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SERS Research Applied to Polymer Based Nanocomposites

Sara Fateixa, Helena I.S. Nogueira and Tito Trindade

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Abstract

Polymer based nanocomposites containing metal nanoparticles (e.g. Au, Ag) have gained increased attention as a new class of SERS (Surface Enhanced Raman Scattering) substrates for analytical platforms. On the other hand, the application of SERS using such platforms can also provide new insights on the properties of composite materials. In this chapter, we review recent research on the development of SERS substrates based on polymer nanocomposites and their applications in different fields. The fundamentals of SERS are briefly approached and subsequently there is a reference to the strategies of preparation of polymer based nanocomposites. Here the main focus is on SERS studies that have used a diversity of polymer based nanocomposites, highlighting certain properties of the materials that are relevant for the envisaged functionalities. A final section is devoted to the joint use of Raman imaging and SERS in nanocomposites development, a topic that presents a great potential still to be explored as shown by the recent research in this field.

Keywords: SERS, metal nanoparticles, nanocomposites, polymers, Raman imaging

1. Introduction

There has been a long-standing interest in the application of metallic nanoparticles (NPs), in particular of gold (Au) and silver (Ag), due to their unique optical properties [1–6]. The dispersion of very small (submicrometric to nanometric) metal particles in materials that act as host matrices (e.g. glass) has been empirically exploited to confer bright and colorful effects, resulting from scattering and absorption of visible light. In fact, there are several examples of earlier technological applications that include the use of fine divided gold in glass materials in order to obtain beautiful colors, such as in stained glass windows [7, 8]. Nowadays, metal NPs are considered crucial in a series of devices derived from nanotechnological approaches

and which are expected to expand in the near future in several applications and techniques. Among these techniques, Surface Enhanced Raman Scattering (SERS) has emerged in the past decades with great importance. Although the discovery of the SERS effect dates back to the 70's, [9] in the last decades, this technique has been improved due to the huge progress observed in Raman instrumentation and also in recent research specific to nanoscale materials. Indeed, the design of SERS active and highly sensitive analytical platforms has been a major goal in several fields, due to the impact in trace chemical analysis, environmental monitoring, medical applications and food safety [10–16].

This chapter intends to present recent developments concerning polymer based nanocomposites containing metal nanofillers for SERS applications, in some situations based on studies of metal loaded polymers prepared in our laboratory. In order to contextualize the SERS application of these polymer based nanocomposites, the synthesis of the nanostructures and some fundamental aspects of SERS are briefly introduced [17–25]. Polymer based composites for SERS, containing metallic fillers, have been largely documented for the vestigial detection of several bio-analytes. Illustrative examples on the use of polymer based composites as new platforms for SERS are described in more detail, reviewing their use for chemical analysis. The importance of Raman imaging in SERS studies is also explored because is a recent development with a great potential for the research on new SERS substrates.

2. Fundamentals of surface enhanced Raman scattering

Chandrasekhara Venkata Raman (Nobel Prize in Physics, 1930) and his student Kariamanickam Srinivasa Krishnan reported in a scientific paper entitled “A new type of secondary radiation,” the phenomenon that we now call the Raman effect [26]. This effect involves inelastic scattering of light when the photons strike a certain medium containing molecules. Although the number of photons resulting from the elastic dispersion (Rayleigh scattering) of light coming from a laser source is greater than that of the inelastic dispersion, thus giving rise to a more intense signal, it is the spectral information collected from the inelastic collision that is of interest for Raman spectroscopy [27–30]. Indeed, the bands that are observed in a Raman spectrum (Stokes and anti-Stokes shifted in relation to the excitation line) are associated to certain vibrational modes existing in molecules and materials and can thus give information about their structure and other properties. The use of Raman spectroscopy in certain areas of application was, until recently, limited by two main factors. One of these factors can be considered extrinsic to the phenomenon and depends essentially on the development of more sensitive and affordable equipment. The other factor is intrinsic to the Raman effect, since it is a physical process that results in low-intensity spectral bands, because of the low scattering cross-section (10^{-29} cm² molecule⁻¹), limiting its use as a high sensitive analytical technique [30–32].

The SERS (surface enhanced Raman scattering) effect was discovered about 44 years ago during studies applied to a silver electrode and an aqueous solution of pyridine [9]. Unexpectedly, this experiment revealed an increase in the Raman signal of pyridine adsorbed on the metal

surface. A few years later, other research groups advanced the currently accepted explanation for this observation [33, 34]. The interpretation given considered that the Raman signal intensification occurred due to adsorption of molecules on rough metallic surfaces. It is generally accepted today that the intensification occurring in SERS is due to two distinct mechanisms: the chemical interaction of the analyte with the metallic surface (signal intensification $10-10^2$) and the enhancement of the local electric field at the junction of the metallic NPs (signal intensification can reach up to 10^{11}) [32, 35, 36]. The chemical mechanism (CM) for the SERS signal enhancement is related to the adsorption of molecular species on the metal surface, namely the surface selection rules, the type of interaction between the metal and the molecule and the chemical nature of the adsorbed molecule itself [36–38]. The electromagnetic mechanism (EM) is the dominant contribution to SERS and does not depend necessarily on the establishment of a chemical interaction between the analyte and the metal surface, contrary to what happens in the chemical mechanism. According to the EM, the intensification of the local electromagnetic field is mainly due to the excitation of the surface plasmons of the metal by the incident light [39–41]. While the CM is a short-range effect, the EM is a long-range effect, in the sense that it does not require that the molecular species is in contact with the metal surface and can still be observed a few nanometers of distance from the metal surface. **Figure 1** presents a scheme of

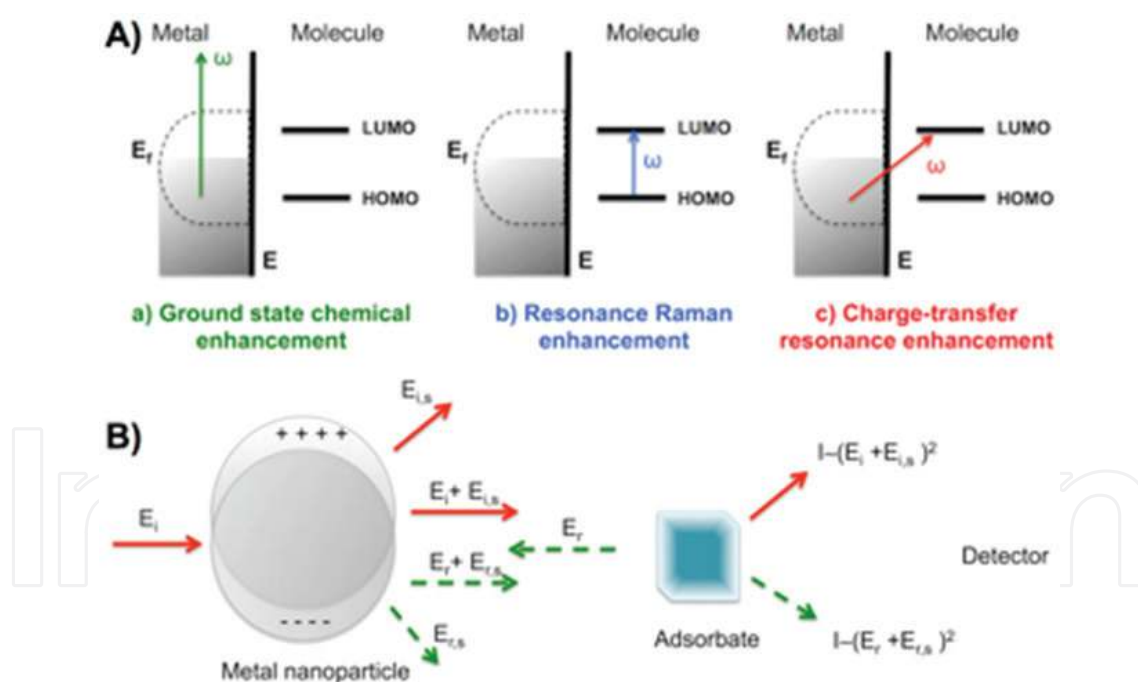


Figure 1. (A) Scheme illustrating the chemical mechanism (CM) that occurs in SERS. (a) Ground state chemical enhancement; (b) resonance Raman enhancement; (c) charge-transfer resonance enhancement, where E_i represents the local electromagnetic field; HOMO represents the highest occupied molecular orbital and LUMO represents the lowest unoccupied molecular orbital); (B) Scheme illustrating the electromagnetic mechanism (EF), in which the I represents the intensity of Raman; E_i represents the incident electric field; $E_{i,s}$ represents the field which is intensified by the metal and $(E_i + E_{i,s})$ represents the incident enhanced field; E_r represents the scattered Raman field, which can be intensified by the metal creating $E_{r,s}$; $(E_r + E_{r,s})$ represents the scattered enhanced field. ([10] - Reproduced by permission of The Royal Society of Chemistry.).

the different types of contributions to the chemical enhancement mechanism and the electromagnetic enhancement mechanism in SERS.

The contribution of nanotechnology, and in particular of the Chemistry of Nanomaterials, to the resurgence of studies and applications of Raman spectroscopy in materials characterization and the improvement of analytical techniques cannot be surprising. Indeed, the SERS effect allows the range of applications of Raman spectroscopy to be expanded but it is still very dependent on the quality of the substrates used to obtain signal intensification. The substrates most used for these purposes are based on Ag and Au nanostructures, although the SERS effect using other types of surfaces have been reported [42–45]. A variety of studies have demonstrated that the enhancement of the localized electromagnetic field occurs in close vicinity of metal NPs, metal nanotips or in metal surfaces with specific nanopatterns. The positions in which the strongest enhancement of the local electromagnetic field is observed correspond to the so called hotspots, due to the strongly enhanced Raman signals observed for certain molecular adsorbates [46–52]. Chemistry provides the synthetic tools to control the morphology and size of metal nanoparticles as well as other nanostructured materials and therefore has been widely used in the development of highly sensitive and reproducible SERS substrates. It should be noted that the sensitivity of some of the SERS substrates reported in the literature allows the analyte detection at the single-molecule level [53–55]. The fact that Raman spectroscopy is a non-destructive technique and can also be used for materials imaging, are additional factors that make this technique increasingly relevant in chemical analysis and materials characterization. In particular, the SERS technique is a valuable tool for the surface characterization of materials. For example, it is possible to obtain information about the surface of a metal using molecules that once adsorbed will function as molecular probes [56]. In addition, it is possible to obtain information about the orientation of these molecules, applying surface selection rules that were established in earlier studies [11, 39, 57].

3. Polymer based nanocomposites

By definition a composite is formed by at least two distinct materials whose chemical identity is preserved in the final material. Typically, a composite contains a material (filler) that is dispersed in a larger amount of a distinct material that acts as the host matrix. In the case of having a polymer as the host, such material is referred as a polymer based composite. For the particular situation, in which the fillers have at least one dimension at the nanoscale, the material is called a nanocomposite. Hence, polymers, either synthetic or of natural origin, that contain inorganic nanoparticles form an important class of nanocomposites. In particular, polymer based nanocomposites containing metallic nanoparticles (NPs) as fillers, are the object of this chapter due to their role as hybrid substrates for SERS analysis. Several approaches have been reported in order to produce polymer nanocomposites containing metal NPs as fillers. Briefly, these preparative methods can be divided in two main categories, depending if the metal nanofillers were generated in situ or previously prepared and then used for the composite fabrication. These approaches will be designated here as i) in situ and ii) ex situ. In the in situ method, the metallic nanofillers are prepared by chemical

reduction methods in the presence of a polymer; in the ex situ approach, the metallic NPs are previously synthesized and then mixed with a polymer matrix, forming homogeneous blends composites (blending method) or, after surface modification procedures applied at the filler's surfaces [10, 58, 59]. These preparative methods will be briefly described in the next sections. **Table 1** lists some methods for preparing these composites based on polymers of natural and synthetic origin.

3.1. Chemical reduction (in situ method)

In this methodology, metallic nanofillers are produced by chemical reduction of a metal precursor using reducing agents such as sodium citrate or sodium borohydride, in the presence of a polymer. This strategy generates nanocomposites whose morphology can vary, such as in a polymeric shell and a metal core [60, 61, 77, 96, 102], a polymeric core and a metal shell [95] or a polymeric matrix having dispersed metallic fillers [68, 69, 97]. In particular cases, the polymer can act as reducing agent due to specific functional groups, avoiding the use of an external reducing agent [61, 73]. The advantages of this one-step approach relies on its

Polymer matrix	Preparative method	Metallic NPs
Natural polymers	Chemical reduction	Ag [60–72]
		Au [73–76]
		Cu [77–80]
	Blending or “grafting to” approach	Ag [66, 67, 81–87]
		Au [88–92]
		Cu [79]
		Au@Ag [93]
	UV light reduction of the metal ions	Ag [66, 94]
		Au [94]
Au@Ag [94]		
Synthetic polymers	Chemical reduction	Ag [95–102]
		Cu@Ag [103]
	Blending or “grafting to” approach	Ag [104, 105]
		Au [106–112]
		In situ polymerization or “grafting from” approach
	Au [58, 108, 116, 119–124]	
	Au@Ag [125]	
	Fe ₃ O ₄ @Ag [48]	
	Electrospinning method	Ag [126, 127]
Au [126]		
Au@Ag [128]		

Table 1. Preparative methods of polymer/metal nanocomposites.

simplicity, although the resulting nanocomposites may exhibit inhomogeneity in terms of morphology and fillers distribution in the polymer matrix [10, 129].

In situ preparation is commonly used to prepare biopolymers based nanocomposites because natural polymers might be used to induce control over NPs size and aggregation state [63, 70], promoting the required biocompatibility for specific applications namely medical diagnostic and target detection in SERS [60, 64]. Polysaccharides such as chitosan [64, 65, 71, 72, 74], agarose [60, 63, 70], glucose [102], hyaluronic acid potassium salt [75] and cellulose [67–69] have been used as polymeric matrices for the one-step preparation of such polymer based nanocomposites. The preparation of composites containing polysaccharides in which in situ chemical or UV light reduction of metal ions occurred has been subject of great interest. Indeed, these nanocomposites can be applied in a variety of domains such as antimicrobial agents [66, 80], platforms for chemical detection [68, 69], textile dyeing monitoring process [67] and electronic paper [79]. For example, bacterial cellulose has been investigated as an alternative host matrix to vegetable cellulose in the preparation of electronic paper, SERS substrates and antimicrobial agents by using metal NPs as fillers. More recently, we have demonstrated that Raman imaging is a useful technique to characterize and monitor the textile dyeing process of antimicrobial fabrics [67]. **Figure 2** provides examples of cellulose composites for diverse applications.

The use of polysaccharides in the form of hydrogels have also been reported as matrices for dispersing metallic NPs, in certain cases showing capacity to collapse or be lyophilized upon drying and recover their structure by rehydration and subsequent use in SERS analysis [60, 63, 65]. For

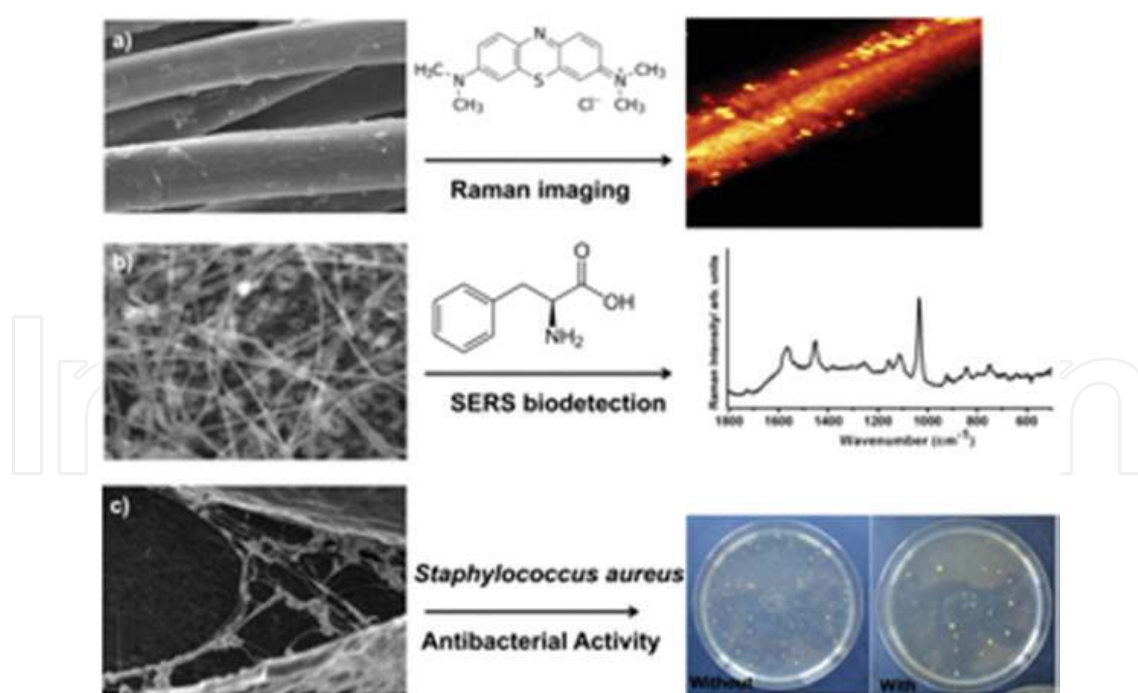


Figure 2. Examples of applications for cellulose based nanocomposites loaded with metal NPs: a) Raman image obtained using the integrated intensity of the Raman band at 1620 cm^{-1} in the SERS spectra of methylene blue 10^{-4} M using a linen based composite containing Ag NPs as substrate (excitation at 633 nm); [67] Ag/bacterial cellulose nanocomposites for SERS biodetection of phenylalanine; [69] c) Nanocomposites containing copper based NPs and cellulose to be used as antibacterial agents against *Staphylococcus aureus* [80].

example, Brust and co-workers have described the preparation of Ag loaded agarose hydrogels, in which the metallic nanofillers are trapped inside the polymer network due to the agarose capability to dry and rehydrate. In this particular case, the use of agarose as polymeric matrix provides the formation of a recyclable SERS substrate, in which the 1-naphthalenethiol used as analyte can be washed out by dialysis and the composite can be reused again [60]

Nanocomposites containing gelatin [61, 76, 77], natural rubber [73] and distinct synthetic polymers [98–101] have been also prepared using in situ methods. For instance, Wu and his team have reported the fabrication of Ag loaded poly(styrene) microspheres using the chemical reduction method for the SERS detection of organic molecules such as dyes. [98]. The authors have used the complex $[\text{Ag}(\text{NH}_3)_2]^+$ as precursor and the poly(vinylpyrrolidone) (PVP) and poly(dopamine) (PDA) as linkers to attach the Ag ions into the PS microspheres surface by hydroxylic and aminic groups.

3.2. Blending or “grafting to” approach

Blending metallic nanofillers with a polymeric matrix is a simple methodology to fabricate nanocomposites with efficient SERS activity [84, 104, 106, 107, 124]. Besides its simplicity, this is a cost-effective and easily scalable method over a large area [90, 130]. In the literature, there are some reports on the use of synthetic polymers such as poly(methyl methacrylate) [105, 109], poly(*t*-butyl acrylate) [107], polystyrene-block-poly(acrylic acid) [110] and poly(vinyl alcohol) [128] as matrices for the incorporation of metallic NPs and subsequent use as SERS platforms. Although not so common in SERS research context, natural polymers can also be used as polymeric matrices for the preparation of polymer based composites, in which water compatible metal NPs are normally used. Marsch *et al.* have reported the development of a surface enhanced resonance Raman scattering (SERRS) substrate containing Ag NPs with a positive surface charge, due to a poly-L-lysine coating, which was then used in the analysis of organic anions [86]. In their work, these polymer based composites were successfully used as SERS substrates for the detection of bilirubin, a organic molecule of clinical interest formed as a metabolic waste product of heme breakdown. More recently, Chang *et al.* have reported flexible SERS substrates based on common filter paper loaded with gold nanorods, which exhibited more than two orders of magnitude SERS enhancement compared to silicon-based SERS substrates [92]. The authors have demonstrated that these platforms are excellent candidates for trace chemical and biological detection due to their efficient uptake, and transport of the analytes from the dispersing liquid to the surface of metal nanostructures.

Other examples of bionanocomposites containing metallic NPs have been reported including those based on chitosan [81], pullulan [83], cellulose [67, 79, 82], gelatin [85, 88] and carrageenan [84, 89]. **Figure 3** illustrates the use of biopolymers and Ag NPs in the fabrication of composites for antimicrobial and SERS applications. In certain situations, these applications can be complementary, such as in the case of producing a gel that due to the presence of Ag not only has the ability for SERS detection but also lasts longer periods of time due to the antimicrobial characteristics.

In ex situ methods, the polymer can be used either as a continuous phase or as an aqueous emulsion. For example, Lee *et al.* have reported the preparation of several metallic nanofillers

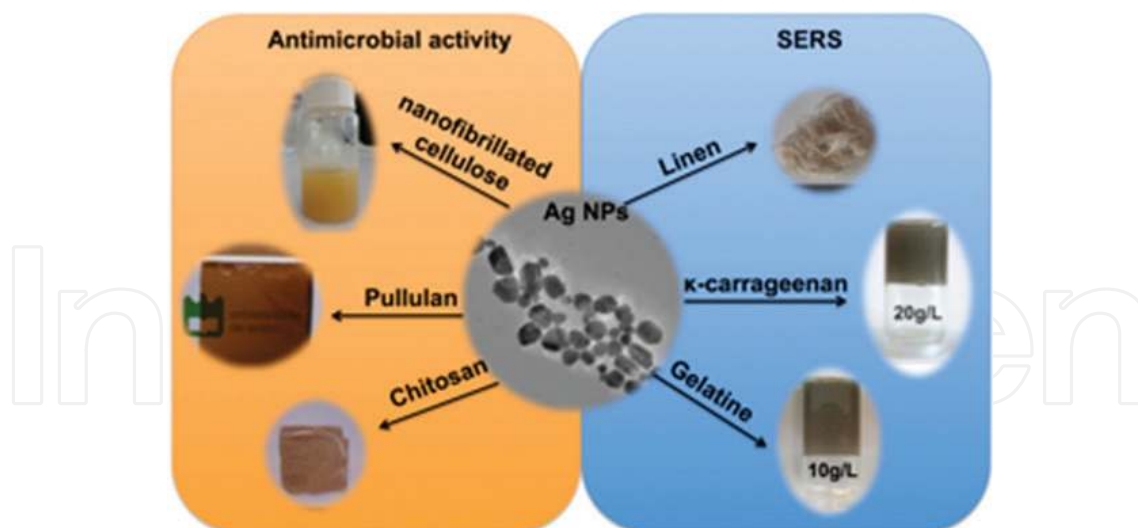


Figure 3. Blending of natural polymers and Ag NPs aiming at the fabrication of nanocomposites for SERS detection of analytes and antimicrobial applications.

with distinct sizes and shapes, which were used to decorated PS spheres stabilized in aqueous emulsion, producing active SERS platforms [104]. In addition, Fernández-López et al. have studied the thermoresponsive optical properties of poly(*N*-isopropylacrylamide) (pNIPAM) microgels doped with Au nanorods (Au NR) characterized by two different aspect ratios, observing a reversible behavior [112]. The thermoresponsive SERS sensitivity of the polymer composites was also analyzed using three different laser lines, demonstrating excitation wavelength-dependent efficiency, which can be controlled by either the aspect ratio (length/width) of the assembled Au NR or by the Au NR payload per microgel.

3.3. In situ polymerization and “grafting from” approach

Current polymerization procedures can be fine-tuned to fabricate metal load composites to be used as SERS active platforms. These include (mini)emulsion polymerization, suspension polymerization, atom transfer radical polymerization (ATRP) and reversible addition fragmentation chain transfer (RAFT). In in situ polymerization methods, the surface of the metallic nanofillers are modified with initiating species or chain transfer agents, allowing the growth of polymer chains from the metallic NPs surfaces [131]

By using the in situ emulsion polymerization, particles of the polymer based composite can be prepared with sizes ranging the micrometer and nanometer scale [117, 132]. In brief, this polymerization technique involves the formation of stable oil-in-water emulsions composed by small droplets of 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.

Other polymerization strategies comprise the “grafting from” approach using reversible addition fragmentation chain transfer polymerization (RAFT) and atom-transfer radical polymerization (ATRP). There are a few reports on the use of ATRP and RAFT to produce metal/polymer SERS

substrates. RAFT is a controlled radical polymerization approach, which involves multistep synthesis and sequential purification procedures. This polymeric approach is commonly used in the preparation of polymers with sulfur end groups, namely xanthates, dithioesters and thiocarbamates, that can be easily reduced to thiols [58, 133]. Besides the control of molecular weight and dispersity indexes of the polymers, several molecular structures can be achieved with the RAFT polymerization namely brush polymers, linear block copolymers, dendrimers and stars [58, 78, 116]. The polymer chains of the polymer based composites prepared by RAFT polymerization can be chemically functionalized with biomolecules that can be further used as SERS reports on the detection of specific analytes. In particular, metal loaded polymer composites functionalized with SERS reporters can be useful to conclude about the influence of the laser light source used in the target molecules or on the diffusion of the molecular probes through the polymer matrix. [58, 78, 134]. For example, Merican *et al.* have reported the surface modification of Au NPs with several SERS reporters, by using RAFT polymerization, in which a variety of polymers containing dithiocarbamate end groups were used. These polymer based composites were successfully used as SERS platforms for the detection of 2-naphthalenethiol and 2-quinolinethiol [58].

On the other hand, the ATRP approach controls the dispersity indexes and the molecular weight of the polymers by comprising an atom transfer step in the polymer chain growth phase in the polymerization [108, 120, 135, 136]. For example, core/shell structures prepared from surface functionalization of Au and Ag NPs by ATRP are often applied in a variety of fields such as catalysis, environmental monitoring, SERS detection and drug delivery [108, 120–122]. Mangeney and co-workers have fabricated Au-pNIPAM composites via ATRP method for the detection of methylene blue [121]. The authors have demonstrated that these hybrid materials are thermosensitive platforms, in which the Raman signal of the dye molecules increase with the increase of temperature. In addition, Yin *et al.* have reported the preparation of Au loaded polymer composites by ATRP approach to be used as SERS sensors with specific selectivity for Cd²⁺ [122].

Our own investigation in this field has the focus on the preparation of such polymer based composites by in situ polymerization using distinct synthetic strategies, such as emulsion [137], suspension [138, 139] and (mini)emulsion polymerization [140, 141], a variant of emulsion polymerization. In the latter, the emulsions are nanosized and organically capped NPs can be allocated in the interior of the hydrophobic monomer droplets [142, 143]. The final properties of the polymer based composites can be tuned by varying several parameters namely the amount of monomer, surfactant, the size and surface organic capping of the inorganic NPs [143]. We have reported several organically capped NPs successfully coated with a series of polymers, using the (mini)emulsion polymerization, namely metallic NPs [113–115, 119], quantum dots [141, 144–146], ferromagnetic NPs [147] and lanthanide compounds [148, 149] Esteves *et al.* have reported pioneer research in this field by describing the encapsulation of TOPO capped CdS and CdSe quantum dots (QDs) using poly(styrene) and poly(*t*-butylacrylate) as polymeric matrices [141]. They have demonstrated that by using the (mini) emulsion polymerization method, organically capped QDs NPs could be used as fillers leading to nanocomposites that still exhibit the typical photoluminescence of the dots at room temperature. Pereira and co-workers have synthesized oleylamine capped EuS nanocrystals from single-molecule precursors and investigated their use as fillers for polymer based

composites [148]. In this work, it was demonstrated that the magnetic properties observed for the EuS/poly(styrene) nanocomposites have varied in comparison to the starting EuS nanocrystals, which result from surface effects due to dispersion of the EuS nanocrystals within the polymer beads. Martins *et al.* have obtained stable aqueous emulsions of distinct polymer based composites containing either Au NPs or CoPt₃ NPs *via* (mini)emulsion polymerization method. In the former, the optical properties of such composites depend not only on the Au NPs employed in their synthesis but also on the resulting morphology for the final composites [119]. In the later, they have demonstrated for the first time the preparation of a ferromagnetic polymer based composite composed by a magnetic core of CoPt₃ NPs encapsulated by poly(*t*-butylacrylate) [147]. As a proof of concept, the chemical binding of bovine IgG antibodies to the hydrolyzed surfaces of CoPt₃/PtBA nanocomposites was described. This strategy has established an interesting route for the development of nanocomposites materials for *in vitro* bioanalysis assays, which have been extended to other magnetic materials [150]. **Figure 4** presents TEM images of several polymer based composites prepared by (mini)emulsion polymerization. Although this method allows the preparation of diverse

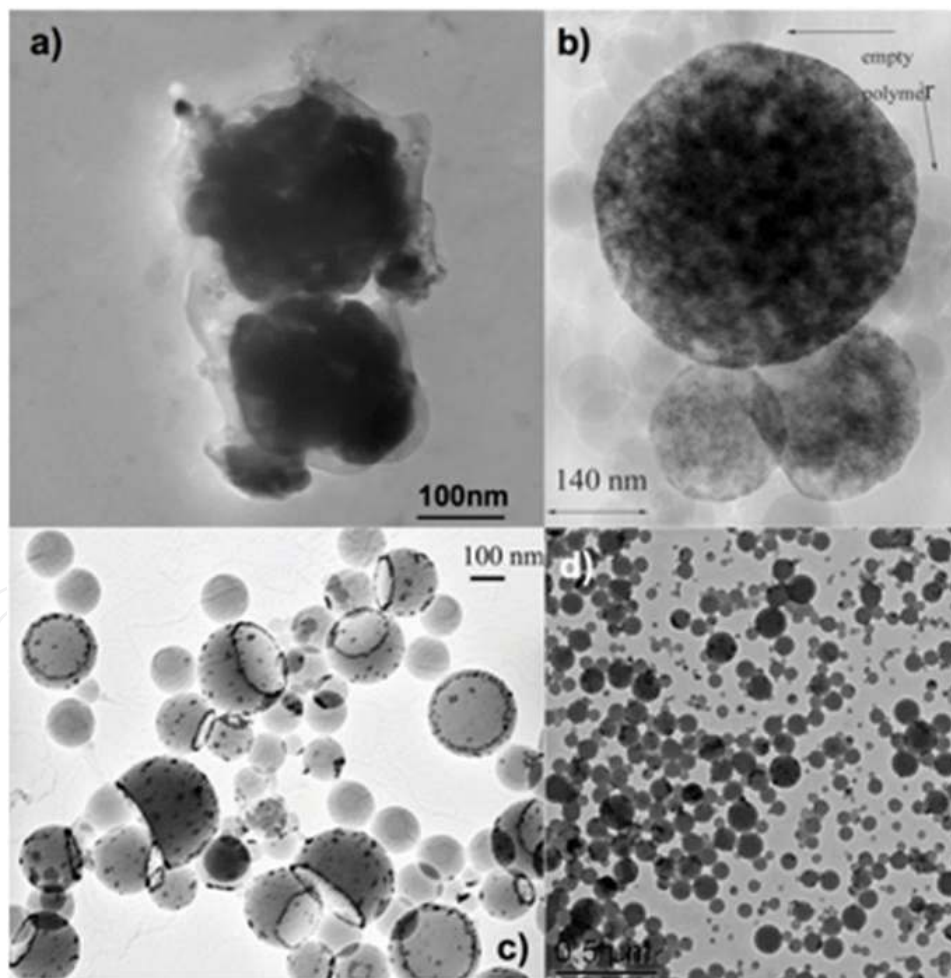


Figure 4. TEM images of nanocomposites prepared by (mini)emulsion polymerization: a) Ag/poly(methyl methacrylate); [115] b) EuS/poly(styrene) ([148]—Reproduced by permission of The Royal Society of Chemistry); c) Au/poly(styrene) (adapted with permission from [119]) and d) Fe₃O₄/poly(styrene) particles mixed with free PS beads (courtesy of P. C. Pinheiro).

metal loaded polymer nanocomposites, there is also the presence of free polymer particles in the final emulsion. For certain applications this is not necessarily a limitation but nevertheless other options should be considered. For example, the use of magnetic NPs as fillers, such as in the case shown in **Figure 4d** for magnetite in poly(styrene), allows the application of magnetic separation in order to separate the nanocomposite from the free polymer beads.

4. Metal loaded polymer nanocomposites as SERS substrates

In the last years, a series of polymer-based nanocomposites containing plasmonic metal NPs have been investigated as a new class of SERS substrates. The preparation and properties of such

Polymer matrix		Metallic NPs	Applications	
Natural	Gelatin	Ag	Biomolecular detection [61] Environmental monitoring [85]	
		Cu	Biomolecular detection [77]	
	Gum Arabic	Ag	Biomolecular detection [62]	
	Agarose	Ag	Biomolecular detection [63, 70] SERS mapping and imaging [60, 63] Ultradetection or single molecule detection [60]	
		Cellulose based materials	Ag	Biomolecular detection [69] SERS mapping and imaging [67, 68]
			Au	Biomolecular detection [91] Medical diagnosis and target detection [157]
	Carrageenan	Ag	Biomolecular detection [84]	
	Paraffin	Ag	Biomolecular detection [90]	
	Alginate	Ag	Biomolecular detection [94]	
		Au	Biomolecular detection [94]	
		Au@Ag	Biomolecular detection [94]	
	Chitosan	Ag	Medical diagnosis and target detection [64] In situ molecular changes monitoring [65]	
		Au	Biomolecular detection [74]	
		Cu	Substrate characterization [71]	
		Au@Ag	Biomolecular detection [72]	
	Poly-L-lysine	Ag	Medical diagnosis and target detection [86]	
	Bovine serum albumin	Ag	Medical diagnosis and target detection [151]	
	Natural rubber	Au	Ultradetection or single molecule detection [73] SERS mapping and imaging [73]	
		Hyaluronic acid potassium salt	Au	Biomolecular detection [75]

Polymer matrix		Metallic NPs	Applications
Synthetic	Poly(amide)	Ag	Biomolecular detection [87]
	Poly(vinyl alcohol)	Ag	Biomolecular detection [95, 101] Substrate characterization [97]
		Au	Biomolecular detection [126] Medical diagnosis and target detection [126]
		Au@Ag	Biomolecular detection [128]
		Cu@Ag	Biomolecular detection [103]
	Poly(styrene)	Ag	Biomolecular detection [98] Substrate characterization [104] Medical diagnosis and target detection [98, 117]
	Poly(vinylpyrrolidone)	Ag	Biomolecular detection [99, 102, 105]
	Poly(aniline)	Ag	Biomolecular detection [100]
	Poly(<i>t</i> -butylacrylate)	Ag	Biomolecular detection [113, 114]
		Au	Biomolecular detection [107]
	Poly(methyl methacrylate)	Ag	Biomolecular detection [115]
	Poly(acrylamide)	Ag	Biomolecular detection [118]
	Poly(acryloyl) Hydrazine	Ag	Biomolecular detection [162]
	Poly(ethylene glycol)	Au	Medical diagnosis and target detection [11, 163] Heavy metal detection [122]
		Au@Ag	SERS mapping and imaging [93]
	Poly(pyrrole)	Ag	Substrate characterization [96]
	poly(ethylene glycol diacrylate)	Ag	Medical diagnosis and target detection [164]
	Poly(ethylene glycol dimethacrylate)	Au	Medical diagnosis and target detection [109]
	poly(ethylene glycol dimethacrylate- <i>co</i> -acrylonitrile)	Au	Medical diagnosis and target detection [124] SERS mapping and imaging [124]
	Poly(styrene)- <i>block</i> -poly(acrylic acid)	Au	Biomolecular detection [110]
	Poly(N-isopropylacrylamide)	Au	Biomolecular detection [121] Ultradetection or single molecule detection [123]
		Au@Ag	Biomolecular detection [125]
		Fe ₃ O ₄ @Ag	Environmental monitoring [48]
	Poly(vinylidene fluoride)	Ag	Biomolecular detection [87]
		Au	Biomolecular detection [165]
	Poly(hexamethylene adipamide)	Au	Ultradetection or single molecule detection [161]
	Poly(acrylonitrile)	Ag	Biomolecular detection [127]
	Poly(sodium 4-styrenesulfonate)	Au@Ag	Biomolecular detection [155]

Table 2. SERS applications of metal/polymer nanocomposites.

composites depends on the type of coating employed to stabilize the metal NPs, which were used as fillers. As discussed in the previous chapter, metal loaded polymer composites can be prepared by using different matrices such as synthetic [107, 113, 114, 123, 132] or natural polymers [61–63, 84, 87, 90, 151]. Polymer based composites containing metal NPs are of great interest due to their multifunctionality and potential for large-scale fabrication at low cost [23, 107, 152–154]

In the context of SERS, these composites appear as a promising alternative for the development of efficient and scalable substrates for the detection of molecular species, such as dyes [68, 73, 95, 102, 103, 105, 121], biomolecules [64, 74, 75, 101, 113, 123, 155], and environmental pollutants [48, 60, 85]. For example, the application of polymer-based composites as stable and active smart devices or SERS chips has increased in the last years [126, 156–159]. Gao *et al.* have described the preparation of chips composed by metal NPs embedded in polymer nanofibers mats. [126]. The authors have demonstrated that such composites doped with distinct metal NPs are facile to store and to transport, and can be easily fixed in slides or in microfluidic channels for SERS detection of a variety of analytes. Long and co-workers have reported SERS assays loaded with Ag NPs that result from a low-cost production process by using screen printing techniques [156]. Chen *et al.* have decorated commercial tape with Au NPs to be used as SERS platforms for the directly extraction and trace detection of pesticide in vegetables and fruits by a “paste and peel off” procedure [158]

Polymer nanocomposites containing metal NPs offer some advantages in SERS applications, namely by considering a judicious choice of the polymer used as the matrix. The polymer can be selected, for example, to provide a stimuli responsive platform or a porous polymeric matrix that facilitates the diffusion and entrapment of the biomolecules under analysis. In this context, an important objective in the application of SERS substrates has been the analysis of vestigial amounts of the target analyte for which minimal specimen preparation is required [69, 70, 72, 73, 107, 114, 115]. This is relevant to implement analytical protocols as many SERS applications are foreseen, such as environmental monitoring [48, 74], SERS mapping and imaging [67, 68, 93], medical diagnosis [109, 124, 126, 151, 160, 161] and substrate characterization [71, 96, 107]. **Table 2** lists polymer based composites mentioned in this chapter with the corresponding SERS applications by taking into account the type of polymer and the metal nanofillers employed.

In these nanocomposites, the polymer can also act as an active coating with influence in the interparticle distances of the dispersed plasmonic metal NPs and their close surroundings. These changes can endorse the formation of SERS active sites, the so called *hot spots*, that can be further accessed by molecular probes through diffusion in the polymeric matrix [113, 114, 152, 164]. Braun *et al.* have reported a general approach to create *hot spots* in SERS substrates via NPs linking, polymer coating and molecular permeation [152]. The polymer coating holds the analyte within the nanojunctions created by several Ag NPs trapped within the polymer. However, this approach requires the use of a linking agent prior substrate preparation and has been reported only for analyte detection in solution. More recently, Kim and co-workers have reported the preparation of microgels containing Ag nanocubes, providing molecular size-selective permeability and high SERS sensitivity for acetylsalicylic acid (aspirin) [164]. The size of the Ag aggregates in the microgel matrix allows selective diffusion of small molecules and also promotes the formation *hot spots* in the close vicinity of the Ag nanocubes. As

such, these nanocomposites enable the Raman analysis of small molecules dissolved in complex mixtures of proteins and cells without sample pre-treatment.

Metal loaded polymer composites are also suitable for applying analyte trapping strategies [22, 118, 123, 152, 166]. For instance, the diffusion of the analyte molecules within the polymer towards the metal surface can be facilitated not only by existent porosity but also by external stimuli such as temperature, pH, ionic strength and dehydration [22, 84, 88, 123, 162, 163, 165]. Fateixa *et al.* have demonstrated that the gel strength of carrageenan hydrogel composites loaded with Ag NPs can be correlated with the signal enhancement observed in SERS studies [84]. This research has focused on the effect of hydrogel strength and temperature on the SERS behavior of these bionanocomposites for the detection of 2,2'-dithiopyridine. In order to vary the gel strength of the biocomposite, several procedures were employed, such as the increase of the polysaccharide content in the gel, the addition of KCl as cross-linker, and varying the type of carrageenan (κ , ι , λ) gel. The authors have reported an increase in the SERS signal as the gel strength increased, which was attributed to the presence of sites with strong local electromagnetic field, that result from the formation of Ag particles nanojunctions as the carrageenan macromolecules tended to rearrange into stronger gels (**Figure 5**). Also, Contreras-Cáceres *et al.* have prepared core/shell microgel particles composed by a poly-(N-isopropylacrylamide) (pNIPAM) shell and a metallic core such as Au and Au@Ag nanospheres or nanorods [41, 123, 125]. In these systems, the molecules under analysis, which were trapped in the thermoresponsive polymer shells and at the vicinity of the metal surface, experience an enhancement of the Raman signal of about 10^5 times [41, 123, 125]. More recently, multifunctional substrates have been investigated by conferring magnetic properties to SERS substrates, thus allowing extraction of the molecular probes from liquid phase prior SERS analysis [48]. In this case, by encapsulating Fe_3O_4 @Ag NPs in thermoresponsive pNIPAM shells, an increase of temperature promoted the formation of *hot spots* close to the Ag NPs. These new platforms were applied to monitor trace amounts of pentachlorophenol, a chlorinated environmental pollutant.

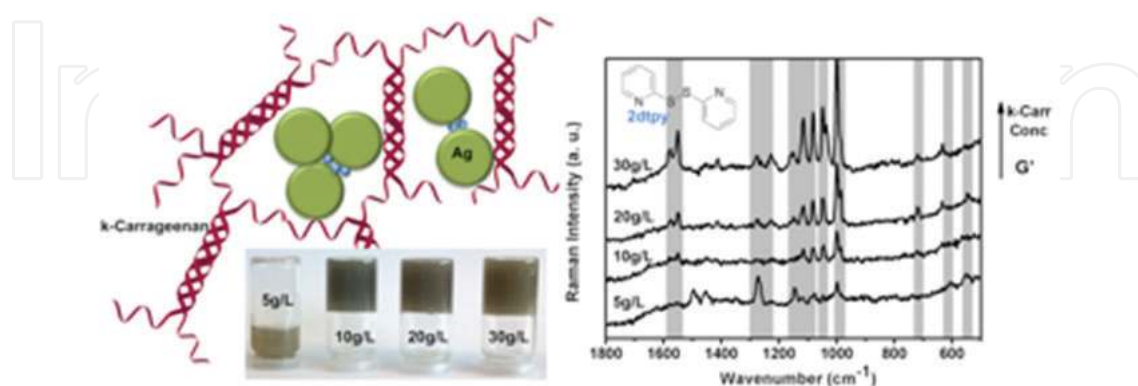


Figure 5. Illustration of biopolymer helices aggregation and consequently the creation of highly SERS sensitive Ag/ κ -carrageenan hydrogels and digital photographs of Ag/carrageenan hydrogels with variable carrageenan amount (left); SERS spectra of 2,2'-dithiopyridine using Ag/ κ -carrageenan hydrogels as substrates with variable amount of biopolymer: (a) 5 g/dm^3 ; (b) 10 g/dm^3 ; (c) 20 g/dm^3 ; (d) 30 g/dm^3 (right) [84] (Reprinted with permission from ([84]). Copyright (2017) American Chemical Society.)

An interesting feature offered by certain polymer nanocomposites employed as SERS substrates is their chemical functionalization envisaging molecular recognition [106, 152, 167]. Nie *et al.* have reported a strategy to detect tumors in living animals, using SERS substrates based on *pegylated* Au NPs [111]. In this research, the surface of Au NPs were functionalized with organic dyes, namely diethylthiatricarbocyanine and malachite green, which acts as Raman reporters. The Au NPs were coated with a polyethylene glycol with a thiol group and then functionalized with antibody fragments, which would target the tumor. The tumor detection was successfully accomplished using the SERS technique, monitoring the signal of the corresponding Raman reporters. Additionally, Batt and co-workers have successfully prepared an apta-sensing SERS substrate composed by polymer-Au NP-aptamer composite microspheres that allows the detection of a target molecule such as malathion [109]. They have demonstrated that these nanocomposites when attached to an aptamer have extraction capabilities for a pesticide, whose Raman signal is strongly enhanced due to the presence of the Au NPs.

Our research group has reported a series of polymer-based nanocomposites that enable the SERS detection of several analytes (**Figure 6**). In this context, synthetic polymers as well as polymers of natural origin have been investigated for these purposes. Examples include nanocomposites based on poly(*t*-butylacrylate), poly(methyl methacrylate), cellulose, linen,

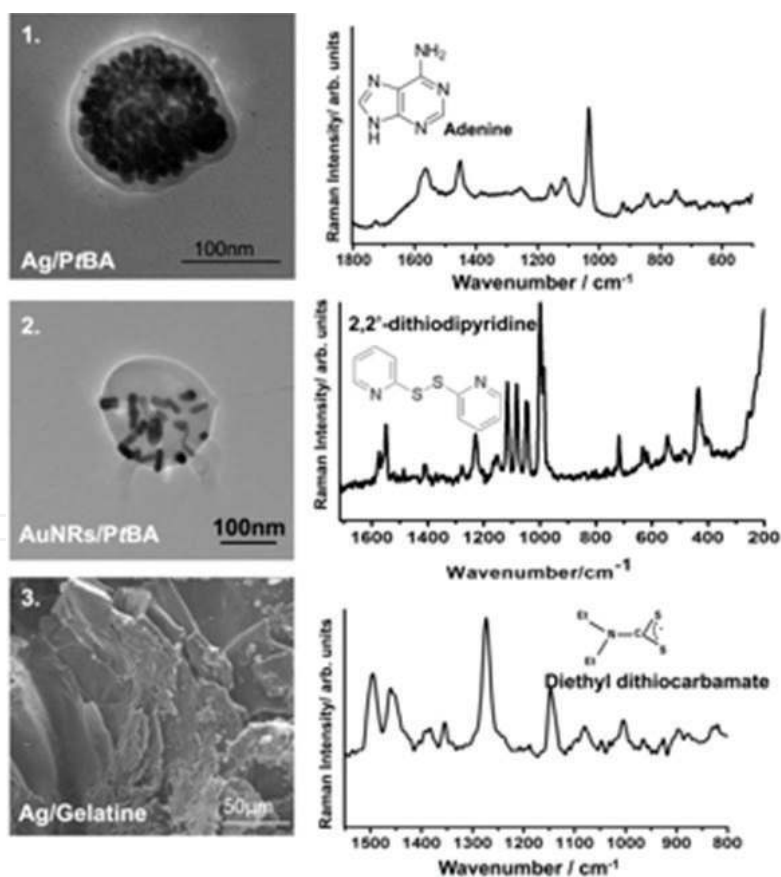


Figure 6. SERS analysis of biomolecules using polymer based composites as substrates. 1. detection of a DNA nucleobase using organically capped silver nanoparticles encapsulated with poly(*t*-butylacrylate) as SERS substrates; [113] 2. Au nanorods with poly(*t*-butylacrylate) for the detection of 2,2'-dithiodipyridine; [107] 3. Ag/gelatin nanocomposites as active SERS platforms for pesticide detection and release [85].

carrageenan and gelatin, loaded with colloidal Ag NPs as SERS substrates. Ultimately, these nanocomposites might find use to fabricate analytical platforms for distinct end uses, such as paper products, smart textiles, thermosensitive materials and drug delivery [67, 69, 84, 85]. Fateixa *et al.* have described Ag/gelatin A hydrogel samples with distinct gel strength as platforms for SERS detection and release of EtDTC, a pesticide model [85]. In this work, SERS was investigated as a spectroscopic method to detect the presence of low amounts of EtDTC in gelatin hydrogels, following the gradual release of the pesticide into water used as the dispersing medium. Noteworthy, this methodology can be used as an alternative to monitor the performance of hydrogel vehicles in the controlled release of pesticides, namely during the formulation and optimization stages of fabrication. On the other hand, PtBA matrices coating organically capped Ag NPs can be used either as aqueous emulsions or as cast films for active SERS substrates [114]. In this research, Trindade and co-workers have reported metal loaded polymer based composites with sensitivity for the SERS detection of thiosalicylic acid, even after the nanocomposite has been submitted to a temperature cycle (-60 to 65°C). The observations were interpreted by considering that the thiosalicylic acid molecules were entrapped within the polymer network and close to the Ag NPs. Similarly, DNA nucleobases, such as adenine, have been reported and detected by SERS using metal loaded polymer nanocomposites obtained by (mini)emulsion polymerization, namely Ag/PtBA and Ag/poly(metamethylacrylate) (PMMA) [113, 115]. In addition, other plasmonic NPs can be used for the preparation of such polymer composites via (mini)emulsion polymerization namely gold nanorods (AuNRs). Fateixa *et al.* have reported SERS substrates obtained by a blending method of colloidal Au nanorods and PtBA aqueous emulsions [107]. The use of the blending method in this case limits morphological modifications of the rods that otherwise could occur in more drastic conditions. The composite blends were evaluated as SERS substrates, showing stronger signal enhancement when compared to the original Au NRs colloid, and using 2,2-dithiodipyridine as the analytical probe. This strategy involves a low-cost process with potential for the up-scale fabrication of SERS substrates, namely by using other types of polymers.

5. Raman imaging of functional polymer nanocomposites

In the last two decades, the rapid development of SERS has been in line with the scientific advances in nanofabrication and Raman instrumentation such as confocal Raman microscopy. Confocal Raman microscopy combines digital imaging technology with Raman spectroscopy in order to evaluate the chemical composition, molecular structure and spatial distribution of molecular components in a certain material, giving information about its homogeneity at the microscale level [168–171]. Delhaye and Dhamelincour have demonstrated for the first time the possibility to combine Raman spectroscopy and mapping microscopy in 1975 on a paper entitled “Raman microprobe and microscope with laser excitation” [172]. The authors have described the technique in detail, giving applications of the system such as the study of various materials such as rocks, plastics, composite materials, phases and inclusions and defects in solids. They emphasized that this new technique could become a valuable tool for the study of chemical reactions in micro-samples and also extended to biological samples.

In Raman imaging, thousands of linearly independent and spatially resolved spectra of the compounds existent in the specimen, are collected and analyzed. Among these spectra, the intensities of diagnosis bands for each species can be analyzed to generate images that are true maps for the spatial distribution of the compounds without the use of strains, dyes or contrast agents. This is a great advantage for materials characterization because little or no sample preparation is needed to characterize heterogeneous matrices [168–171, 173]. In fact, this technique is so versatile that has been applied in several fields, including pharmaceuticals' analysis [174–179], biology [180–182], biomedicine [183–186], label-free cell imaging [187–191], food industry [192–194], threat detection [195–197] and more fundamental research [198–202].

For pharmaceutical industry, the Raman imaging technique became an important analytical tool to trace the active pharmaceutical ingredient (API) heterogeneity in tablet or granulates, controlled release systems, and orally inhaled and nasal drug products [174–176]. Šašić has reported the use of Raman imaging for the spatial distribution of the API and major excipient (mannitol) on common pharmaceutical tablets and granulates [175, 176]. In the same year, Widjaja *et al.* have reported the combination of Raman imaging with advanced multivariate data analysis method, namely band-target entropy minimization (BTEM) for the identification of minor components of pharmaceutical drug tablets [177]. They have detected, in model pharmaceutical tablets, minor components level as low as 0.2% by weight. In addition, the identification and quantification of polymorph forms, unique crystal packing lattice forms of molecules, of API is another important issue for pharmaceutical analysis and nowadays is routinely performed using Raman imaging. For example, Henson and Zhang have reported the detection and spatial distribution of a polymorphic impurity (0.05% w/w) of active pharmaceutical ingredient in a tablet, using Raman imaging [178]. Lin *et al.* have demonstrated the use of Raman mapping for microscopic characterization of the surface of tablets containing chloramphenicol palmitate polymorphs [179]

Besides the chemical specificity, Raman spectroscopy coupled with microscopy maps may hold several other desirable properties for imaging applications, such as high spatial resolution, multiplexing capability, low background signal, and excellent photostability [170, 171]. Over the past years, Raman imaging techniques have been developed in step with the latest Raman fields, such as coherent anti-Stokes Raman spectroscopy (CARS) [203–207], surface enhanced Raman scattering (SERS) [67, 169, 173, 208–210] and tip-enhanced Raman scattering (TERS) [170, 211–215].

The current developments in Raman imaging have brought a new overview on SERS platforms. There are few reports on the use of Raman imaging together with SERS methods, which makes SERS imaging an unexploited resource to answer unsolved questions about the materials functionalities and NPs synthesis, and complement substrates characterization in SERS platforms [67, 169, 173, 208–210]. SERS imaging has been successfully applied in different areas such as cellular imaging [173, 208, 216, 217], in vivo biosensing [218–221], pharmaceuticals and cosmetics [209, 210] and textile industries [67, 68]. Some examples can be cited, Chao *et al.* have reported the use of diamond nanoparticles with two different sizes (5 and 100 nm) as SERS probes to bio-label human lung epithelial cells [217]. The interaction of the nanoparticles and the cells were probed by SERS imaging, demonstrating that

the nanoparticles are not toxic to the cells. Gambhir and co-workers have injected Au@SiO₂ nanoparticles into a live mouse and have studied the mouse's liver through the skin using SERS mapped images [221]. In addition, Firkala et al. have reported, for the first time, the application of surface enhanced Raman imaging on pharmaceutical tablets containing an API in very low concentrations, using Ag colloids as SERS probes [209].

It is of special interest to mention in the context of this chapter that SERS imaging has been a useful technique to identify the SERS active sites in polymer based nanocomposite substrates [60, 63, 67, 68, 73, 93, 160]. SERS imaging has been applied to Ag/agarose beads films, giving an idea of the distribution of the *hot spots* in the polymer matrix [63]. Highly sensitive biological imaging of HEK293 cells expressing PLC γ 1 cancer markers were obtained, using Au/Ag core-shell NPs, conjugated with monoclonal antibodies [93]. A porphyrin-phospholipid conjugate with quenched fluorescence have been reported as a Raman reporter molecule for SERS based

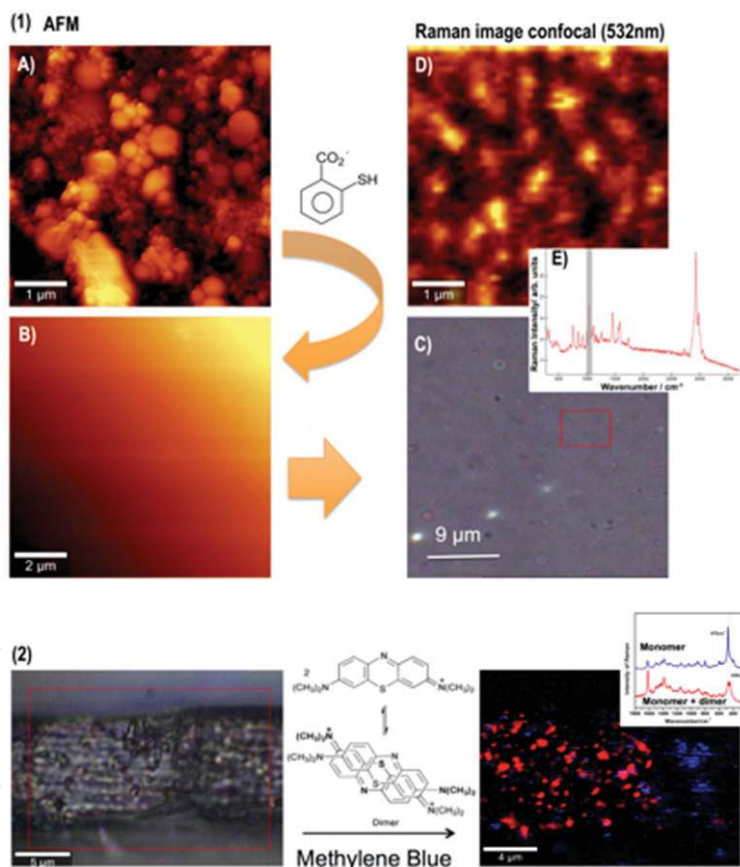


Figure 7. (1) AFM topography image of Ag/PtBA composites prepared by (mini)emulsion polymerization (A) before and (B) after the addition of 10 μL of an ethanolic solution of thiosalicylic acid 10⁻³ M; C) optical photograph of the sample with the scanned area marked in red; D) Raman images obtained using the integrated intensity of the Raman band at 1035 cm⁻¹ in the SERS spectra of thiosalicylic acid 10⁻³ M using the Ag/PtBA composite as substrates; E) SERS spectrum of thiosalicylic acid (10⁻³ M) using Ag/PtBA composites as substrate (laser source: 532 nm); (2) Optical photograph (left) and combined Raman image (right), using two different Raman spectra of methylene blue (100 μM) adsorbed on Ag/linen composite Inset: Raman spectra of monomer form and a mixture of monomer and dimer of MB used to create the combined Raman image [68].

imaging [160]. The spatial distribution of thiophenol and an organic dye were achieved by SERS mapping using smart films composed by natural rubber containing Au NPs [73]

We have been particularly interested in exploring Raman imaging in the characterization of SERS substrates. An illustrative example comprises the development of SERS substrates based on PtBA polymer beads coated with organically capped Ag NPs, accomplishing information at the level of both the substrate surface and the molecular adsorbate distribution (**Figure 7-1**) [114]. By coupling SERS images with AFM, we observed a rearrange of the polymeric chains of the PtBA after the addition of the analyte dispersed in ethanol, allowing a better diffusion of the molecular probe through the matrix and closer to the Ag NPs. This proximity enhanced the Raman signal of the thiosalicylic acid and their spacial distribution can be observed in the SERS images. In addition, linen fibers loaded with Ag NPs and then stained with methylene blue (MB) were investigated using SERS imaging. MB was selected as the molecular probe not only because it is a common organic dye but also due to the formation of dimer or monomer species, each one with characteristic visible absorption and Raman spectra. We have demonstrated that the SERRS effect together with confocal Raman microscopy offer a new tool to map the local distribution of the MB dye in the fibers and consequently the distribution of Ag NPs over the fabrics, using Raman imaging [67]. In addition, it is also possible to assess the preferred adsorbate form of MB on distinct types of nanocomposite fibers and their local distribution (**Figure 7-2**) [68]. This investigation allows to foresee the use of this approach in terms of quality control of antimicrobial Ag containing fabrics, which is a market in great expansion.

6. Conclusions and outlook

The development of polymer based composites as active SERS substrates has contributed considerably to the rise of this methodology as an important and significantly tool in several analytical contexts. This improvement could only be achieved due to the development of more versatile and powerful instruments, including portable Raman equipment, and a deeper knowledge about the underlying mechanisms in the Raman effect that occur in molecules adsorbed at metal surfaces. It should be also emphasized the unprecedented progress observed in the past decades on the synthesis of nanostructures having controlled morphology. Interestingly, it has become clear that improvements in SERS have also impact on the knowledge that we have about the materials required as substrates for applying such spectroscopic technique. In this chapter, the most recent developments in metal loaded polymer nanocomposites for SERS studies were reviewed, showing their applicability into diverse areas due to their multifunctional properties. The vestigial SERS detection of specific molecules using Raman reporters, SERS tags and specific external stimuli are examples of further developments in SERS technologies dependent on materials development. This research has also shown that Raman imaging combined with other techniques such as SERS are valuable assets that complement or eventually provide unique characterization data, with particular relevance in the use of polymer based composites as SERS platforms.

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Author details

Sara Fateixa*, Helena I.S. Nogueira and Tito Trindade

*Address all correspondence to: sarafateixa@ua.pt

Chemistry Department, CICECO-Aveiro Institute of Materials, University of Aveiro, Portugal

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