detection [85–89] (Figure 9)

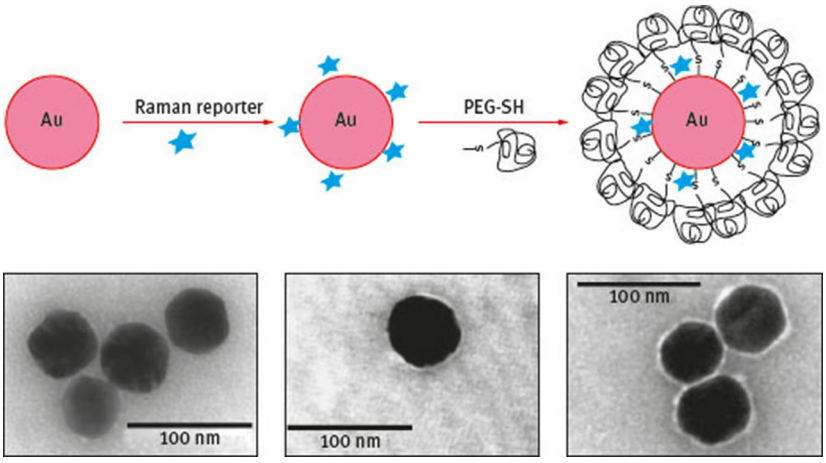

Figure 9: Preparation and schematic structures of the gold pegylated colloid nanoparticles, and transmission electron microscopy (TEM) of each colloid particles [97].

Moreover, colloidal gold nanoparticles have been safely used to treat rheumatoid arthritis for half a century [90, 91]. However, recent work indicates the pegylated gold nanoparticles (colloidal gold coated with a protective layer of polyethylene glycol or PEG) exhibit excellent *in vivo* biodistribution and pharmacokinetic properties upon systemic injection [92–94]. In contrast to quantum dots, containing cadmium and other toxic or immunogenic nanoparticles, gold colloids have almost no long-term toxicity [95, 96].

Another very important feature of this technique is not only the compatibility in size and geometry of the sample of SERS-active substrates (Figure 10); but also "chemical" compatibility to a "biological environment". In general, due to its chemical inactivity, gold should be more suitable for incorporation inside biophysical systems. It has been shown that gold colloidal clusters have SERS enhancement factors (SERS EFs) comparable to those of silver clusters, when Near infrared (NIR) excitation is applied [45].

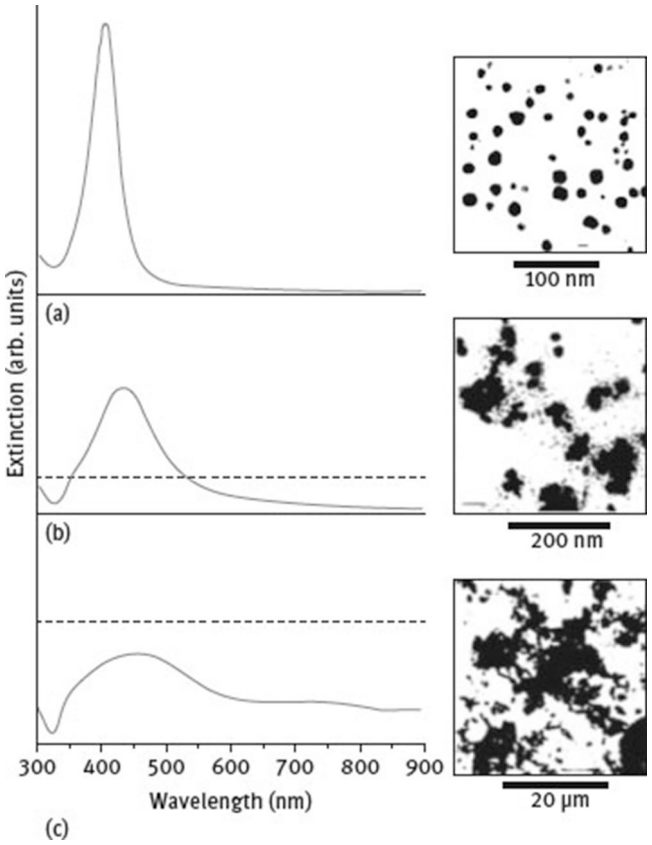

Figure 10: SERS-active colloidal silver particles in different aggregation stages, demonstrating the fractal nature of these structures together with the appropriate extinction curves [96].

6 Application of SERS

The SERS has a very wide range of possible applications: SERS microscopy [98], biosensing [99], diagnostics [100], imaging [101], and clinical translation [102]. This spectroscopy is used to identify explosive materials [103], therapeutic agents [104], drugs of abuse [105], food additives [106], cells and spores and DNA sequence analysis [27, 107–115]. SERS allows detection of very small quantities of molecules, even a single-molecule and its identification moreover could be useful for detecting a known molecule and for monitoring its distribution [116].

Several reviews have described the preparation of SERS substrates (e.g. nanosphere lithography [5], nanofabrication techniques [31], surface functionalization [117], and fibre sensors [118]) and their performance in specific applications as well as *in vitro* cancer detection and diagnostics and for cancer imaging [1, 2].

SERS has been used to investigate a wide variety of problems in science. Recently Natan's group has published an interesting series of papers on the development of novel SERS substrates based on the self-assembly gold colloids [119]. They studied the compatibility of biomolecules with gold colloids coated with silver as a potential substances useful in SERS. The versatility of this approach is a promising development for analytical applications. Weaver's group has found a way to extend the SERS technique to transition metal surfaces by electrodepositing the metal of interest on a suitably prepared enhancing gold substrate. Although attempts at

realization of this idea had been made before, the inability to make pinhole-free in the layer prevented the technique from being generally useful. High quality films were prepared by slow deposition at a constant cathode current rather than by a more rapid constant potential deposition method used formerly. These films must be thick enough to behave chemically as the bulk metal of interest and at the same time thin enough to support the electromagnetic enhancement of the underlying substrate. Recently, promising applications of Weaver's *in situ* method to study gas phase heterogeneous catalytic reactions and electrocatalytic processes have been reported. The future of this area looks very promising [120].

Gold nanoparticles, because of their biocompatibility, were investigated in cell biology. The nanoparticles were used directly as a probe of the chemical composition of endosomes of different stages and for the detection of specific cellular molecules, such as adenosine monophosphate (AMP) [121]. Gold as well as silver nanoparticles can be exported as labels that highlight cellular structures based on the enhanced Raman surface [122–124]. The Raman spectra recorded have fingerprint of molecules linked to the surface material. Other biomolecules such as as amino acids, purine or pyrimidine bases and "large" molecules such as proteins, DNA and RNA "intrinsically colored" biomolecules such as chlorophylls, hem-containing proteins and other pigments were studied by SERS. Gold nanoparticles were capped with a biofunctional molecule capable of forming a covalent link with the aromatic residues of the protein moiety, antithrombin as a sensitive recognition element [125].

Moreover SERS can be used to monitor transport through membranes and the results show that this technique can discriminate between the movement of different molecules across a membrane and to observe different interfacial arrival times and concentration growth rates in the receiving (colloidal silver) solution [126].

An extraordinary challenge is to apply SERS in living systems for real medical problems [127, 128]. The detection, identification and quantification of neurotransmitters in the brain fluid is an important question in neurochemistry [129]. SERS represents an interesting approach for studying charge-transfer processes, for instance in cytochrome c, which has been investigated on bare and coated silver electrodes [130].

The first SERS spectra of DNA adsorbed on a silver surface were reported in 1981 [131] and thereafter SERS studies of nucleic acids and their components quickly developed [110, 132–135]. In most of the SERS studies, the target nucleic acids were applied in relatively high concentrations (10^{-5}–10^{-8} mol/L), but the most interesting aspects of SERS on nucleic acids might be attributed to the ultrasensitive and single-molecule capabilities of the method.

A first *in vivo* application of SERS was demonstrated for quantitative glucose measurements in an animal model [11]. The result of the study indicated that glucose binds reversibly to the SERS-active surface and that changes in concentration as rapid as in 30 s can be measured. Glucose sensing has great medical value but the SERS spectrum of glucose is generally of relatively low intensity. Van Duyne and co-workers created a modified surface designed to adsorb glucose effectively on a solid state substrate made by depositing silver on a layer of polystyrene beads and then removing the beads to reveal a SERS-active surface of closely spaced essentially triangular deposits of silver [136]. Reproducible surface and strong signals were possible to create a monitor for glucose detection based on SERS technology.

Gold nanoparticles or nanoaggregates can be used as nanosensors to probe small biological structures such as cells and bacteria [121, 122, 137–141]. Applications of SERS in biomedical sensing includes SERS labels based on highly selective surface-enhanced Raman spectrum of a reporter attached to an enhancing silver or gold nanostructure [77, 142, 143]. Au or Ag cores functionalized with Raman active molecules can also be encapsulated in a glass shell, which provides the SERS label with mechanical and chemical stability [128].

Entities such as mammalian cells and spores give broader, more complex spectra. The origin of these signals is likely to be the part of the cell or spore closest to the enhancing surface on the spectra, and various bands that are indicative of proteins can be identified. Remarkably, the spectra can be used for effective discrimination of different cell types. The data are usually analyzed by methods such as least squares and principal component analysis and this information can discriminate between genetically different species of intact bacillus spores [42, 108].

The progress in SERS techniques could be used in cancer diagnostics, including multiplexed detection and identification of new biomarkers, single-nucleotide polymorphisms, and circulating tumor cells. In these experiments, colloidal silver particles were incorporated inside the cells and SERS was applied to monitor the intracellular distribution of drugs in the whole cell and to study the antitumor drugs/nucleic acid complexes. SERS is also used as a non-invasive tool for cancer imaging with immunoSERS microscopy, histo-logical analysis of biopsies, and *in vivo* detection of tumors [144].

The high sensitivity and multiplexing capabilities of SERS technologies were supported by their integration into molecular diagnostics for *in vitro* cancer detection. A common approach involves immunoassays that rely on the recognition of biomarkers (cell surface markers, membrane receptors) with antibodies that are conjugated to SERS substrates. For instance mucin protein (encoded as *MUC4* gene) might be used as a serum marker for early detection of pancreatic cancer using a quantitative SERS-based platform [145]. The possibility of monitoring more than one biomarker enhanced the accuracy of lung cancer diagnostics (Figure 11) [146, 147].

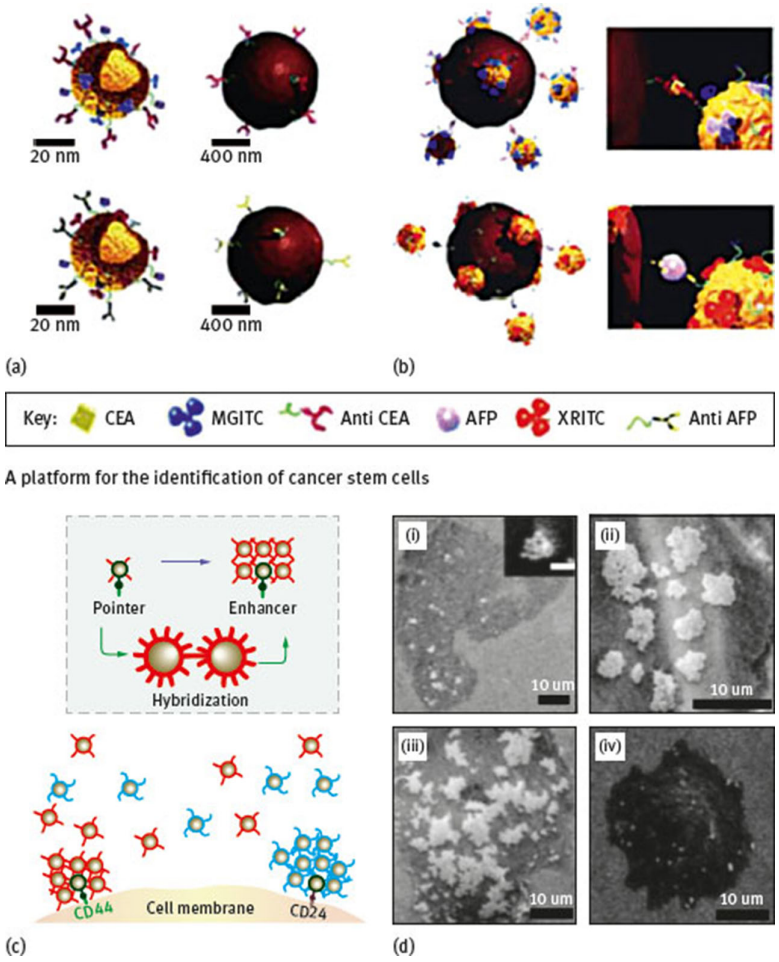

Figure 11: Multiplex SERS immunoassays combining Au nanospheres and magnetic beads. (a) Conjugation of nanospheres and beads with reporters (malachite green isothiocyanate, MGITC; X-rhodamine isothiocyanate, XRITC), anti-carcinoembryonic antigen (CEA) and anti-α-fetoprotein (AFP). (b) Sandwich immunocomplexes after recognition of CEA and AFP [146]. (c, d) Platform for identification of cancer stem cells. (c) Schematic illustration, (d) backscattering SEM images [147].

SERS technologies, because of their high sensitivity, are ideal for the development of diagnostic assays and imaging tools and have progressed towards the quantification of biomarkers in the form of cell surface markers, mutant genes, and alleles. Moreover the assays require small sample volumes (a few microliters) and have extremely low detection limits (up to femtomolar level). SERS optical imaging with its modality for mapping biomolecules in cancer tissue with single-cell resolution has multifarious capabilities. Nowadays SERS technologies guide intraoperative imaging for tumor resection and endoscope-based imaging and have a significant impact on the next generation of molecular imaging tools for cancer detection and therapeutics [144].

Another biological application of SERS spectra is the enzyme immunoassay of the enzyme reaction product [148]. Antibodies immobilized on a solid substrate bind antigen, which binds to a second antibody labeled with peroxidase. If these immunocomplexes are subjected to the reaction with o-phenylenediamine, azoaniline is generated. The reaction product is adsorbed on colloidal silver particles, resulting in a strong SERS spectrum of azoaniline, whose signal strength is proportional to the concentration of the antigen. The method of silver colloidal SERS of the enzymatic product has been applied to direct detection of enzymes in cells. Moreover, the method has been successfully used to detect and to quantify prostaglandin H synthase-1 and 2 in normal human hepatocytes and human hepatocellular carcinoma cells [149].

Additionally, colloidal gold may be supported by the gold surface and that "SERS-active substrate" could bind immobilized antibodies and capture antigens from solution. Gold nanoparticles labeled with both specific antibodies and a specific reporter bind to the captured antigen. By immobilizing different antibodies and using different reporters, the presence of different antigens can be detected by the characteristic surface-enhanced Raman spectrum of the specific reporter molecules. There are several potential advantages of using SERS as a read-out method (Figure 12).

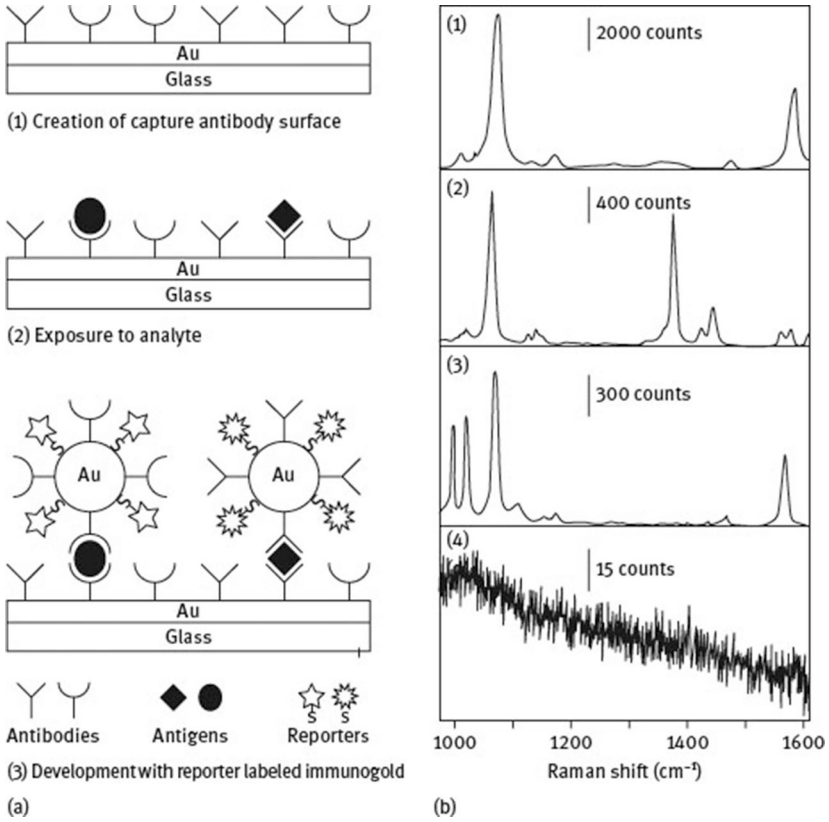

Figure 12: (a) Scheme of an immunoassay system using two different SERS labels. (b) SERS signatures of three types of reporter-labeled immunogold colloid [150].

The SERS gene technique has been used for determination of the human immunodeficiency virus (HIV) gag gene sequence. The results of this study are potentially useful for HIV detection by SERS gene probes [151]. Progress in DNA and genome research results in quick development of SERS techniques for rapid characterization of DNA fragments [152]. A SERS-based method has been proposed for monitoring the concentration of double-stranded DNA amplified by polymerase chain reactions. Methods for labeling can employ radioactive or fluorescence reporters [153]. Recently, quantum dots and nanoparticles have been suggested as interesting new fluorescence labels for characterizing DNA fragments and for detecting specific nucleic acid sequences [154, 155].

Another example of using SERS spectroscopy is identification of artificial neural networks in aqueous solutions of different neurotransmitters [156]. Spectra of neurotransmitters have been measured on silver electrodes and on colloidal silver particles in water [114, 157–160]. The high sensitivity of SERS has been also applied for identification of relatively small amounts of bacteria. The first SERS studies of bacteria were reported in 1998 [161] and in that work, silver colloidal particles were produced selectively within the bacterium on its wall, forming there a rough silver coating. Considering the number and diversity of biomolecules in the bacterial wall, the SERS spectrum is a selective effect showing predominantly those molecules and functional groups that are in the immediate proximity of the silver colloid [161, 162].

Enkephalin, an endogenous substance in the human brain, was detected at the single-molecule level based on the surface-enhanced Raman signal of the ring breathing mode of phenylalanine, which is one building block of the molecule. The SERS signal of phenylalanine can be used as an intrinsic marker for detecting a single enkephalin molecule without the use of a specific label [116].

Moreover, gold or silver nanoparticles could be used as intracellular pH probe [124, 141, 163–165]. Determination and monitoring pH in cells and cellular compartments is of particular importance for a better understanding of a broad range of physiological and metabolic processes (Figure 13).

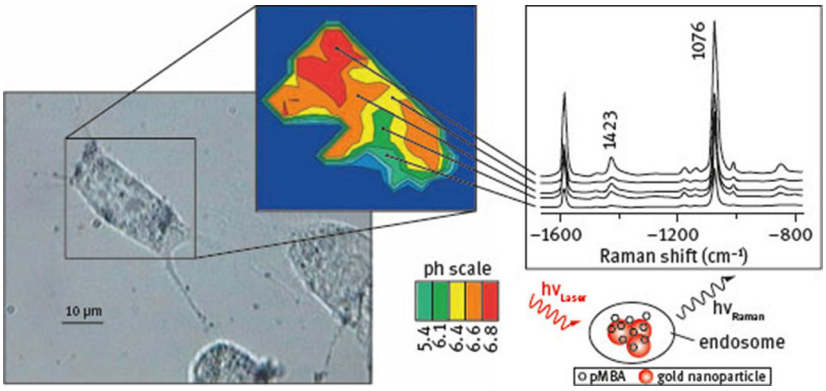

Figure 13: Probing and imaging pH values in single live cells using a SERS nanosensor, which exploits the pH-sensitive SERS spectrum of 4-mercaptobenzoic acid (pMBA) [141].

Conversely, SERS has been proposed for detection of a range of explosives and other trace materials. Some of the key explosives such as TNT, and components of plastic explosives such as RDX and PETN, have very low vapor pressures so the detection limits of any analytical method are required to be low. The SERS technique is effective if a gold substrate is treated with sodium hydroxide [103] and chemical derivatization of TNT produces a molecule that adheres strongly to silver surfaces, again giving good detection limits [166].

Acknowledgments

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