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Hybrid nanostructures for SERS: materials development and chemical detection

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This review focuses on recent developments on hybrid and nanostructured substrates for SERS (Surface-Enhanced Raman Scattering) studies. Thus substrates composed by at least two distinct types of materials, in which one is a SERS active metal, are considered here aiming their use as platforms for chemical detection in a variety of contexts. Fundamental aspects related to the SERS effect and plasmonic behaviour of nanometals are briefly introduced. The materials described include polymer nanocomposites containing metal nanoparticles and coupled inorganic nanophases. Chemical approaches to tailor the morphological features of these substrates in order to get high SERS activity are reviewed. Finally, some perspectives for practical applications in the context of chemical detection of analytes using such hybrid platforms are presented.

1.Introduction

Metal nanoparticles (NPs) have been of technological interest for a long time due to their unique properties.[1-6] Hence, the optical properties of these metals have been empirically exploited to confer distinctive optical effects to other materials (e.g. glass) in which they have been dispersed, as result of scattering and absorption of visible light. Earlier technological applications of dispersed small metal particles include their use as pigments for stained glass windows or to fabricate dichroic glass such as in the now famous Lycurgus cup.[7, 8] Interestingly, the synthesis of colloidal Au nanoparticles has also been associated to earlier practices that somehow had important consequences in future developments, such as the alchemy of Paracelsus on Aurum Potabile or seminal studies performed by Michael Faraday using gold hydrosols.[9] Nowadays, metal nanoparticles are the basis for a number of devices coming from nanotechnological approaches that are expected to increase in near future. Among these technologies, those based on Surface-Enhanced Raman Scattering (SERS) have been recently used with acute relevance. Although the SERS effect was itself discovered during the 70's, this spectroscopic method is benefiting from the unprecedented progress observed in the last decades on instrumentation and materials development specific to nanoscale science. Indeed, the design of SERS active nanomaterials is a key aspect in further exploitation of SERS in diverse areas, including medicine, environmental monitoring and trace chemical analysis.

This review aims to give a concise perspective on late developments concerning materials for SERS analysis, with a particular emphasis on hybrid nanostructures containing metal nanophases, mostly of Au and Ag. Here these hybrid nanostructures are considered as composed of at least two distinct materials in which one is necessarily a SERS active metal with nanosized dimensions. In order to put in context the application of these hybrids in SERS analysis, some fundamental aspects related to the use of plasmonic metals in Raman spectroscopy will be briefly introduced. Then there will be review of a series of hybrid materials for SERS that are based on metal substrates and whose extensive use has been largely documented. Efficient strategies have been used on the preparation of metal NPs with diverse size, shape and composition, and with skilful plasmonic properties, all crucial for an efficient SERS response.[3, 10-12] Huge progress has been made for the assembly of metal NPs into organized nanostructures for the preparation of stable, reproducible and highly active SERS substrates.[13-21] These more conventional substrates will be firstly mentioned before the main focus of the review on hybrid nanostructures, that include coupled inorganic nanophases and organically coated metals, including polymer nanocomposites. Finally illustrative examples of SERS applications will be provided along with perspectives of development in the context of chemical detection applied to real contexts.

2. Plasmonic metal nanostructures for SERS (gold and silver)

Gold and silver are commonly used as the metal substrates in chemical detection by SERS. Hybrid nanostructures used as SERS substrates invariably contain such metals and therefore it is useful to consider here some fundamental concepts related to their properties, which seem relevant in the context of SERS. First, it should be clear that a detailed explanation of the plasmonic behaviour of metal nanoparticles necessarily requires the convergence of multiple aspects on electromagnetic field and plasmon resonance theories in metals. For the purposes of this review, a brief qualitative explanation on the plasmonic behaviour of Au and Ag colloidal NPs will be sufficient. The reader is encouraged to consult timely publications that specifically consider the plasmonic properties of metals.[10-12, 22-29]

For metal NPs with sizes much smaller than the wavelength of incident electromagnetic radiation, it can be assumed as an approximation that the conduction electrons feel a uniform electric field oscillating at a certain frequency. The electric field causes a displacement of the virtually free electrons in relation to the positive lattice defined by the metal atoms nuclei.[4, 22, 26, 28, 30] These separated regions of opposite charge originate dipoles that act as a restoring force that move back the electron cloud. Hence, the interaction of the electromagnetic radiation with the metal gives rise to a collective oscillation of the free electrons, which is in phase with the electric field. Plasmons are the quanta of oscillation of the free electron cloud in such plasma-like systems. This process is resonant for incident light of the same frequency as the oscillation frequency of the delocalized electron cloud in the metal considered. For Au and Ag NPs this results in strong light absorption/scattering in the visible region that are recorded in their spectra as surface plasmon resonances (SPR) (Figure 1).

Already in 1908, Gustav Mie had explained the optical behaviour of metal microspheres dispersed in a dielectric by solving Maxwell's equations for absorption and scattering of electromagnetic radiation by small particles.[31] A few years later, Richard Gans extended the Mie formalism in order to explain the optical behaviour of oblate and prolate spheroidal metal particles.[32] According to Mie theory, the extinction cross section (C_{ext}) for dispersed metal spheres of sizes much smaller than the incident light wavelength (λ) is given by the product of a wavelength dependent term related to scattering and a second term that depends on the dielectric constants of the metal and dispersing medium:

$$C_{ext} = \frac{24\pi^2 R^3 {\varepsilon_m}^{3/2}}{\lambda} \frac{\varepsilon''}{(\varepsilon' + 2\varepsilon_m)^2 + \varepsilon''^2} \quad (1)$$

In equation 1, ε' and ε'' are respectively the real and imaginary components of the complex dielectric function $\varepsilon(\lambda)$, for metal particles with radius R, dispersed in a material with a dielectric constant ε_m. The second term has a maximum value for:

$$\varepsilon' = -2\varepsilon_m \quad (2)$$

stating the surface plasmon resonance condition, assuming small values of ε''. In the optical spectra of Au and Ag hydrosols, this is observed as strong absorption bands and explains the strong colours observed in these colloids.

The optical properties of Au and Ag NPs depend on their size and shape, dielectric properties of the surrounding medium and interparticle distance.[4, 28, 33-36] This knowledge has been exploited to develop substrates with variable morphological characteristics that result in materials with distinct SERS response. As an illustrative example, one can consider the use of colloidal Au nanorods, which are anisotropic nanostructures with an optical response dependent on the direction of the rod in relation to the electric field component of the incident light (Figure 1). In this case, two resonance frequencies are observed, a longitudinal mode for the oscillation of the electron cloud along the long axis of the rod and a transverse mode when the oscillation occurs perpendicularly to this axis. While the latter originates a SPR band at a wavelength close to that observed in Au nanospheres, the longitudinal mode shifts from the visible to the NIR region of the spectrum by increasing the length of the rod, i.e. for increasing particle aspect ratios. This is a property well-suited for bioapplications using Au nanorods as SERS substrates.[37-42] As mentioned above, the optical spectra for rod particles can be calculated by taking into consideration the formalism derived by Gans in the beginning of twenty century.[32] For a number of purposes, the use of the empirical equation 3 has became a practical way to relate the nanorod aspect ratio (AR) with the longitudinal plasmon resonance at the absorption maximum wavelength λ_{max}:[43, 44]

$$\lambda_{max} = 33.34\ \varepsilon_m\, \mathrm{AR} - 46.31\ \varepsilon_m + 472.31 \quad (3)$$

The distinct morphologies of Au nanospheres and Au nanorods have noticeable consequences on optical properties of relevance for SERS analysis. The relative arrangement of the metal particles and respective geometry also perturbs the electric field of the electromagnetic radiation at the surface of the metal. The Local Field Intensity Enhancement Factor (LFIEF) translates the change on the intensity of the electromagnetic field in a region due to the presence of the metal, in relation to the situation of metal absence.[45, 46] The LFIEF at a given point (r) can be expressed as the square of the electric field amplitude, $E(r,\omega)$, in that point, in relation to the square of the electric field amplitude $E_0(r,\omega)$ of the incident electric field:

$$LFIEF(r,\omega) = \frac{E(r,\omega)^2}{E_0(r,\omega)^2} \quad (4)$$

It turns out that for a given point at the metal surface, the LFIEF achieves a maximum at the plasmon resonance frequency of the metal nanoparticles. In brief, molecules adsorbed at the metal substrate will experience in these conditions strongly enhanced local electric field. The adjustment of resonance frequencies in metal nanoparticles by controlling the particle morphology, associated to the existence of hot spots at the metal surface, where there is strong enhancement of the local electric field, is therefore of great relevance for the development of materials highly sensitive as SERS substrates.

The creation of hot spots in nanostructured metal substrates can be achieved in another distinct way by promoting plasmonic coupling between interacting metal NPs. For metal NPs close to each other, the formalism summarized above is no longer valid and more complex theoretical tools apply that take into consideration namely the effect of induced dipoles interactions on the local field.[47-51] Nevertheless, a qualitative description of hot spots formation due to coupled plasmon resonances allows to appreciate the importance of this effect on SERS analysis. Compared to the case of having well-dispersed particles in a medium, the coupled plasmon resonance frequencies of interacting particles shift to lower energy. This is clearly observed experimentally for example by recording the optical spectra of Au hydrosols submitted to an aggregation process due to an increase of the ionic strength of the medium. The metal nanojunctions formed between two or more metal particles can originate strongly enhanced local electric fields (hot spots), allowing the SERS analysis of adsorbates that in certain cases might reach the molecular level detection. This is consequence of an increase of the LFIEF, which is also highly localized in the hot spot.

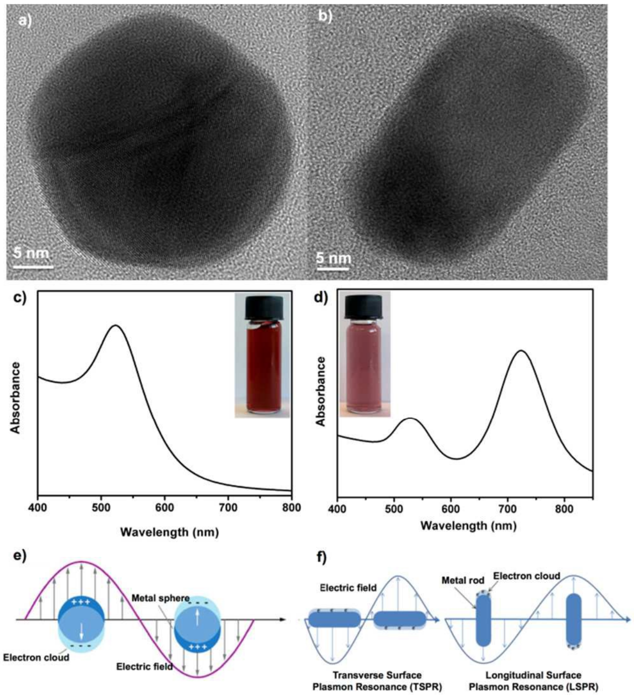

Figure 1: Gold nanostructures: HRTEM images of a single nanosphere (a) and a single nanorod (b); optical spectrum nanospheres (c) and nanorods (d) and the respective photographs of the colloids; scheme illustrating the collective oscillations of delocalized electrons in response to an external electric field for nanospheres (e) and nanorods (f).

The existence of hot spots has emerged in the past decade as an explanation for the observation of enhanced local electromagnetic fields in certain highly sensitive SERS substrates.[51-55] The existence of such hot spots has been associated to nanojunctions between closely spaced metal NPs or to specific morphological features in metal surfaces.[56-58] Thus the well-known practice of adding an ionic salt (e.g MgCl$_2$) to Ag colloids to obtain better SERS signals might be associated to the formation of hot spots as consequence of particle aggregation.[59-61] Some examples in line with these explanations, include studies of the SERS activity in regions between Ag nanowires and Ag nanocubes using 4-methylbenzenethiol or 1,4-benzenedithiol as molecular probes[62] or by deposition of Ag nanocubes on the surface of Au or Ag substrates.[63] Stranahan *et al.* have studied the interaction between rhodamine 6G molecules and Ag NP hot spots using high-resolution optical images.[64] Li *et al* have reported dimers of Ag NPs and their activity as SERS substrates for the detection of 4-methyl-benzenethiol. Figure 2 shows morphological well-defined systems forming nanojunctions between Ag NPs dimmers.[55] The existence of hot spots has also been reported for single metal NPs presenting sharp morphological features at the surfaces, such as in spiked nanoparticles and nanostars.[65-68]

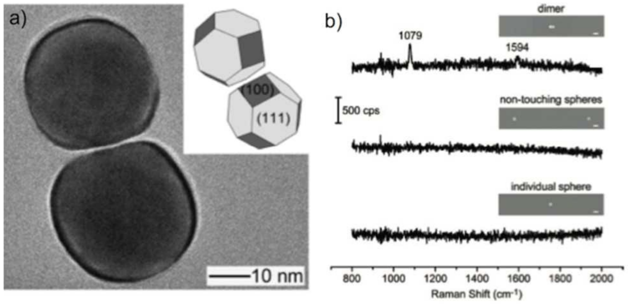

Figure 2: a) TEM image of silver nanospheres dimers with the inset illustrating a scheme of the nanocrystals; b) SERS spectra of 4-methyl-benenethiol recorded using a dimer silver nanospheres (top), two silver nanospheres separated by ~600 nm (midle) and silver nanosphere (botton) as substrates Copyright © ACS Publishing (2008).[55]

The above paragraphs indicate the relevance of the morphology of nanostructured metal substrates in order to obtain enhanced local electric fields in certain regions of the substrate due to their plasmonic properties. However, it is of the uttermost importance to make clear that other effects are necessarily present in the observation of a SERS signal. For example, it is well documented the observation of SERS signals in spectra recorded in non-resonant conditions, i.e. for cases in which the excitation line wavelength does not match that of the SPR band of the metal substrate.[40, 69-71] Also, SERS spectra have been reported for adsorbates on SERS substrates that do not contain plasmonic metals, such as metal oxides[72-74] or semiconductors.[75, 76] Although a mechanism that fully explain SERS in its diverse modalities is still a matter of intense research, two main effects have been considered that take into account enhanced local electric fields (electromagnetic effect) and the formation of a surface chemical complex (chemical mechanism). Nonetheless, the electromagnetic effect has a stronger contribution to the

SERS signal and depends strongly on the type of metal substrate used, including particle size, shape and interparticle distance.

3. Surface enhanced Raman scattering (SERS)

Inelastic light scattering by irradiated molecules was predicted theoretically in 1923 by Smekal.[77] Experimental evidence for this phenomenon was observed and explained five years later by Chandrasekhara Venkata Raman and his student Kariamanickam Srinivasa Krishnan, in a Nature report entitled *"A new type of secondary radiation"*.[78] The Nobel Prize in Physics (1930) was awarded to Raman for the discovery of such type of light scattering effect, which was then named in his honor. Most of the scattered light that result from the incidence of monochromatic light in a sample will be at the same wavelength of the excitation line, still a small part of it will be inelastically scattered at different wavelengths, which are indicative of the vibrational transitions in the molecule.[79-82] In Raman spectroscopy the spectral information is in the inelastically scattered radiation. As only a small fraction of photons will be scattered at a different wavelength from the incident light, the Raman cross- sections are extremely low.[83, 84] This originates very low sensitivity, that can be improved in electronic resonance conditions as in resonance Raman scattering, or using Raman scattering enhancement effect by adsorption of the analyte in specific metal surfaces. The latter effect will be discussed next.

Surface enhanced Raman scattering (SERS) was discovered in 1974 by Martin Fleischmann and co-workers, when observing intense Raman scattering from an aqueous solution of pyridine in contact with a rough surface of a silver electrode.[85] In this experiment, a rough surface Ag electrode was used to increase the number of surface sites available for the adsorption of pyridine molecules. The experiment revealed an unexpected enhancement of the Raman signal of pyridine. A few years later, in 1977, Jeanmaire and Van Duyne[86] and Albrecht and Creighton,[87] working independently, have recognized that the observed intensities of the Raman signal could not be explained simply by the increase in the surface area and proposed that an enhancement of the scattered intensity occurred due to adsorbed molecular species onto the metal surfaces. In this context, the enhancement of the Raman signal has been interpreted as consequence of two distinct mechanisms: the chemical interaction of the molecule with the metal surface (chemical mechanism) and the electric field enhancement due to the metal surface (electromagnetic mechanism).

Since its discovery the mechanisms underlying the SERS effect have been subject of continuous debate.[88-91] The chemical mechanism (CM) considers the effect of the adsorption of the molecule on the metal surface, including the electronic interaction with the metal, the chemical nature of the adsorbed molecule itself and surface selection rules.[92-95] A few theoretical models have been proposed to explain the chemical effect on SERS enhancement.[96-101] Jensen *et al.* have identified three distinct contributions to the chemical mechanism, that may happen separately.[93] First, the enhancement due to ground state chemical interactions between the adsorbate and the metal surface that are not associated with any excitation of the metal-adsorbate system, the so called non-resonance Raman enhancement. Secondly, the excitation wavelength being in resonance with a molecular transition promotes the resonance Raman enhancement. Third, the excitation wavelength can be in resonance with metal-adsorbate charge-transfer (CT) transitions, which is called CT resonance Raman enhancement.[93] Figure 3 presents a scheme of these different types of contributions to the chemical enhancement mechanism.

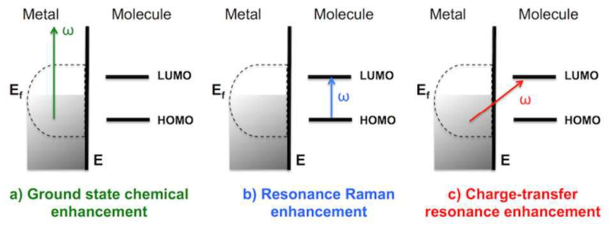

Figure 3: Illustration of the three different types of chemical enhancement mechanism in SERS. a) ground state chemical enhancement; b) resonance Raman enhancement; c) charge-transfer resonance enhancement. (HOMO - highest occupied molecular orbital and LUMO - lowest unoccupied molecular orbital; E_f is the local electromagnetic field) (Adapted from reference[93])

The electromagnetic mechanism (EM) is the dominant contribution for the enhancement in SERS[11, 90, 102, 103] and it is not dependent of the formation of a chemical bond between the metal surface and the molecule. EM arises from the optical excitation of the localized surface plasmon resonance (SPR) of the metallic nanostructure, increasing significantly the electromagnetic field strength at the particle surface. In other words, the incident electromagnetic radiation (E_i) with a specific frequency, excites the SPR and induces oscillating dipoles given by the expression $\mu(t) = \propto E_i(t)$, where $\propto$ is the polarizability tensor.[21] The induced polarization generates large local fields ($E_{i,s}$) at the surface of the metal.[21, 88, 91, 104] The Raman signal originated from vibrational transitions in the molecule within these electromagnetic fields will be greatly increased and the enhanced intensity is given by $(E_i + E_{i,s})^2$. However, the metal nanostructure can also be polarized by the scattered Raman field (E_r), which further promotes the enhancement ($E_{r,s}$). In this case, the enhancement increase is expressed by $(E_r + E_{r,s})^2$.[21] Figure 4 presents an illustration of the electromagnetic enhancement mechanism in SERS.

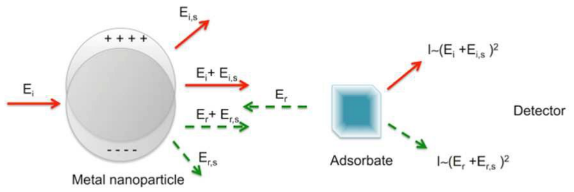

Figure 4: Illustration of the electromagnetic enhancement mechanism in SERS, where I is the Raman intensity; E_i represent the incident electric field; $E_{i,s}$ is the metal intensified field and $(E_i + E_{i,s})$ represents the incident enhanced field; E_r is the scattered Raman field, that is also intensified by the metal originating $E_{r,s}$; $(E_r + E_{r,s})$ is the scattered enhanced field (Adapted from reference[21])

4. Nanoengineering metal substrates

Since its discovery, that the observation of the SERS effect has been strongly dependent on the properties of the metal substrate employed. Thus the metal used and the morphological properties of the substrates are among the most critical factors that influence SERS, because they affect the surface plasmon resonance (SPR) and molecular adsorption.[16, 91, 92, 105, 106] Indeed, the preparation of SERS substrates has been a very active research area, in particular with the emergence of nanotechnologies that allow tailoring nanoscale features, namely by chemical strategies.[19, 91, 92, 106] We start to give an overview on common metal substrates used in SERS. These substrates are mainly based on Ag or Au, which in the context of this review can be considered as conventional substrates, thus making a distinction to those described in the subsequent section as hybrid substrates. i.e. composed by two or more components of distinct chemical nature.

4.1 Metal Electrodes

Electrodes roughened by oxidation-reduction cycles (ORC) are the earliest and most stable SERS substrates, showing reproducible EF for pyridine of about 10^6.[85] These substrates are often applied in research or *in situ* SERS monitoring of catalytic reactions and other electrochemically active systems.[107-111] Several electrochemical methods are available for the preparation of such substrates; the most used include double-potential step ORC or current-controlled ORC.[110, 111] These oxidation-reduction procedures produce particles typically 25-500 nm in size on the electrode surface. The surface structure depends on the current inferring, hydrogen bubble evolution before the roughening process and on light irradiation of the electrode during the ORC.[106, 110-113]

Silver has been the metal most commonly used, although other metals have been investigated as active SERS substrates in electrochemical cells.[114-119] During the first half of the cycle, the Ag at the electrode surface (e.g. polished mirror) is oxidized ($Ag \rightarrow Ag^+ + e^-$) when a positive potential is pulsed. A roughened silver surface is reproduced by the inverse process $Ag^+ + e^- \rightarrow Ag$, when the potential is moved back to a negative potential (Figure 5). Due to the roughness at the Ag electrode surface, adsorption of the molecular probe will be facilitated and a strong SERS signal for the adsorbate is achieved after monochromatic light irradiation.[106, 112, 113]

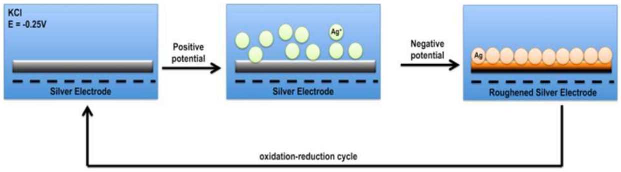

Figure 5: Scheme illustrating the oxidation-reduction cycle of a silver electrode in KCl solution.

Other electrochemical deposition methods have been reported in order to deposit roughened metal layers onto inorganic substrates, such as indium tin oxide (ITO) or anodic aluminium oxide (AAO). These strategies include galvanostatic methods,[120, 121] templated deposition in membranes[122, 123] and cyclic voltammetry.[124, 125] The metal can be directly electrodeposited yielding evenly coatings over the substrate surfaces, by using reducing agents[120, 121, 124, 126-128] such as sodium borohydride and citric acid. More recently, researchers have investigated other SERS active surfaces using oxidized forms of metal electrodes[129-131] and polymers[132]. The main advantages of using such roughened electrodes are their large surface area (more adsorbed target molecules), uniform structures and selective detection *in situ* (molecular adsorption depends on voltage and orientation).[112, 113, 124] Metal electrodes for SERS might have great interest in the fabrication of nanodevices for label-free chemical and biomolecular detection processes. An important research line for further technological development might include the coupling of such electrodes to monitor specific bioanalytes associated to brain diseases, such as in neurotransmitters detection.[125]

4.2 Colloidal metal nanoparticles

Colloidal metal NPs have been used very often as SERS substrates due to their high sensitivity in quite distinct analytical contexts.[51, 133-137] Also metal nanoparticle synthesis techniques are now available that allow to control the size, shape and particle arrangement, which are parameters that affect markedly SERS activity.[10, 138-141] Figure 6 shows images of colloidal Au NPs with variable morphologies that have been used as SERS substrates. These metal colloids are generally prepared by adding a reducing agent to an aqueous solution of the respective metal salt, that also contains chemical species to confer colloidal stability,[142-147] but other methods exist such as laser ablation[148-153] and photoreduction.[152, 154, 155] Table 1 lists preparative methods for obtaining SERS active colloids of variable composition and morphology.

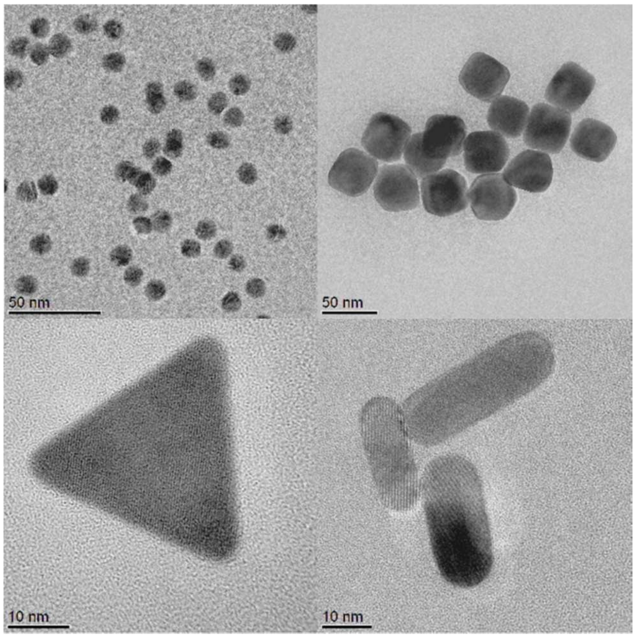

Figure 6: TEM images of Au NPs with different morphologies.

Table 1: Colloidal metal nanoparticles used for SERS and synthesis methods

Particle shape	Method of synthesis	Colloidal NPs
Spheres	Creighton method (Borohydride method)	Ag[142, 144, 156-158] Au[142]
	Lee – Meisel method (Citrate method)	Ag[143, 152, 157-160] Au[143, 145, 161-163]
	Other reduction method	Ag[159, 164] Cu[165]
	Laser ablation	Ag[148, 149, 152] Au[148, 149] Cu[151]
	Seed-mediated method	Au[146, 166]
	Photoreduction	Ag[153-155]
Cubes	Polyol method	Ag[56, 63, 167-169]
	Seed-mediated method	Ag[170] Au[168, 171, 172]
Pyramides	Seed-mediated method	Au[172]
	Oxidative etching process	Ag[173]
Plates	Dual-reduction method	Ag[174-176]
	Light-irradiated seed-growth method	Ag[177]
	Polyol method	Pd[178]
	Electrodeposition method	Ag[179, 180]
Wires	Polyol method	Ag[181-183] Au[184]
Rods	Seed-mediated method	Au[169, 185-188] Ag[189]
	Electrochemical method	Au[40, 190]
Stars	Seed-mediated method	Au[66, 67]

Earlier methods of preparation of Ag colloids are still in use for producing substrates for routine SERS analysis. Hence the reduction of aqueous $AgNO_3$ with $NaBH_4$, known as the Creighton method,[142, 191, 192] or the use of trisodium citrate as the reducing agent, known as Lee and Meisel method,[61, 143, 193, 194] are very common for the synthesis of Ag colloids. These are very simple methods but very sensitive to a number of experimental factors namely temperature, glassware impurities and rate of addition of the reducing agent, thus needing adjustment when fine control on the particle morphology is required.[14, 144, 145, 158, 172] In order to improve colloidal stability, stabilizers can be used such as cetyltrimethylammonium bromide,[146] poly(ethylene glycol),[195] sodium dodecyl sulphate,[196] poly(vinylpyrrolidone),[197, 198] polyamine spermine,[159] poly(ethyleneimine)[199, 200] or poly(L-lysine).[201] However, it should be noted that the use of organic surfactants could interfere with the SERS spectrum of the analyte under study. Similarly, for Au colloids there are also well-established syntheses at least since the work reported by Turkevich for reducing Au(III) with citric acid,[202] a method developed further by Frens.[203] Unlike Ag NPs that are cytotoxic, Au NPs have been proving their value as biocompatible SERS substrates, namely as rod shaped particles in which the wavelength of the longitudinal SPR mode can be adjusted to the near infrared (NIR).[51, 91, 204] In particular, radiation with wavelength in the 700-1100 nm window is very useful for SERS applications in biomedicine because absorption/scattering from living tissues is weak and auto-fluorescence is very low, which allows deep penetration of light.[36, 51, 205, 206]

As illustrated by the last example, the shape of colloidal metal NPs might have strong influence on the SERS detection of certain analytes. Usually spheres show smaller intensity of the SERS signal compared to ellipsoidal or spiky particles of comparable dimensions, including cubes,[56, 63, 167, 168] plates,[175, 176, 178] wires,[182, 183, 207] rods[185-189] and stars.[66, 67] The higher SERS enhancement observed in these cases has been associated to localized surface plasmon resonances that create high local electromagnetic fields in specific regions within the nanoparticle. Thus plasmonic mapping using energy loss spectroscopy (EELS) has shown plasmon resonances at specific regions of metal nanoparticles, namely at the corners of Ag triangular plates,[208] ends of Au nanorods,[209] and as shown recently, at the sharp apexes of Au nanostars.[65] Figure 7 shows the local electromagnetic field mapping on anisotropic particles using such technique applied to Ag triangles and Au nanostars.

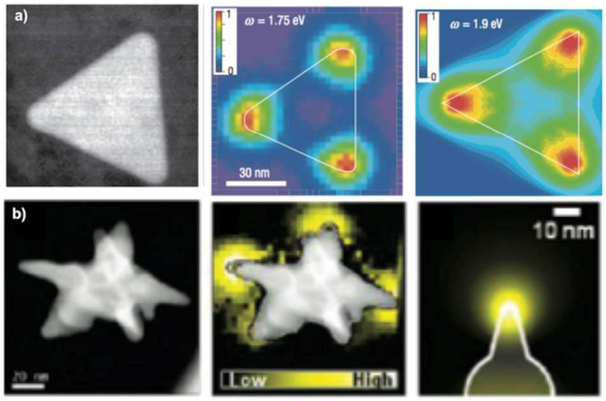

Figure 7: High-resolution scanning transmission electron microscopy (HR-STEM) dark-field image, electron energy loss spectroscopy (EELS) intensity mapping and calculated EELS intensity map of a) a single Ag triangle and b) an Au nanostar (Adapted from[47, 65]). Copyright © Nature Publishing Group (2007) and ACS Publishing (2009).

The synthesis of such anisotropic structures required the development of methods, which express elegantly the emergence of Nanochemistry as a field with important consequences for SERS research. Colloidal nanorods (NRs) are examples of anisotropic plasmonic particles that have been intensively studied[42, 204, 210, 211] aiming applications in medical imaging,[212, 213] biosensors,[42, 214, 215] controlled drug delivery[41, 216] and photothermal therapy.[217, 218] Because of the anisotropic shape, Au NRs show two surface plasmon resonance bands, in the visible and visible/near infrared (NIR) corresponding respectively to the transverse surface plasmon resonance (TSPR) mode and to the longitudinal surface plasmon resonance (LSPR) mode. The TSPR mode appears at lower wavelength and the LSPR at higher wavelength. The latter can be tuned from the visible to the NIR region by varying the NRs' aspect ratio (A.R.); therefore, the higher the A.R., the more shifted for higher wavelength the longitudinal plasmon resonance.

From a fundamental point of view, Au and Ag NRs have also been useful to acquire information on the relationship between the SERS intensity and SPR band location, because they allow to tune surface plasmon resonances accordingly to the excitation wavelength.[186, 189, 214] Alternatively, the SPR can move further away from the excitation laser in order to study the contribution of other enhancement mechanisms.[40, 219, 220] Nikoobakht and El-Sayed have investigated Au NRs as SERS substrates exhibiting enhancement factors of 10^4-10^5 for pyridine and 2-iminothiophenol, while for Au NPs there was no signal enhancement under off-resonance excitation conditions.[40] Thereafter, these anisotropic materials have been implemented in biological application as SERS substrates in the detection of different molecules such as pesticides residues,[169, 186] biomolecules,[40, 221-223] cells,[224, 225] DNA,[226] and anti-bodies.[215] Anisotropic metal nanostructures, such as Au nanostars, open a new avenue towards nonlinear optical devices with important consequences for optical switching and up-conversion applications.[65] Other perspectives for further developments include their use in nanodevices aiming high-throughput screening, biosensing and diagnosis, as well as in combinatorial chemistry associated to drug discovery.

5. Coupled inorganic materials

Although colloidal metal NPs have been commonly used as SERS substrates, there are some limitations associated to the application of this type of substrates, namely in terms of colloidal stability with time and upscale production. A strategy to circumvent these problems is the production of substrates by supporting the SERS active metals in solid surfaces.

5.1 Metal coated surfaces

SERS substrates have been developed using the SERS active metal NPs chemically or electrostatically attached to other inorganic materials. Table 2 shows examples of metal nanophases supported on inorganic solids that have been used as SERS substrates.

Table 2: Inorganic solids supported nanometals as SERS substrates.

Nanostucture	Inorganic substrate
Metal islands films	Fused quartz,[227] Alumina,[228] Glass,[229-232] GaN,[233] InGaN,[234] Filter paper,[235] Cleaved mica,[236] Stainless steel,[237] Copper,[238]
Chemically etched metals	Alumina,[239, 240] ITO-glass,[241] Silica,[242-244]
Metal-coated nanospheres (NSL)	Glass,[245-248] Silicon,[249]
Metal films over nanospheres (FON)	Alumina,[250] Silica,[251] Copper,[252]

A method to prepare such types of SERS substrates involves the coating of rough substrates using metal NPs or metal islands. The metal islands can be prepared by direct deposition of a thin layer of a metal, about 10 nm thick, onto the support by using vapour deposition or vacuum evaporation methods.[229-232, 234, 236, 238] Experimental parameters such as the deposition rate, growth temperature, geometry and post-deposition annealing, influence largely the size and the shape of the final metal nanostructures.[106] Optical absorption, AFM and Scanning Near Field Optical Microscopy (SNOM) combined with SERS have been used to optimize the deposition of the metal islands over the substrates.[231, 253, 254]

Nanolithographic methods are very often used to fabricate SERS substrates that are based on ordered nanostructures directly made at the surface of a solid platform. These methods include electron beam lithography,[239, 241-244] electromigration,[255] electrochemical metal growth,[256] nanosphere lithography[245, 246, 248, 257] and film deposition over nanospheres.[251, 252, 258, 259] For example, electron beam lithography (EBL) has been an elective technique to obtain nanostructured features on solid surfaces by selective area etching using the electron beam. Variable shapes with a few nanometers size are accessible which can then be coated with a SERS active metal by sputtering or evaporation methods.[239, 241, 242] This approach provides high resolution and reproducibility at the nanometer scale, with a precise control over the geometry and separation of the nanostructures. Wang *et al.* have studied the preparation of Au nanostructures using two processes based on EBL.[243] One process involved the use of metal lift-off and the other involved the use of plasma etching. Both processes allowed the successful preparation of Au nanostructures with distinct geometrical shapes, different periodic arrangements and SERS activity. This is an illustrative example of the potential of nanolithography to produce hybrid substrates in which the observed SERS signal enhancement is highly dependent on the geometries and arrangement of the nanostructures. This is an area in which other possibilities of nanofabrication can emerge, due to technological developments occurring at the level of increasingly sophisticated electron microscopes with better resolution.

Nanosphere lithography (NSL) leads the formation of ordered assemblies on a solid surface by the deposition of a metal film on nanospheres (e.g. polystyrene latex spheres). With this methodology, the SERS substrate is formed by removal of the polymer used as template, leading to ordered arrangements of metal nanostructures. Haynes and van Duyne have reported strong Raman signal enhancement for benzenethiol molecules adsorbed onto Ag surfaces obtained by the NSL method.[247] As an alternative strategy, rough metal films deposited over nanospheres (FON) have been also reported as efficient SERS substrates in which the film thickness and the dimensions of the template are easily controlled. In this methodology the nanospheres used as templates will not be removed from the substrate. Li *et al.* have demonstrated that dual layer and multilayer Ag FON substrates can show signal enhancements of about two orders of magnitude superior as compared to conventional single layer silver FON substrates.[259] Metal coated solid substrates having specific morphological features can originate highly active SERS tips. Sputtering and evaporation methods are common metal deposition techniques that are available for these purposes. Hence, Boisen and co-workers have reported a gas sensor composed by Si pillars coated with Ag, for SERS detection.[260] In this case, gas molecules forming a uniform adsorbate will originate strong SERS signal when a solvent is dropped on the substrate and then evaporated, because surface tension will cause the nanopillars to lean towards their nearest neighbours, thus creating self-assembled hot spots (Figure 8).

These SERS platforms are particularly interesting due to their robustness and SERS sensitivity. In the future, several applications might be envisaged for these substrates, noteworthy the possibility for their storage in specific atmosphere/vacuum, contributes for their relevance in long term use and shell life, with the ability for analyte detection in either gas or liquid phase.

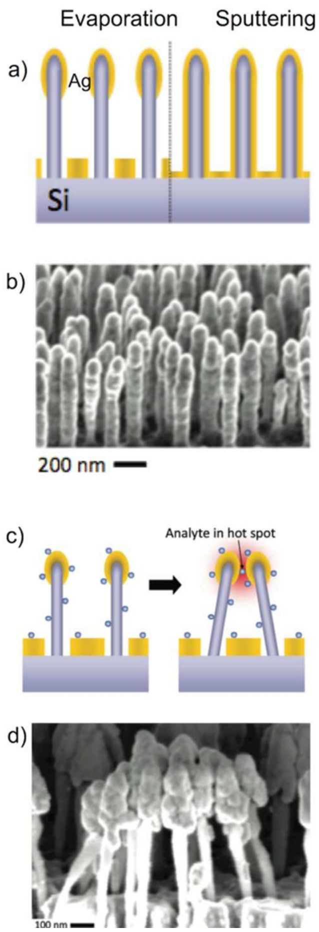

Figure 8: a) Evaporation results in Ag tips at the top of the silicon pillars while sputtering yields conformal coatings; b) SEM image of the Ag coated silicon nanopillars; c) Scheme of the enhancement mechanism - the solvent evaporates and this surface tension will pull the silicon nanopillars together, trapping the analyte at the "*hot spot*" giving rise to a large Raman signal; d) SEM image of a cluster of leaning silver coated silicon nanopillars[260] Copyright © Wiley Publishing Group (2012).

5.2 Core/shell particles

Hybrid nanostructures such as metal core/shell particle have gained special attention for SERS applications. Typical core/shell NPs for SERS comprise a dielectric core surrounded by thin metal shells[261] or the coupling of two metals.[262] Seed growth methods are commonly employed to prepare core/shell metal/metal nanospheres,[263-266] but other chemical methods are available.[267, 268] In the seed growth method, the cores are coated by metal shells grown upon the dropwise addition of the metal salt and the reducing agent (e.g. hydroxylamine hydrochloride).[264] A great advantage in using this type of metal-metal core/shell nanoparticles is the ability to adjust the SPR frequency by varying the relative geometry of the nanostructure, for instance the core and the shell dimensions,[261, 269] which allows optimum matching of the SPR wavelength with the excitation line wavelength.[263, 267-270]

Metal core/shell nanostructures for SERS are not limited to spherical particles. Yi *et al* have prepared Ag/Au plates by a dual-reduction method aiming the detection of Rhodamine 6G (514.5 nm laser source)[271] and Xie *et al* have prepared Au/Pd nanobars by the seed growth method. In both cases the SERS activity of the metal substrates was varied by tuning either the aspect ratio of the Au core or the Pd shell thickness.[272] Currently, there is need of a more deep understanding of the mechanisms underlying the synthesis of these nanostructures in order to facilitate the preparation of new core/shell materials. This is an important aspect that put in perspective how a number of fascinating applications anticipated for these core/shell structures are dependent on fundamental knowledge that goes beyond recent areas of research, such as Nanosciences. A clear example involves the adaptation of current laboratorial protocols to up-scale units of production, for which engineering approaches are dependent on a number of factors of more fundamental nature.

Coupling of metal nanophases and dielectrics has been an important process to obtain hybrid SERS substrates. Silica coating of colloidal inorganic NPs is now a well-established method to achieve colloidal and chemical stability, and also to modify the optical properties of the colloid by varying the shell's thickness.[21, 261, 273-275] Additionally, various silica derivatization methods are available that make silica shells handy platforms for the conjugation of diverse molecular probes.[276-279] Although in such core/shell structures the metal active SERS particles are coated, the porosity of amorphous SiO_2 shells might allow diffusion of analytes towards the internal metal cores and subsequent SERS detection.[280-283] Such metal/SiO_2 core-shell structures have also been used to study the physical and chemical mechanisms involved in the observation of SERS effects,[280, 281] to induce formation of hot spots using the silica porous[281] and to detect organic molecules.[282, 283] Doering and Nie have prepared SiO_2-coated NPs embedded with SERS tags as Raman reporters.[284] Similar approaches have been employed to obtain Ag/SiO_2 core/shell NPs for protein detection, using Au[277] or Fe_3O_4 magnetic NPs[268, 276, 277] as cross linkers, and to develop SERS tagged core/shell nanostructures as markers for breast cancer cells[285] and tumour cells.[286] In comparison with other biological labels, core/shell SERS tags provide important features such as spectroscopic information and high sensitivity for multiplexed analysis and for multi-parameter flow cytometry. This is a field that will tend to develop in the near future, namely by implementation of these tags in clinical research.

Metal coated magnetic nanoparticles are particularly interesting core/shell SERS substrates aiming multifunctional applications. A few cases illustrate the potential of these nanostructures for SERS when associated to their use as magnetic vectors. Hence, Zhang and co-workers have used magnetic Fe_3O_4/Au core-shell nanostructures,[267] while Kumar et al. have demonstrated that Ag or Au coated with γ-Fe_2O_3 NPs give SERS signal at low concentrations of dyes, such as R6G and 2-naphthalenethiol.[265] The magnetic properties of these core/shell particles, coupled with the optical properties of the metal, make these hybrid nanostructures unique, with perspectives of applications in several biomedical applications.

Although there are reports on surface enhancement of Raman signals for adsorbates on semiconductor substrates, the signals are relatively weak when compared to typical enhancements observed for Ag or Au.[75, 76, 287] On the other hand, semiconductors nanostructures that form the basis of current nanotechnologies can be coupled to SERS active metals, aiming synergistic applications. Hence semiconductors of diverse structural dimensionality have demonstrated high enhancements in Raman scattering when attached to metallic NPs, including TiO_2,[288-292] ZnO,[293-296] CuO,[297] Cu_2O[298] and Si[299, 300]. In this context, TiO_2 is an interesting example because it is an important photocatalyst whose activity can be improved when coupled to metal NPs. The metal NPs not only serve as a Raman signal amplifier but also facilitate charge transfer at the metal/semiconductor interface. [288, 301] These multifunctional hybrid nanostructures are regarded as recyclable and self-cleaning SERS substrates,[288, 290, 291] for the detection of biomolecules[289] and treatment/decomposition of organic pollutants.[288, 290, 292]

5.3 Metal/Carbon nanostructures

Carbon nanostructures decorated with metal nanophases form an important class of hybrid substrates for SERS. Table 3 lists some methods for preparing SERS active metal/carbon hybrid materials of variable structural dimensionality, that include those based on carbon nanotubes (CNT) and graphene materials.

CNTs are particularly interesting platforms to fabricate SERS substrates due to their characteristic Raman bands and one-dimensional geometry.[302, 303] The Raman bands of CNTs attached to metal nanophases can be enhanced by several orders of magnitude and sensitive Raman measurements can be carried out;[302, 304, 305] for example, the first reported Raman spectrum of individual SWCNTs was obtained by SERS.[306] Also, individual SWCNTs can be used to probe the electric field distribution around individual metallic nanoparticles[307] and to probe the dynamic behavior of topological defects.[308] Because the characteristic Raman bands of CNT can be enhanced due to the presence of attached metal phases, this has also been used as a way to characterize these substrates.[304, 309-311]

Carbon nanotubes decorated with metal NPs have been reported in the literature as efficient SERS substrates, showing good stability in solutions of variable pH.[312] A number of analytes were studied by SERS using CNT/metal substrates namely in the detection of aminothiophenol,[312-314] adenine,[313, 314] and pyridine.[315] Anastasopoulos *et al.* have prepared SERS active pyridine moieties via CNT functionalization, yielding SERS sensitive graphitic surfaces in the presence of Ag colloids.[316] It is expected that the above hybrid materials will contribute to the development of new optoelectronic platforms that merge both the optical and electronic properties of the components. This synergism might result in new nanodevices of interest for example in biomedicine and in loco monitoring technologies.

Table 3: Carbon based nanostructures used for SERS and preparative methods

Carbon/metal Nanostructure	Method of preparation
CNT/Ag	Electrochemical deposition,[304, 315, 317] Ultrasound assisted electroless deposition,[306] Thermal evaporation,[305, 309] Surface polishing,[308] Chemical reduction,[313] Magnetron sputtering,[310] Seed deposition and growth,[318]
CNT/Au	Thermal evaporation,[307, 309, 319] Seed deposition and seeded growth,[311, 319] Electrostatic interaction,[320]
CNT/Cu	Magnetron sputtering,[310]
CNT/Au@Ag	Electrostatic interaction,[312, 314]
C/Au@Ag	Hydrothermal synthesis,[321]
C/Ag/Ag	Hydrothermal synthesis,[322]
Graphene/Ag	Chemical vapor deposition,[323-325] Chemical reduction,[326-328]
Graphene/Au	Chemical vapor deposition,[323, 329-332] Chemical reduction,[326] Bend method,[333]
Graphene/Cu	Chemical vapor deposition,[323]
Graphene/Au@Ag	Chemical reduction,[334]
GO/Ag	Microwave irradiation,[335] Chemical vapour deposition,[336] Electroless deposition,[337] Chemical reduction in the presence of GO,[338] Self-assembly via electrostatic interaction,[339-341]
GO/Au	Electrostatic self-assembly,[342] Chemical vapor deposition,[343] Electroless attachment,[337]

Graphene based nanostructures are becoming important substrates for SERS because the conjugation of metal NPs with such materials enable multifunctionality based on enhanced electronic, optical, mechanical and electrochemical properties.[327, 333, 340, 344-346] The use of graphene monolayers decorated with metal NPs allows SERS analysis using atomically thick surfaces,[329] additionally these substrates can enhance the characteristic bands of graphene,[326, 330] also acting as fluorescence quencher[331] and protective shell.[323, 324] Environmental monitoring and biomedical diagnostics are key areas for the application of such hybrid nanostructures. Li *et al.* have developed disposable graphene/Ag hybrid sensors for *in situ* detection of polar antibiotics residues using a SERS method.[328] Ray and co-workers have fabricated GO substrates containing Au nanocages for trace level identification of explosives, such as cyclotrimethylenetrinitramine (RDX) and trinitrotoluene (TNT).[347] These hybrid substrates allowed the SERS identification of RDX at a level as low as 500 fM and as 10 fM for TNT. Kim *et al.* have encapsulated Au NPs with GO for studying neural stem cells differentiation based on spectroelectrochemical and SERS measurements, thereby demonstrating the potential of SERS as a non-destructive detection tool for *in situ* monitoring of stem cell differentiation.[343] Other examples on the use of graphene based materials for SERS detection of chemical compounds include studies on several dyes,[323, 324, 330-332, 337, 339, 342] 4-amino-benzenethiol,[326, 335] 4-

mercaptobenzoic acid [336] and folic acid.[340]

Metal cores coated with carbon shells are an example of other carbon based nanostructures used as SERS substrates. Hu and co-workers have coated monodispersed metal NPs with carbon shells in order to obtain biocompatible SERS tags aiming quantitative immunoassays.[321] These materials were also investigated in ultrasensitive detection of biomolecules, in vivo molecular imaging of animal and plant tissues. Zhang *et al.* have investigated hybrid structures comprising Ag cores decorated with smaller Ag NPs and coated with carbon shells, for the SERS detection of methylbenzenethiol (MBT) and mercaptobenzoic acid (MBA).[322] In this case, Ag NPs with different sizes (4-73 nm) have been encapsulated by carbon shells and the distance between the Ag NPs was used to adjust the SPR band location.

5.4 Metal/porous materials

Another strategy to prepare stable solid SERS substrates involves the incorporation of metal nanoparticles in porous matrices, such as sol-gel produced materials,[348-351] cellulose acetate gels[352-354], polycarbonate films,[355-357] zeolites,[358-361] porous glass ceramics[362] or templated nanoporous metals.[363] These template materials are relatively cheap and can facilitate the interaction between the analyte and the embedded metal nanoparticles.[355] These solids offer additional advantages as matrices for SERS because provide high stability in device fabrication, prevent the agglomeration of the embedded metal NPs, the metal phase has an uniform distributed particle size and a thin coating on the surface of the porous material and analyte selectivity based on pore size can be explored.[112, 355, 358, 360] For instance, zeolites are crystalline aluminosilicates with unique pore structures that have been used as templates for the preparation of SERS platforms. These platforms can be used in chemical detection using a distinctive approach that takes advantage on the presence of loosely bound cations. Thus negatively charged zeolites have been used as SERS substrates for the detection of cations such as uranyl ions.[359] A great advantage of using zeolitic substrates for SERS include their inexpensive and straightforward preparation, in which the metal phase can be incorporated into the zeolite by vacuum deposition[359] or chemical plating.[358] Other important features include good chemical stability, and reproducibility, as well as the possibility of using SERS for in situ detection and single-molecule SERS studies.[358] Zeolites have been of technological interest for a long time in diverse fields and have potential to be also used as innovative SERS substrates when coupled to metal nanophases. This trend will require new approaches in terms of materials chemistry that takes in consideration not only the synthesis of the hybrid materials but also their transposition into active platforms, such as on-chip devices.

6. Polymer based nanocomposites for SERS

In recent years, a number of polymer-based nanocomposites have appeared as a new class of hybrid materials containing plasmonic metal nanoparticles. In certain cases, the successful preparation of such substrates depends on the type of coating employed to stabilize the metal nanoparticles used as composite fillers. Organically coated metal NPs can be obtained by using distinct strategies, including the *in situ* generation of metal NPs in polymers, or by post-synthesis processes. Hence, the nature of the organic coating can vary considerably and important examples of SERS substrates prepared by these approaches involve the use of synthetic or natural polymers[364-370], phospholipids[371, 372] and proteins [373, 374], or by applying analyte trapping strategies.[15, 375-377] In these SERS substrates, the polymer matrix can alter the interparticle distance of the dispersed metal NPs and their close surrounding, promoting the formation of SERS active sites that are accessible to small molecule probes due to diffusion through the polymer.[365, 366, 370, 375, 378] In addition, these polymers also provide means to attach functional molecules for specific molecular recognition.[375, 379, 380] The interaction of molecular probes with the metal nanofillers can be facilitated by submitting the polymer matrix to external stimuli, such as changes in pH, temperature and ionic strength.[15, 377, 381-383] Noteworthy, polymer nanocomposites are of great interest due to their multi-functionality, ease to process-ability and strong potential for large-scale manufacturing at low cost.[16, 375, 384-386]

Several approaches have been used to produce polymer composites for SERS. In general, these methods fall into two main categories depending if the metal NPs have been produced *in situ* or were previously prepared and then chemically manipulated. *In situ* methods involve the reduction of the metal salt in the presence of the polymer matrix, thus in general the reduction of the metal ions occurs in the presence of the polymer matrix that also acts as colloidal stabilizer. On the other hand, previously prepared metal NPs can be mixed with a polymer forming homogeneous blends (blending method) or submitted to surface modification procedures such as polymer grafting at the metal surfaces. In the following sections these methodologies to prepare polymer nanocomposites as active SERS substrates will be briefly reviewed.

6.1 Chemical reduction

In this method, the metal NPs are generated by reduction of the respective metal salt typically by using sodium borohydride or sodium citrate, in the presence of a polymer, yielding hybrids composed by metal NPs wrapped by the polymer chains.[387-389] In some cases the polymer matrix contains functional groups that act as reduction sites, making unnecessary the use of an external reducing agent.[369, 390] For example, this methodology has been used for preparing diverse nanocomposites based on biopolymers [368, 389, 391, 392], including the polysaccharides chitosan,[392-396] cellulose,[397] agarose,[368, 389, 391] glucose,[387] and hyaluronic acid [398]. Some polysaccharides form hydrogels that can be lyophilised and recover their gel nature by rehydration, showing ability for molecular trapping of analytes in the biopolymer network and subsequent SERS analysis.[368, 389, 394] Aldeanueva-Potel *et al.* have reported that bionanocomposites of agarose containing Ag NPs trapped inside the matrix network can be recyclable, i.e. the molecular probe can be washed out by dialysis and the SERS platform can be reused.[389] Trindade *et al.* have investigated the use of bacterial cellulose (BC) as a potential alternative to vegetable cellulose in the fabrication of paper based SERS platforms (Figure 9).[397] Metal loaded biopolymer substrates for SERS have not been fully exploited for their potential in terms of bioanalysis; for example the authors have demonstrated the usefulness of Ag/cellulose nanocomposites for the detection of the amino acids L-phenylalanine, L-glutamin and L-histidine.[397] Another interesting possibility to be further developed involves the SERS monitoring of these Ag based substrates, which are well known for their antimicrobial activity,[399, 400] namely by using Raman imaging techniques.

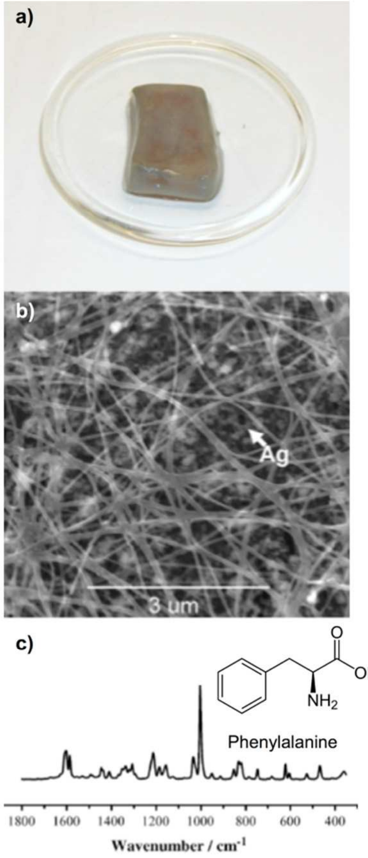

Figure 9: a) Digital photograph and b) SEM image of silver-bacterial cellulose nanocomposite; c) SERS spectrum of L-phenylalanine using a Ag-bacterial cellulose composite as substrate.[397]

SERS platforms based on hydrogels containing metal NPs have also been used for SERS detection of dyes,[387, 392] proteins,[392] nucleobases,[401] amino acids,[397] and several molecular analytes including p-aminothiophenol (ATP),[402] 2-chlorothiophenol,[393] dibenzyl disulphide,[396] 1-naphthalenethiol,[368], 4-mercaptobenzoic acid,[398] and trans-1,2-bis-(4-pyridyl) ethylene,[391] dichlorodiphenyl-trichloroethane [368] and also to monitor changes occurring in bacteria.[394] Other polymers used for *in situ* methods include gelatin,[369, 388, 403] natural rubber [390] and diverse synthetic polymers.[404-407] Thus, Zhu *et al.* have prepared PS/Ag composite microspheres by *in situ* reduction of $[Ag(NH_3)_2]^+$ aiming the SERS detection of dyes [404]. In this work, polyvinylpyrrolidone (PVP) and polydopamine (PDA) played an important role in the attachment of Ag^+ into the PS matrix via the hydroxyl and amine groups. First, mono-dispersed PS microspheres were dispersed in a mixture of ethanol and water using PVP as the dispersant; then the PS microspheres were modified with PDA. The $[Ag(NH_3)_2]^+$ ions were added to the PS microspheres and after their adsorption to PDA-PS beads, the temperature was raised up to 80ºC, obtaining a brown PS/Ag composite which showed SERS sensitivity. These composites have great potential for application in areas such as catalysis, antibacterial materials and the optical detection of macromolecules, antibody-antigen interaction and DNA hybridization.

6.2 Blending

The blending of previously prepared metal NPs with polymers can be a simple process to obtain nanocomposites exhibiting SERS activity.[364, 367, 378, 386, 408-413] Besides the simplicity, these methods are cost-effective and easily scalable though lack some control in terms of their homogeneity at the molecular level.[364] Synthetic polymers such as poly(methyl metacrylate),[367, 410] poly(*tert*-butyl acrylate),[386] polystyrene-block-poly(acrylic acid)[411] and polyvinyl alcohol[412] have been used as matrices to incorporate metallic NPs that confer SERS activity to the final composites. Although not so exploited in this context, natural polymers can also be employed as matrices namely by using water compatible metal NPs. Fateixa *et al.* have observed a correlation between the gel strength of Ag/carrageenan hydrogels used as substrates and their SERS sensitivity (Figure 10).[378] The effect of temperature and hydrogel strength on the performance of these bionanocomposites as SERS substrates using 2,2′-dithiodipyridine as the analyte was investigated. The gel strength was varied by increasing the polysaccharide content in the gel, by adding KCl as cross-linker, or by using distinct types of carrageenan (κ, ι, λ). An increase of the SERS sensitivity with increasing gel strength has been reported as consequence of the formation of metal nanojunctions between particle aggregates that follows rearrangement of the polymer chains into stronger gels.[378] This research can motivate future developments on the design of thermosensitive polymers used as matrices for SERS substrates, aiming a judicious control on the analytical sensitivity triggered by temperature variations and also the use of such bionanocomposites for the encapsulation of active compounds in controlled release processes.

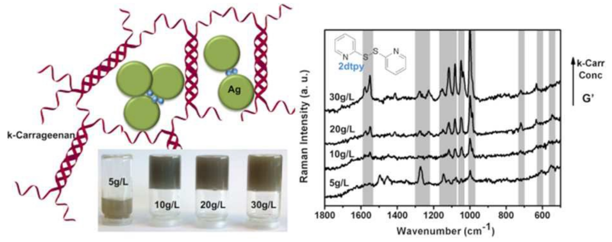

Figure 10: Scheme for the formation of SERS sensitive Ag/κ-carrageenan hydrogels due to biopolymer helices aggregation and digital photographs of nanocomposite samples with variable Ag amount (left); SERS spectra of 2-dtpy using Ag/κ-carrageenan hydrogels of increasing concentration in biopolymer (a) 5 g/L; (b) 10 g/L; (c) 20 g/L; (d) 30 g/L (right).[378] Copyright © ACS Publishing (2014).

Depending on the type of polymer used, hybrid nanostructures that result from blends with metal NPs might offer additional advantages for SERS applications, which include stimuli responsive platforms and a porous network that allows diffusion of small molecules. Among other applications, these substrates have been used in medical diagnosis[410], bioimaging,[408] environmental applications[413] and SERS detection of several molecular compounds [367, 378, 411, 412] Blending methods do not necessarily involve a polymer as a continuous dispersed phase. Discrete polymer beads can be decorated with metal NPs for producing SERS platforms, in which heat and mass transport are facilitated due to the polymeric carriers.[408] Lee *et al.* have prepared a range of metallic NPs with different sizes and shapes, which were then attached to poly(styrene) (PS) beads using a combined swelling-heteroaggregation method.[408] Also poly(*t*-butylacrylate) beads prepared by mini-emulsion polymerization and then decorated with Au nanorods of distinct aspect ratios have been reported as SERS substrates.[386] The simplicity of this approach, associated to well established methods for metal nanoparticles synthesis, is well-suited for the up-scale fabrication of such composites and their application as sensitive analytical platforms.

6.3 In situ polymerization or "grafting from" approach

Current polymerization techniques can be adapted to obtain nanocomposites containing metal NPs as the SERS active phases. These include polymerization techniques such as (mini)emulsion, suspension, atom transfer radical polymerization (ATRP) and reversible addition fragmentation chain transfer (RAFT). In "grafting from" approaches, usually the metal NPs are first surface modified with initiators or chain transfer agents that allows polymer growth from the metal surfaces.[414] In situ emulsion polymerization has been used to coat inorganic particles ranging the micrometer to nanometer scale.[415, 416] In brief, this polymerization process involves the formation of stable oil-in-water emulsions composed by small droplets of the hydrophobic monomer dispersed in water that act as reactors after an initiator has been added. These micelles might contain surface modified inorganic NPs that at the end of the polymerization are coated or attached to the as prepared polymer. These nanocomposites can result in highly sensitive SERS platforms because the porosity of the polymer coat can trap diffusing molecules in regions close to the metal surfaces. This molecular entrapping effect has been reported by Contreras-Cáceres *et al.* for microgels of poly-(N-isopropylacrylamide) (pNIPAM) containing Au and Au@Ag nanospheres or, Au and Au@Ag nanorods. [21, 377, 417] In these nanocomposites, the thermoresponsive polymer shells can trap molecules of the analyte and enhancement factors of about 10^5 have been reported.[21, 377, 417] This allowed ultra sensitive SERS analysis of organic molecules such as 1-naphtalenethiol, 2-naphtoic acid and Nile blue A.[21, 377, 417] More recently, magnetic properties were added to such SERS platforms that allowed fast removal of the analyte from solution prior the SERS analysis.[52] The encapsulation of Fe_3O_4@Ag NPs with thermoresponsive pNIPAM shells promotes the creation of dynamic hotspots by temperature increase, because the metal particles became closer to each other. The usefulness of these substrates has been demonstrated in the monitoring of pentachlorophenol Raman which is an environmental pollutant.

A variant of emulsion polymerization involves the use of mini-emulsions containing organically capped NPs that form nanosized reactors for polymerization.[418, 419] The final properties of the nanocomposites depend on several parameters such as the amount of monomer, (co)surfactant, size and surface coating of the inorganic NPs (Figure 11).[419] Several nanocomposites obtained via miniemulsion polymerization have been reported including some of interest for SERS analysis.[366, 420-423] For example, Ag NPs encapsulated in poly(butyl acrylate) (PBA) are effective for SERS detection of thiosalicylic acid, even when submitted to a temperature cycle (-60ºC to 65ºC), suggesting that the thiosalicylic acid molecules were retained close to Ag NPs and trapped by the polymer network.[366] Also, DNA nucleobases have been studied by SERS by using polymer nanocomposites obtained via miniemulsion polymerization.[365, 423] An interesting perspective for further developments using these nanocomposites as SERS substrates is the functionalization of the polymer chains aiming the capture of target analytes.

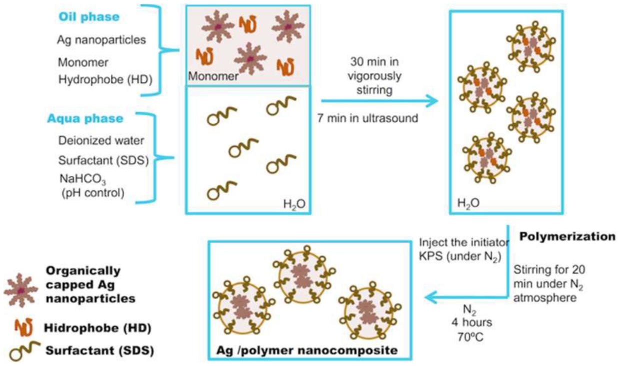

Figure 11: Illustrative scheme for the preparation of Ag/polymer nanocomposites using minimemulsions.

There are a few reports on the use of Atom-Transfer Radical Polymerization (ATRP) and Reversible Addition Fragmentation Chain Transfer Polymerization (RAFT) to produce metal/polymer SERS substrates. ATRP involves an atom transfer step for polymer chain growth and offers the ability to control the molecular weight and dispersity of the resulting polymer.[424-426] Core/shell structures obtained by ATRP from surface modified Ag and Au can be applied in several areas such as catalysis, drug delivery, environmental monitoring and SERS detection.[425-428] Hence, Gehan *et al.* have reported the SERS detection of methylene blue using Au/pNIPAM hybrids.[427] The Au/pNIPAM nanocomposites behave as thermosensitive platforms, showing enhanced Raman signals for the dye molecules when increasing temperature. Duan and co-workers have fabricated SERS sensors selective for Cd^{2+}, by coating via ATRP Au NPs with a Raman reporter with specific affinity for Cd^{2+}.[428] Multiplex detection of heavy metal ions by using this strategy is regarded as an interesting perspective for such composites.

RAFT polymerization is a controlled radical polymerization technique very often used to prepare polymers containing sulphur end groups, such as dithioesters, thiocarbamates, and xanthates, which can be further reduced to thiols.[370, 429] This technique involves multistep synthesis and sequential purification procedures, allowing the control of the polymer molecular weight, the dispersity and promotes variable molecular architectures, such as linear block copolymers, stars, brush polymers and dendrimers.[370, 430, 431] Due to the diversity of different functionalization that can be performed on the polymer chains, nanocomposites prepared by this route are of great interest for SERS namely in fundamental research. For example, these functionalized hybrid materials can provide information about diffusion of analytes within the polymer network until adsorption at the metal surface and allows assessment of SERS tags and laser source for molecular targeting.[370, 430, 432] Blakey *et al.* have coated the surface of Au NPs encoded with a variety of SERS reporters, using different polymers obtained via RAFT that contained dithiocarbamate end groups for the detection of 2-naphthalenethiol and 2-quinolinethiol.[370]

7. Self-assembled monolayers (SAM)

Self-assembled monolayers (SAM) can be employed to modify the surfaces of metal NPs in order to confer diverse types of functionalization groups.[433] In this case, the adsorption of organic molecules with pendent functional groups on the metal surfaces envisages the formation of ordered monolayers that coat the metal NPs.[433-435] These monolayers not only change the interface properties of the NPs[436, 437] but also preserve the integrity of the metal cores, preventing particle agglomeration[434] and protecting the SERS tags attached to the metallic NPs.[195, 438]

The interaction between metal surfaces and thiol compounds have been investigated by SERS and using metal NPs combined with SAM.[439-442] Organosulphur molecules such as alkanethiols and dialkyl disulphides coordinate to metal NPs, namely those of Au, Ag, Cu and Pd.[433, 443] Hence, well-ordered and densely packed SAM formed by these molecules on metal NPs have been exploited to produce SERS substrates. SAM attached to metal NPs have also been described for other compounds, including thio-amines, organosilicon derivatives, polymers and biomolecules.[444-446] The attachment of compounds of biological interest to SAM coated metals has been achieved by several mechanisms that differ on the type of bonding between the biomolecule and head groups of the SAM (Figure 12): I) immobilization through non-covalent interactions (A,C); II) immobilization through covalent interaction (B,D).[433]

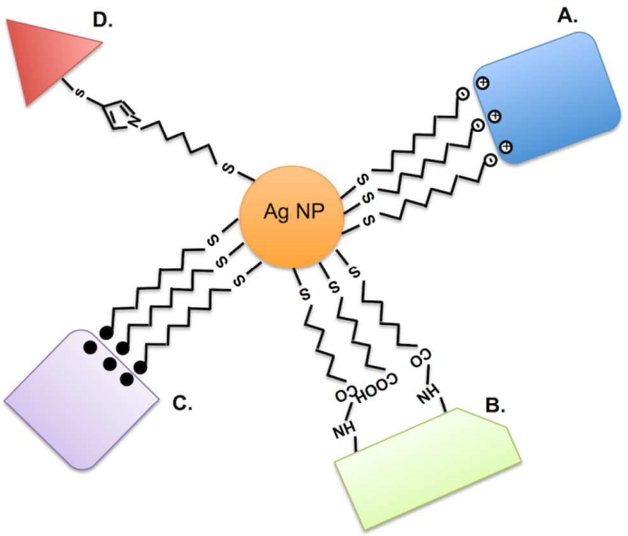

Figure 12: Immobilization strategies of biomolecules to SAM coating metal NPs mediated by distinct types of chemical interactions: A) electrostatic interaction; B) covalent bonding; C) hydrophobic forces; D) molecular recognition such as antigen–antibody.

Mechanisms of group I, include the attachment of biomolecules on SAM through electrostatic, hydrophilic and hydrophobic interactions.[433] SAM with positively charged ammonium groups or negatively charged carboxylate groups are likely to attach biomolecules via electrostatic interactions.[433] Kalaivani *et al.* have reported the attachment of methemoglobin to head carboxyl groups of 9-mercaptononanoic acid SAM formed at the surface of Ag NPs, by electrostatic interaction.[447] The electrostatic attachment of (ferro)cytochrome C to 2-mercaptoethanesulfonate SAM over Ag have also been described at variable pH.[448]

The immobilization of proteins on functionalized SAM can be achieved via covalent bonds by reacting unprotected functional groups of the protein.[433] For example, the amine groups available in the protein (e.g. lysine residues) can react with carboxylic, epoxide or aldehyde groups of SAM; the carboxylic groups available in the protein (e.g. aspartame residues) can react with terminal amine groups of SAM.[449] Thus SAM coated metal NPs have been used in SERS analysis of covalent attached breast cancer gene,[450] anti-human insulin,[451] and DNA.[449] Bioconjugates due to specific molecular recognition involving antigen–antibody, avidin-biotin, streptavidin-biotin or neutravidin-biotin interactions, are frequently used in SERS analysis of spotted peptide, peptide-protein or protein-antibody systems.[433, 452-455] These strategies generally aim low detection limits and high selectivity in SERS bioanalysis. Hence, Sa *et al.* have reported a detection limit of 48 ng/mL for biotin, using avidin attached to Ag NPs as the substrates, using excitation lines at 633 and 532 nm[454]; Wang and co-workers have demonstrated selective recognition of IgG when biotin modified with antibodies have been attached to Au NPs, followed by immobilization of avidin modified with Raman-active dyes.[455]

Because the application of SERS substrates based on NPs coated with SAM has been of special relevance for biorecognition, biotagging and selective detection,[449, 456-458] non-specifc random adsorption of untargeted molecules should be limited [434] and thereby the use of cross-linkers to promote specific functionalization of the SERS substrates.[457-459] SERS-encoded NPs involves the attachment of one or multiple organic dyes as signature reporters onto metal NPs to produce plasmonic encoded tags.[445] These SERS tags attached to metallic NPs can be encapsulated by polymers, biomolecules or glass shells, aiming biocompatibility and targeting functions.[375, 460] For instance, Boca *et al.* have produced SERS tags using small aggregates of Au NPs coated with PEG-SH for the detection of L-ascorbic acid inside human retinal cells.[460] Nie and co-workers have reported the use of PEG-SH coated Au NPs for in vivo tumor targeting and DNA detection by SERS.[195, 461]

8. Nanocomposites as new SERS platforms for chemical detection

As reviewed above, the last decade has assisted to significant developments on the fabrication of SERS substrates that placed this spectroscopic method as one of the most sensitive analytical tools to identify chemical species at vestigial levels. Table 4 lists hybrid nanostructures presented in the sections above and their respective applications, which clearly show the diversity of fields in which SERS can be applied. This section highlights a few applications with a particular emphasis on hybrid SERS substrates used as platforms for chemical detection.

8.1 Enhancement factors in SERS chemical detection

In practical terms, it has been useful to define a parameter that accounts for experimentally observed SERS enhancement factors. In its simplest definition, the EF is the ratio between the Raman signal obtained under SERS conditions and the signal obtained under conventional Raman conditions, using the same instrumental set up for the same analyte.[45, 462, 463] However, this is a simplified definition to obtain a quantitative parameter describing the EF due to the diversity of possible situations of SERS analyses [462]. Le Ru *et al.*[45, 462, 463] have distinguished three types of SERS EF: i) single-molecule enhancement factor (SMEF), ii) SERS substrate enhancement factor (SSEF) and iii) analytical enhancement factor (AEF).

The single-molecule enhancement factor (SMEF) comes from theoretical estimations and can be defined as the SERS enhancement obtained by a certain molecule at a specific point of the substrate. This SMEF depends on several parameters such as the Raman tensor of the probe and its orientation/exact position on the SERS substrate, the SERS substrate geometry, the orientation of the SERS substrates in relation to the direction and orientation of the incident laser.[45, 462, 464] Thus, the SMEF is defined as the ratio of the SERS intensity of the probed molecule (I_{SMSERS}) over the average Raman intensity per molecule of the same probe (I_{SMRS}):

$$SMEF = \frac{I_{SMSERS}}{I_{SMRS}} \qquad (5)$$

Table 4: Hybrid nanostructures and their applications

Hybrid nanostructures	Applications
Metal coated solid surface	Biomolecular detection,[231, 243, 245, 246, 251] Biomedical diagnosis and target detection,[252, 260, 465-470] Environmental monitoring,[471-476] Cellular imaging,[246] Chemical fingerprinting,[256] Preservation and cultural heritage,[477-483] Security applications,[484, 485]
Core/shell nanoparticles	Immunoassay analysis,[264, 276] Biomedical diagnostic and target detection,[260, 265, 268, 277, 278, 286, 299] Sensing and therapy,[267] SERS mapping and imaging,[254, 374] Biomolecular detection,[266, 270-272, 277, 279, 282, 289, 293, 297, 486-490] Environmental monitoring,[290, 292, 491] Assisted photocatalysis [288]
Metal/Carbon nanostructures	Biomolecular detection,[304, 314, 319, 322, 323, 326, 337, 339, 340, 342] Heavy metals detection,[317, 338] Biomedical diagnostic and target detection,[312, 313, 316, 321, 332, 343] SERS mapping and imaging,[331, 335, 336] Photothermal therapy,[318] Immunoassay analysis,[321, 340] *In vivo* molecular imaging of animal or plant tissues,[321] Environmental pollutant detection,[328, 332, 347]
Metal/porous materials	*In situ* sensing,[348] Environmental monitoring,[349, 352] Biomolecular detection,[353, 354, 356-358, 492] *In vivo* monitoring,[355]
Metal/natural polymers	Biomolecular detection,[364, 369, 390, 391, 393, 397, 398, 493] SERS mapping and imaging,[368, 372, 375, 389] Immunoassay analysis,[373] Biomedical diagnostic and target detection,[373, 392, 396] Single-molecule detection,[375] Environmental monitoring,[375, 413] Detection and quantification of anionic chromophores,[494]
Metal/synthetic polymers	Biomolecular detection,[365-367, 377, 386, 405, 409, 417, 495] Environmental monitoring,[52, 375] SERS mapping and imaging,[375, 408, 409] Bioassays detection,[370, 412] Thermosensitive sensors,[496] Biomedical diagnostic and target detection,[396, 404, 410, 415, 423, 427, 497] Heavy metal detection,[428]
SAM metal nanostructures	Biomolecular detection,[437, 440, 441, 447, 448, 459, 498] Biomedical diagnostic and target detection,[195, 445, 450, 453, 456, 499-510] Environmental monitoring,[471, 511] Immunoassay analysis,[451, 452, 454, 455] SERS analysis in living cells,[460] Security applications,[512]

The SERS substrate enhancement factor (SSEF) takes into account the intrinsic enhancement of the SERS substrate itself, by relating the SERS intensity with the number of molecules adsorbed on the substrate (N_{NRS}) and is expressed by [45, 462, 463]:

$$SSEF = \frac{I_{SERS}}{I_{NRS}} \times \frac{N_{NRS}}{N_{SERS}} \qquad (6)$$

I_{SERS} and I_{NRS} are the SERS and conventional Raman scattering intensities, respectively, and N_{SERS} and N_{NRS} are the number of molecules that contribute to the scattering intensity in the SERS and conventional experiments, respectively. This definition does not provide enough details about the quantification of the molecules probed under SERS and non-SERS conditions. These values are normally calculated as the number of molecules that cover the metallic surface in SERS and as the scattering volume of molecules in the solution for the conventional Raman.[23] The SSEF has been extensively used because gives a good estimate for the average enhancement observed for a given SERS substrate.[23, 62, 187, 189, 513] However because the SERS effect is distance dependent, it is appropriate only for substrates in which a surface monolayer is under analysis.

For colloidal metal substrates, the use of the analytical enhancement factor (AEF) has been very common and is calculated by the expression:[45, 462, 463]

$$AEF = \frac{I_{SERS}}{I_{RS}} \times \frac{C_{RS}}{C_{SERS}} \qquad (7)$$

C_{RS} is the concentration of the analyte in a test bulk solution, C_{SERS} is the concentration of the analyte adsorbed on the substrate in the sample analysed by SERS, I_{SERS} is the SERS intensity, and I_{RS} is the conventional Raman scattering intensity. The AEF should be analyzed with some caution because depends on several parameters such as the adsorption properties and surface coverage (monolayer or multilayers) of the chosen analyte.[462] However, because the calculations rely on the use of experimental data ready available, the AEF has been widely used on analytical applications using metal colloids as SERS substrates.[378, 386, 514, 515]

8.2 Biodetection

In the context of biodetection, fundamental SERS studies have been applied to study the structure, conformation and charge transfer in biomolecules, interactions between different biomolecules or drugs due to their molecular structural modifications and interaction between metal-adsorbate. This subject has gain special attention in the last years due to the availability of SERS active platforms to study metal-analyte interactions and molecular conformation and orientation on the metal surface. [283, 293, 311, 325, 329, 435, 461, 490, 497]

SERS biosensors based on hybrid nanostructures have been investigated in targeting DNA,[300, 500] proteins,[465] cancer markers,[276, 450, 456] HIV gene[470] and bacteria[466, 501]. The diagnosis of cancer [195, 286, 467, 502], neurodegenerative diseases [498, 503] and diabetes.[504, 505, 508, 509] have also been attempted by using such materials. Van Duyne *et al.* have reported SERS-based glucose sensors for *in vivo* protocols that help to control diabetes.[252, 504, 506, 507] The preparation of such substrates involved the functionalization of silver films deposited over nanospheres (AgFON) surfaces with SAM of decanethiol and mercaptohexanol. Lower blood glucose concentrations, as low as 15 mg/dl, i.e. complying with International Organization Standard requirements (DIN EN ISO 15197), have been reported.[510] Nie et al. have described the use of SERS based on pegylated Au NPs for tumor targeting in living animals.[195] In this work, molecular Raman reporters, such as organic dyes, were attached to citrate-stabilized Au NPs and then stabilized by thiol-modified polyethylene glycols. The pegylated Au NPs were conjugated to tumour-targeting ligands such as single-chain variable fragment antibody. The tumour link to the pegylated Au NPs was accomplished and confirmed by SERS with the enhancement of the SERS tags already attached to the metallic NPs such as diethylthiatricarbocyanine and malachite green. In this particular work, they have succeeded on the targeting of tumour such as epidermal growth factor receptors on human cancer cells and in xenograft tumour models.

8.3 Environmental monitoring and security applications

The trace detection of explosives [512, 516] and chemical warfare species [475, 484] have gained special interest in the last decades.[14, 135, 517, 518] Hybrid nanostructures that facilitate diffusion and trapping of organic pollutants at the SERS active surfaces, are particularly effective for these purposes. In this sense, solid supports with attached metal NPs are attractive for environmental monitoring because are also robust in real analytical contexts, have long shelf life and can be made selective.[471-474, 485, 519] Olson *et al.* have demonstrated that complex environmental matrices can be analyzed by selective adsorption of organic pollutants onto SERS substrates comprising immobilized Au NPs coated with C-18 alkylsilanes.[472] Alvarez-Puebla *et al.* have prepared evaporated Au films for SERS analysis of humic acid; the Au NPs were fixed on glass supports onto which drops of fulvic acid could be analyzed by SERS.[474] Alak and Vo-Dinh have prepared filter papers containing Ag coated microspheres for the detection of organophosphorus chemicals in soil samples, such as methylparathion, fonofoxon and cyanox.[485] Silver substrates obtained by the NSL technique have been employed for the detection of half-mustard agent.[475] In this case, spherical particles coated with Ag were surface modified by functionalized SAM and exposed to 2-chloroethyl ethyl sulphide vapor over 24h. Interestingly, the authors have shown possibility for device integration by coupling the SERS sensor to a field portable spectrometer, promoting real-time detection with high quality spectra.

8.4 Other practical applications

Counterfeiting has been appointed as a major illicit activity with significant negative impact in economics, because many brand items are subject of forging or product diversion, resulting in significant loss of revenue for the brand owner. In order to limit this activity, valuable objects can be tagged with robust and covert identification labels. In this context, SERS nanotags have been successfully used for authentication of different objects, encode jewellery goods and implanted in coinage or bank notes during the printing process [520, 521]. An illustrative example involves the use of Au spheres functionalized with trans-1,2-dipyridylethylene or 4,4'-dipyridyl, which has a specific Raman signature and can act as molecular reporters. The SERS tagged Au NPs are encased in silica shells and then added to a variety of supports to be used for the labelling and authentication of different objects.

The SERS technique has been implemented in other areas such as art preservation or cultural heritage studies. SERS became an adequate method for the detection and identification of colorants, natural dyes and glazes in artworks.[477, 478, 481-483] Usually these methods aim high fluorescence quenching with concomitant enhancement of the Raman signal by using SERS active metal surfaces. A possible approach involves dye extraction from an host material by using diminute amounts of sample material that can be easy handled. For example, Whitney *et al* have prepared Ag island films using electron beam deposition on carminic acid and laccaic acid, which are colorant particles extensively used in old masters' paintings.[483] Brosseau *et al.* have prepared films by thermal deposition of Ag NPs onto SiO_2 particles coating a glass substrate (AgFON) for the identification of organic dyes of interest to art conservation.[482] The combination of thin-layer chromatography (TLC) and SERS was used for the separation and identification of historical textile samples such as lac dye and cochineal in red and pink dyed fibres from historical artworks.

Recent progresses on new hybrid nanostructures as SERS substrates have been associated to the development of new instrumentation capabilities, namely portability equipment to be used not only in the laboratory, but also in other contexts, such as fieldwork. Currently, portable Raman spectrometers are available, allowing real-time chemical detection by SERS in areas such as environmental, forensic science and home security.[135, 476, 491, 522, 523] Young *et al.* have performed SERS studies using portable Raman equipment and AgFON substrates, using polystyrene latex nanospheres as template, for the detection of a variety of analytes, namely dyes and benzene molecules.[476].This work is an illustrative example of the growing literature demonstrating that SERS is becoming a low-cost technique when associated to compact and readily available equipment while retaining the necessary sensitivity for analytical applications. Also, Li *et al* have demonstrated that vestigial pesticides can be detected in fruits by using portable Raman spectrometers applied to shell-isolated nanoparticles spread on the fruit peel.[491] In this case, Au NPs (55 nm) coated with ultrathin shells of silica or alumina (Au/SiO_2 or Au/Al_2O_3 NPs) have been used as substrates. As an example, it has been reported that each nanoparticle can act as an Au tip in the TERS system, and thus this technique simultaneously brings thousands of TERS tips to the substrate surface to be probed.

The current developments of techniques such as Raman imaging, through high resolution Raman mapping with short measurement times, have brought a new look on SERS substrates. Using Raman imaging, substrates can now be evaluated for its SERS activity over a specific area, with spacial resolution within the submicrometric range. This allows to clearly identify which parts of the substrates are the most intensive SERS active, e.g. in hybrid substrates or in lithography patterns.[524] A SERS-based quantitative biosensing on aptamer-functionalized nanopillars, using a large area Raman mapping technique was recently reported.[525] Reliability and statistical reproducibility of quantitative SERS analysis were improved by the large area Raman mapping. A SERS imaging method was also explored that allows simultaneous determination of two or more biomarkers on a cell surface.[526] Using DNA-gold nanoaggregates as Raman probes, the signal can be significantly enhanced and the distribution of biomarkers can be readily visualized by SERS imaging.

Conclusions

Since the discovery of SERS, the development of chemical detection methods based on this technique has been associated to the use of more efficient substrates. Among other factors, including the availability of more powerful and versatile Raman instruments and deeper knowledge on underlying fundamental phenomena, the research in SERS active nanomaterials has contributed significantly to regard today this spectroscopic method as an important tool in chemical detection, especially for trace analysis and biodetection. In this work, a review of recent developments on hybrid materials for SERS studies and diverse applications was made. Apart from showing in certain cases increasing SERS sensitivity, hybrid nanostructures can also be designed aiming multifunctional purposes, thus putting in perspective the application of SERS in innovative analytical contexts. Trace detection of targeted analytes by using functionalized platforms and chemical monitoring under the action of specific external stimuli, are examples of future developments in this field, which will also boost more sensitive instrumentation with portability capabilities.

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