DOI: 10.1070/RCR4804

Surface-enhanced Raman spectroscopy in modern chemical analysis: advances and prospects

Olga E. Eremina,[a] Anna A. Semenova,[b] Elena A. Sergeeva,[a] Nadezhda A. Brazhe,[c] Georgy V. Maksimov,[c] Tatyana N. Shekhovtsova,[a] Evgene A. Goodilin,[a, b] Irina A. Veselova [a]

[a] *Faculty of Chemistry, Lomonosov Moscow State University Leninskie Gory 1, stroenie 3, 119991 Moscow, Russian Federation*
[b] *Faculty of Materials Science, Lomonosov Moscow State University Leninskie Gory 1, stroenie 73, 119991 Moscow, Russian Federation*
[c] *Faculty of Biology, Lomonosov Moscow State University Leninskie Gory 1, stroenie 12, 119991 Moscow, Russian Federation*

The review concerns the state of the art, the advances in and prospects for application of surface-enhanced Raman spectroscopy (SERS) in chemical analysis. Key advantages (nondestructive origin, high sensitivity and selectivity, easiness of sample preparation) and drawbacks (a relatively small number of analytes, insufficient metrological characteristics of certain objects) of the method are pointed out. Particular attention is paid to the development of novel chemical approaches and to the design of versatile optical sensors to significantly enhance the analytical potential of the method and to extend the range of analytes. Examples are given of the application of SERS in key branches of science and technology that require both qualitative and quantitative chemical analysis of complex objects, *viz*., environmental monitoring, fuel and energy area, medical diagnosis, biology and biochemistry.
The bibliography includes 502 references.

Contents

1. Introduction 741
2. Key prerequisites for practical application of surface-enhanced Raman spectroscopy 742
3. Application of surface-enhanced Raman spectroscopy in analysis of various objects 746
4. New experimental approaches in the field of SERS sensorics 757
5. Conclusion 761

1. Introduction

Surface-enhanced Raman spectroscopy (SERS) is a promising optical method for nondestructive analysis of samples of different nature. It has a record-high sensitivity and is thus a unique method for rapid diagnostics.[1–15] Most SERS investigations have applied character which points to great potential of application-related orientation of their results in analytical practice. Objects of high-priority interest for SERS studies include biological systems of different level of organization (cells and cell organelles,[16–19] erythrocytes,[20–23] bacteria,[24–28] viruses,[15, 29, 30] stem cells,[31–34] various types of human cells[35–37] including cells in disease, in particular, malignant neoplasms[38–41]), pharmaceuticals, food[42–46] and environmental objects upon technogenic pollution.[47–50] The most important analytes from the standpoint of further progress in SERS-based multiplex analytical techniques include proteins,[15, 33, 51, 52] peptides,[32, 33, 51, 53] DNA[54–56] and blood components acting as biomarkers of diseases,[40, 57–59] as well as explosives[12, 60–63] and toxic substances.[64–70]

The SERS effect was discovered in 1974,[71] and since then one deals with continuous extension of fields of its application.[2, 3, 5] However, in some cases practical application of SERS remains problematic because specific features of the behaviour of nanosystems employed depend on a large number of parameters. Targeted control of key factors responsible for the SERS sensitivity and selectivity will considerably extend the potential of the method in analysis of complex objects compared to the current situation.

The authors of most studies on practical application of SERS pay particular attention to extremely high sensitivity of the method, which is indeed of great importance for the detection and determination of analytes at a level of impurity concentrations, down to the detection of single molecules. However, conventional techniques are aimed to detect and determine only a single analyte (often, a model one), whereas SERS is expected to be a multiplex technique. This is a topical

© 2018 Uspekhi Khimii, Russian Academy of Sciences and Turpion Ltd.

task in studies of samples with complex matrices. Successful solution to this problem can make SERS a priority method for analysis of real samples. Of course, SERS has a potential for moving this way since the SERS spectrum reflects the molecular structure of matter, which makes it possible not only to identify analytes in complex mixtures by their molecular fingerprints, but also to analyze molecular conformations.

Rapid progress of SERS in the last two decades is undoubtedly based on advances in targeted synthesis of nanostructured SERS-active materials[2, 3, 5, 72, 73] and on the design of new experimental equipment. In particular, SERS can be combined with *in vivo* visualization[74] as well as with microfluidic[75] and other devices[10] which allow one to significantly improve the potential of SERS as a flexible and powerful analytical method suitable for practical applications. Entering the era of portable Raman spectrometers has made SERS a technique for analysis of real-world samples directly in the field, which undoubtedly is of great importance for practical applications of SERS.

There is considerable literature concerning tentative Raman signal enhancement mechanisms,[76 – 80] methods for the design of SERS-active materials[21 – 23, 63, 81 – 92] and their potential for practical applications.[16, 35, 42, 64, 93 – 111] Besides, there are a few prospective reviews devoted to methods for the design of SERS-active materials, commercialization of SERS sensors and the use of SERS sensors directly in the field.[112, 113] Practical value of systematic studies in the field is obvious, being a consequence of basic research,[61, 76 – 92] which creates prerequisites for the wide use of SERS in analytical chemistry, biochemistry, medicine and ecology.

In connection with elaboration of novel approaches and accumulation of new results, as well as taking account of modern trends and prospects for the development of SERS, this review is devoted to systematic consideration and analysis of practical application of the method.

2. Key prerequisites for practical application of surface-enhanced Raman spectroscopy

An important trend in the development of SERS is the emergence of new avenues of research that use specific features of the physical principles underlying the SERS effect and improved materials science approaches.[9, 10, 12, 14, 15, 19] Key prerequisites for the development of the potential of practical application of these methods in innovation analytical systems include:

— possibility of practical implementation of quantitative analysis using SERS;

— development of various SERS versions adapted to solve particular practical tasks;

— design of chemically and structurally modified nanomaterials as a key materials science factor of progress in the field of SERS.

Unfortunately, high sensitivity of SERS in solving complex analytical tasks such as the detection and identification of ultrasmall amounts (from a few fmol litre^{-1} to nmol litre^{-1}) of analytes present in multi-analyte matrices often do not provide any opportunity for quantitative determination of compounds under study. Indeed, SERS is a local analytical method since enhancement of the Raman signal, which occurs at distances of at most 10 – 30 nm from the nanostructured surface, depends strongly on the surface structure and on the state, size, anisotropy and mutual arrangement of nanoparticles, on specific features of analyte sorption on these particles and on the possibility of formation of aggre-

O.E.Eremina. Junior Researcher at the Faculty of Chemistry, MSU.
Telephone: +7(495)939 – 3346,
e-mail: olga.eremina@analyt.chem.msu.ru
Current research interests: chemical analysis, molecular spectroscopy, optical sensors, surface-enhanced Raman spectroscopy, polyaromatic oil quality markers, neurotransmitter metabolism markers, technogenic objects, biological objects.
A.A.Semenova. PhD in Chemistry, Assistant Professor at the Faculty of Materials Sciences, MSU.
Telephone: +7(495)939 – 4609, e-mail: annette_semenova@mail.ru
Current research interests: chemical materials science, nanochemistry, inorganic synthesis, materials for surface-enhanced Raman spectroscopy, new approaches to design of silver-based nanostructured materials.
E.A.Sergeeva. Junior Researcher at the Faculty of Chemistry, MSU.
Telephone: +7(495)939 – 3346, e-mail: elena.sergeeva3001@gmail.com
Current research interests: chemical analysis, molecular spectroscopy, optical sensors, surface-enhanced Raman spectroscopy, polyaromatic oil fuel quality markers, neurotransmitter metabolism markers, technogenic objects, biological objects.
N.A.Brazhe. PhD in Biology, Senior Reseacher at the Faculty of Biology, MSU.
Telephone: +7(495)939 – 1966, e-mail: nadiya.brazhe@gmail.com
Current research interests: biology, biophysics of cell and its organelles, Raman spectroscopy of biological objects.
G.V.Maksimov. Doctor of Biological Sciences, Professor at the Faculty of Biology, MSU.
Telephone: +7(495)939 – 1966, e-mail: gmaksimov@mail.ru
Current research interests: biology, neurophysiology, biophysics of cell and its organelles, modern methods for analysis of biological objects.
T.N.Shekhovtsova. Doctor of Chemical Sciences, Professor at the Faculty of Chemistry, MSU.
Telephone: +7(495)939 – 3346, e-mail: tnshekh@yandex.ru
Current research interests: chemical and biochemical methods of analysis, molecular spectroscopy, optical sensors, biologically active compounds, ecotoxicants, environmental monitoring, technogenic objects, recognizing membranes, films, coatings, biocatalysts, ionic liquids.
E.A.Goodilin. Corresponding Member of the Russian Academy of Sciences, Doctor of Chemical Sciences, Professor at the Faculty of Chemistry, Deputy Dean of the Faculty of Materials Sciences, MSU.
Telephone: +7(495)939 – 4609, e-mail: goodilin@yandex.ru
Current research interests: composite materials for optical sensors and analytical systems, composites based on noble-metal nanoparticles and layered materials; solid state chemistry, electrochemistry, perovskite solar cells, nanomaterials, inorganic chemistry.
I.A.Veselova. PhD in Chemistry, Assistant Professor at the Faculty of Chemistry, MSU, Head of Laboratory of the National Research Centre Kurchatov Institute.
Telephone: +7(495)939 – 3346, e-mail: irina.veselova@mail.ru
Current research interests: chemical and biochemical methods of analysis, molecular spectroscopy, surface-enhanced Raman spectroscopy, optical sensors, biologically active compounds, ecotoxicants, environmental monitoring, technogenic objects, recognizing membranes, films, coatings, biocatalysts, organized media.

Received 8 December 2017
Translation: A.M.Raevskiy

gates and nanostructures on the surface.[16, 81, 114 – 118] Because of this the final functional properties of a material being designed are governed by a large number of morphological and microstructural characteristics and by the physicochemical properties that cannot always be unambiguously classified as particular factors, although it is these characteristics taken altogether that predetermine the efficiency of SERS.[119 – 121]

Recently, there has been an increasing number of publications concerning quantitative analysis by SERS (Table 1); however, reproducible signals are obtained using complicated and expensive methods. Besides, most procedures were developed for the determination of single analytes, whereas certain practical tasks require a multiplex determination of compounds, *e.g.*, a number of biomarkers for simultaneous diagnosis of diseases or detection of a number of pollutants in the course of environmental monitoring.[131] Usually, the widest linearity range and the lowest limits of detection (LOD) are attained in dye determination using SERS.[127 – 133] However, procedures developed to analyze practically important objects are of greater interest.[138, 139] Information on quantitative analysis of real samples is scarce, while most of available procedures are aimed to detect various food additives.[1, 135] Concentration of the minor components being determined on SERS-active surfaces is attained by different means, *e.g.*, by modification of metallic nanoparticles with antibodies, aptamers[139] or molecularly imprinted polymers.[138]

To improve the reproducibility, sensitivity and selectivity of SERS, the method is modified in different manner to solve particular practical tasks. An important topic is the investigation of so-called hot spots, *i.e.*, areas with greatly enhanced local electromagnetic field within nanometre-sized gaps between nanoparticles, *e.g.*, in nanoparticle aggregates from dimers[140] and trimers[141]

Table 1. Results of quantitative determination of organic compounds using SERS.

Analyte	Coordinates	Linearity range /mol litre^{-1}	Limit of detection /mol litre^{-1}	R^2	Ref.
		Dyes			
Sudan-I	$\log I - \log c$	$6.4 \times 10^{-6} - 1.3 \times 10^{-4}$	–	0.985	122
Rhodamine 6G	$\log I - \log c$	$1 \times 10^{-17} - 1 \times 10^{-8}$	1×10^{-17}	–	123
Crystal violet	$S - c$	$1 \times 10^{-6} - 1 \times 10^{-5}$	–	0.982	124
	$I - c$	$1 \times 10^{-7} - 5 \times 10^{-5}$	2×10^{-8}	0.998	125
Malachite green isothiocyanate	$I - c$	$1 \times 10^{-12} - 1 \times 10^{-9}$	1×10^{-12}	–	126
		Pharmaceuticals and biologically active substances			
Ciprofloxacin	$\log I - \log c$	$2 \times 10^{-7} - 2 \times 10^{-4}$	–	0.981	127
Nicotine	$I_{1030}/I_{1360} - c$	$6 \times 10^{-7} - 6 \times 10^{-5}$	$< 6 \times 10^{-7}$	0.998	128
		Technogenic pollutants			
Tricyclazole	$I/I_{ref} - c$	$2 \times 10^{-7} - 3 \times 10^{-6}$	1×10^{-8}	0.995	129
Methamidophos	$I - c$	$7 \times 10^{-7} - 7 \times 10^{-3}$	7×10^{-7}	0.985	130
Dibenzothiophene	$I - c$	$5 \times 10^{-7} - 5 \times 10^{-4}$	1×10^{-7}	0.987	131
Dipicolinic acid	$I/I_{ref} - c$	$6 \times 10^{-6} - 3 \times 10^{-4}$	6×10^{-6}	0.986	132
Carbaryl	$\log I - \log c$	$1 \times 10^{-7} - 1 \times 10^{-2}$	1×10^{-7}	–	133
		Toxins			
Aflatoxin B1	$\log I - \log c$	$5 \times 10^{-5} - 1 \times 10^{-3}$	5×10^{-5}	–	134
Aflatoxin B2	$\log I - \log c$	$1 \times 10^{-4} - 1 \times 10^{-3}$	1×10^{-4}	–	134
Aflatoxin G1	$\log I - \log c$	$5 \times 10^{-6} - 1 \times 10^{-3}$	5×10^{-6}	–	134
Aflatoxin G2	$\log I - \log c$	$5 \times 10^{-6} - 1 \times 10^{-3}$	5×10^{-6}	–	134
		Food additives			
Butylhydroxyanisole	$I - c$	$5.5 \times 10^{-5} - 5.5 \times 10^{-3}$	5.5×10^{-5}	0.980	135
		Biomolecules			
Thymine	$I/I_{ref} - c$	$1 \times 10^{-5} - 5 \times 10^{-4}$	–	–	136
Thiocholine	$I - c$	$1 \times 10^{-6} - 5 \times 10^{-5}$	2.6×10^{-7}	0.996	137

Note. Notations are as follows: R^2 is the determination coefficient, I is the spectral line intensity, c is the concentration, S is the integrated intensity of the spectral line, and I_{ref} is the intensity of the reference spectral line.

to complex structures formed by silver or gold nanospheres.[142] Hot spots on the metal surface play a significant role in SERS enhancement since it is believed that it is these areas where the electromagnetic field strength increases greatly; as a consequence, signals with enhancement factors of more than $10^7 - 10^8$ can be detected.[143]

Combined methods developed to date, *e.g.*, a combination of SERS and atomic force microscopy (TERS, Table 2), allow one to visualize the surface structure and to obtain enhanced Raman signals with nanometre spatial resolution ($\sim$20 nm).[144, 150] Since the probe of an atomic force microscope coated with, *e.g.*, noble metal nanoparticles enhances the Raman signal, the SERS effect is observed only in the vicinity of the probe. Single probe particle SERS was proposed.[151]

The SERS spectral signal of a dye (10^{-14} mol litre^{-1}) can be produced using ultrasmall volumes of a dilute hydrosol of small aggregates of silver nanoparticles.[1] An analysis of the SERS spectra of this system measured with an increment of 1 s revealed oscillations of signal intensities with time; these oscillations were related to molecular fluctuations. The signal intensity histogram for the band chosen had a Poisson distribution pattern rather than a Gaussian shape as in the case of more concentrated solutions. This was explained by the detection of signals from one, two or three molecules. More recent calculations showed that if a molecule is located at a hot spot in interstitial position between two silver nanoparticles and excited by light polarized parallel to the axis of the nanoparticle dimer, the enhancement factor due to the contribution of the electromagnetic mechanism can be as high as 10^{11} and that an additional enhancement of three orders of magnitude is provided by the 'chemical' mechanism.[152] This effect underlies a particular SERS version called single-molecule SERS.[16]

To verify the possibility to detect single molecules and to improve the reproducibility or results, a bianalyte method was proposed.[146] It implies the use of a concentrated mixture of two dyes that compete for sorption on the nanostructure surface (it is necessary that there should be at least one dye molecule per Raman-active spot for most spots). Owing to a large number of molecules, the SERS signal is the sum of signals from both types of molecules. If the spectrum exhibits signals characteristic of one type of dye molecules, the corresponding spot is covered with a small number of one type of molecules. This technique allows one to interpret the experimental results obtained for new objects.

The hot-spot effect was used in single-molecule detection experiments.[153, 154] High enhancement factors are attained using the SERS effect from shell-isolated nanoparticles[145] with, *e.g.*, silica gel or alumina as the shell material. Each shell-isolated nanoparticle can act as a 'nanoantenna'.[155 – 158] Ultrafast SERS methods[13, 159] are of great interest since they allow one to study molecule – molecule and molecule – plasmon interactions on the femto- and picosecond time scales[160 – 162] and to establish the reaction mechanisms.[163]

Surface-enhanced resonance Raman scattering (SERRS) deserves particular attention. The effect is due to resonance between the absorption frequency of the molecule under study and the laser radiation frequency; it is usually associated with excitation of the electronic structure of the molecule.[4, 164 – 167] The authors of the early studies (since 1983) attempted to compare the enhancement factors observed in the SERS, SERRS and surface-enhanced fluorescence (SEF)[168] experiments with

Table 2. Selected methods based on the SERS effect.

Method	Abbreviation	Distinctive features	Ref.
Surface Enhanced Raman Spectroscopy	SERS	SERS with enhancement of spectral signal owing to high strength of local electromagnetic field upon excitation of local plasmons or plasmon polaritons at dielectric/metal interface	2, 87
Tip-Enhanced Raman Spectroscopy	TERS	Combination of SERS with atomic force microscopy through probe modification with plasmonic nanoparticles	144
Shell-Isolated Nanoparticle-Enhanced Raman Spectroscopy	SHINERS	SERS using dielectric shell-isolated nanoparticles	145
Single Molecule SERS	SM-SERS	General name of SERS versions for detection of single molecules	146, 147
Bi-Analyte SERS 148	BiASERS	SERS using the main analyte and a reporter (internal molecular reference)	
Surface Enhanced Coherent Anti-Stokes Raman Spectroscopy	SECARS	Coherent anti-Stokes surface-enhanced Raman scattering	13
Tip-enhanced Coherent Anti-Stokes Raman Spectroscopy	TECARS	Coherent anti-Stokes surface-enhanced Raman scattering combined with atomic force microscopy	13
Femtosecond Stimulated SERS	FS-SERS	SERS stimulated by femtosecond excitation pulse	13, 87
Surface Enhanced Hyper-Raman Spectroscopy	SEHRS	Surface-enhanced hyper-Raman scattering	17, 149
Surface Enhanced Resonance Raman Spectroscopy	SERRS	Surface-enhanced resonance Raman scattering	4

various dye ions and molecules (*p*-nitrobenzoate, rhodamine 6G, fuchsine) on identical silver nanostructures. The intensity ratios of the enhanced signal to that measured under usual conditions normalized to the concentration ratio were 10^5 for SERS, 10^3 for SERRS and 10^{-1} – 10^1 for SEF depending on the quantum yield of fluorescence.[169] Such a difference between the enhancement factors makes it possible to get rid of undesired background fluorescence in the case of SERRS. It is difficult to exactly match the frequencies; however, SERRS is also observed if the wavelength difference reaches a value of 250 nm.[170] A distinctive feature of SERRS compared to SERS is much higher signal enhancement. For instance, Raman scattering of pyridine is enhanced by a factor of 10^6, while the enhancement factor of rhodamine 6G is 10^{13} – 10^{15}. Also, SERRS is characterized by higher selectivity owing to excitation of vibrations whose frequencies match those of electronic transitions and the plasmon resonance frequency of the metal. Unfortunately, the authors of many publications do not distinguish between SERS and SERRS owing to complexity of the differentiation procedure, although experience shows that these differences are significant.[1]

Mention should be made of the two-photon version of Raman scattering called surface-enhanced hyper-Raman scattering (SEHRS) when the molecule of interest interacts with two photons.[171] The first SEHRS study was reported in 1982.[172] In 1988, a SEHRS experiment with picosecond excitation was carried out.[173] Although SEHRS is a weak process,[13] it has found application in the form of SERS due to its unique features. First, unlike the SERS intensity, the SEHRS intensity is proportional to the squared laser intensity.[13, 174] This should be first of all taken into account in the experiments with biological samples that can undergo photodegradation by too long action or too high intensity of laser radiation. Second, the symmetry selection rules for SEHRS differ from those for SERS.[175] Therefore, SEHRS allows one to observe SERS-forbidden vibrations.[174, 176] Third, the SEHRS enhancement factors determined using silver nanoparticle aggregates can be as high as 20 orders of magnitude.[174, 175]

Thus, one deals with gradual emergence of narrower-scope versions of SERS in accordance with specific enhancement mechanisms. At the same time, generally it is unreasonable to use a single method for enhancement of the spectral signal. From the standpoint of progress of SERS as a field of research it seems more appropriate to design novel nanomaterials and to structurally or chemically modify the available ones. The method of preparation predetermines the optical properties and signal enhancement ability of the nanomaterial. For instance, there is a number of reviews on targeted synthesis of nanoparticles with hot spots.[81, 177 – 184] Also, it was assumed (see, *e.g.*, Refs 71 and 177 – 179) that SERS is observed only on rough surfaces, especially at a surface roughness of the order of 10 – 100 nm because the Raman scattering enhancement is attained when the particle size is about tens of nanometres, being small compared to the laser wavelength.[185 – 189] Small particle size enables localization of plasmons.[187]

Most SERS experiments are carried out using silver nanostructures.[190] The discovery of the SERS effect was soon followed by publications devoted to recording SERS spectra from trace amounts (to 10^{-10} g) of organics adsorbed on the surface of silica gel treated with silver hydrosol,[191] on cellulose fibres[192] and chromatographic plates.[193]

Modern methods of chemical synthesis allow one to prepare silver nanoparticles of different size and shape (spherical, octahedral, cuboctahedral, decahedral, triangular and hexagonal plates, disks, rods, wires, *etc.*) in rather high yield.[3, 5, 194 – 203] There are a number of reviews on the preparation of nanoparticles of complex morphology, *e.g.*, 'nanoflowers', 'nanostars', 'corals', 'sea urchins', 'nanowheels'.[204 – 206] The morphological variety is due to the fact that chemical methods of synthesis of nanoparticles are based on reduction of reactants containing silver or gold ions (nitrates, diammine complexes, sulfates for Ag and mainly $HAuCl_4$ for Au) in the presence of stabilizers that sterically and electrostatically stabilize nanoparticles, as well as reactants for selective growth of nanoparticle faces. Thus, chemical synthesis of silver nanoparticles should be carried out taking account of the following three main factors:[207 – 249]

— the choice of the medium, *viz.*, the solvent (usually, water, ethanol, ethylene glycol);

— the choice of the reducing agent (sodium borohydride, sodium citrate, ethylene glycol, ascorbic acid, chitosan, hydroxylammonium chloride, poly(ethylene glycol), polyvinylpyrrolidone, aldehydes, *etc.*, photochemical action);

— the choice of the stabilizer (sodium citrate, polyvinylpyrrolidone, cetyltrimethylammonium bromide, polyvinyl alcohol, chitosan, hexadecyltrimethylammonium bromide, poly(ethylene glycol), dodecyl sulfate, polyaldehyde dextran, sodium 3-mercaptopropionate, perfluorodecanethiol, *etc.*).

Physical methods for preparation of silver nanoparticles include laser ablation, thermal evaporation, arc-discharge synthesis, electronic evaporation, ion sputtering, ion implantation, as well as methods using various radiation techniques.[196, 250 – 257] Methods for the synthesis of nanoparticles using natural products are also of interest.[258 – 268]

The design of novel materials for SERS also involves fabrication of planar structures for, *e.g.*, microfluidic, chromatographic and 'lab-on-a-chip' devices.[87, 269 – 273] Traditionally, this is done using lithography, electrochemical methods,[274 – 276] spray deposition,[277] chemical methods for deposition of nanoparticles on substrates,[278 – 281] the Langmuir – Blodgett method to form films,[282 – 284] copolymer micelles,[285] grafting of pre-synthesized nanoparticles to the surface of amino- or thiol-modified microspheres,[286, 287] as well as aerosol[90, 91, 288, 289] and physical methods of nanoparticle deposition on various substrates including cellulose fibres and polycarbonate surfaces, and also replica-modified surfaces.[290 – 298]

Trends and prerequisites for the design of reliable SERS-active materials and sensors and for elaboration of methods of analysis using novel analytical systems (see above) underlie great prospects for application of SERS in various fields of science and technology.

3. Application of surface-enhanced Raman spectroscopy in analysis of various objects

SERS of nanostructured materials has found application in various fields including biology,[299 – 315] medicine,[2, 22, 87, 88, 316 – 382] pharmaceutics,[239, 382 – 399] food industry[121, 122, 123, 310, 400 – 422] and environmental monitoring.[47, 112, 307, 309, 423 – 488] The central objects of analysis (Fig. 1) include biological fluids, food and environmental objects. Yet another important task is to detect and determine analytes of different structure and nature, namely, trace amounts of pharmaceuticals,[239, 388 – 395] drugs,[396 – 398] biological markers,[21, 22, 324 – 332] pesticides,[120, 125, 411 – 414] technogenic pollutants[131, 440, 442, 458, 471, 478 – 489] and explosives.[12, 60 – 63] Besides, being a nondestructive method, SERS offers prospects for solving certain fundamental problems, in particular, in biochemistry (structure elucidation of biomolecules, establishment of the mechanism of action of drugs, *etc.*).[40, 299 – 312] However, most publications are devoted to the detection of single analytes and subsequent qualitative or semiquantitative analysis.[131, 313 – 315]

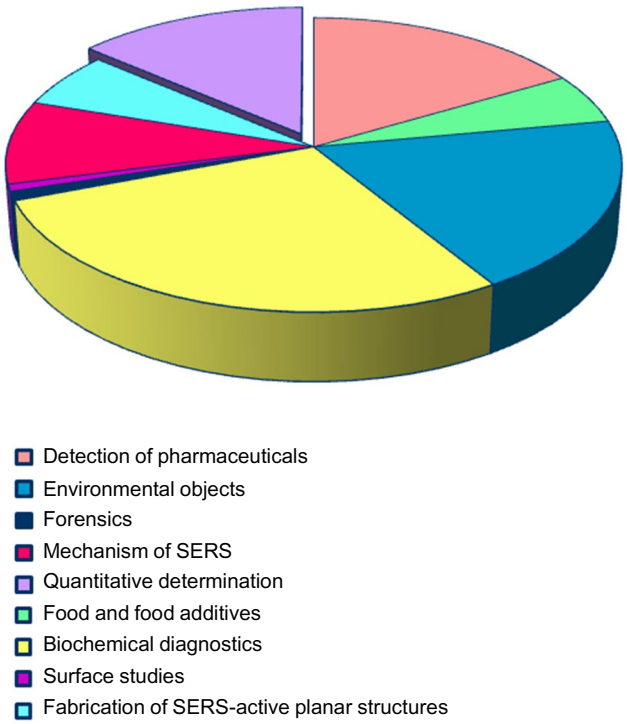


Figure 1. Pie chart illustrating the distribution of scientific publications devoted to SERS analysis of various objects in the past 15 years. Data analysis was performed using a set including nearly 7000 publications retrieved from the Web of Science database with the terms listed below.

3.1. Analysis of biomedical objects

Biomedical diagnostics in the interests of personal medicine and mass health screening, including analysis of living cells and their organelles, tissues and metabolites, is one of the most important and expected fields of application of novel analytical SERS systems. This is directly related to such undoubtful advantages of SERS as noninvasive character, rapidity and high sensitivity not only to the concentration, but also to the structure and conformation of analyte molecules.[40, 299 – 301]

3.1.1. Detection of biologically active molecules

At present, the application of SERS for highly sensitive detection of biologically active molecules in physiological fluids (blood, saliva, cerebrospinal fluid, *etc.*) aimed at early disease detection is of principal interest. The discovery of the SERS effect was very soon followed by studies of different classes of biological molecules, *viz.*, amino acids, nucleotides, water-soluble, membrane and light-sensitive proteins and nucleic acids.[2] An important feature of SERS-based analysis of certain biological molecules, in particular, proteins is a probable change in the molecular conformation upon adsorption on the SERS-active surface (often, no conformational changes occur).[1, 2] SERS is a unique method for determining the molecular conformations and redox potentials of proteins, *e.g.*, cytochrome *c*.[90, 316] It is used to study the mechanisms of biochemical processes in cells (mechanism of interaction between nitrogen(II) oxide, a muscle relaxant, and cytochrome P-450 in the presence of oxygen,[317] the mechanism of charge transfer inside and outside living cells[90]); chemical substances secreted by cells during growth, metabolism, proliferation and apoptosis.[318] Detection of a single adenine molecule adsorbed on silver nanoparticle cluster was reported.[319]

SERS can be used to detect various biomarkers in diagnosis of human diseases.[24, 57] For instance, the SERS spectra of haemoglobin on silver nanoparticle films are available[320] and approaches to early cancer detection were proposed.[321 – 323] Usually, in such studies blood plasma samples taken from patients and from healthy persons are mixed with silver nanoparticles and the SERS spectra are recorded. Possible biomarkers include proteins, lipids and nucleic acids since their content in the blood samples taken from patients and from healthy persons is different.[321] The first biochemical analysis[321] of blood plasma aimed to detect cancer was based on comparison of the SERS spectra of blood plasma samples from patients with nasopharyngeal carcinoma and from healthy persons (control group). Statistical processing of the results obtained revealed an increased content of nucleic acids, collagen, phospholipids and phenylalanine and a decreased content of amino acids and saccharides in the blood plasma samples taken from patients with carcinoma. Apparently, further development of this approach will lead to elaboration of novel methods for rapid diagnosis of cancer (Table 3).

Prospects for application of SERS in the design of sensors for biomarkers and biologically active substances present in fluids at submicromole concentrations deserve particular attention. As an example, modified gold nanoparticles were proposed to detect neurotransmitter molecules.[340]

Combining SERS and immunochemical assay based on specific binding of antigens to complementary antibodies seems to be promising for the detection of certain physiologically active molecules in biological samples.[341] Corresponding devices are based on metal nanoparticles labeled with Raman-active reporter molecules have found

Table 3. Results of SERS detection of biomolecules and analysis of living cells.

Analyte	SERS-active surface	λ_{ex} /nm (see [a])	c_{min} /mol litre^{-1} (see [a])	Ref.
	Recognition of biomolecules			
Adenine	Gold layer 40 nm thick	785	1×10^{-9}	324
Glucose (in rat blood)	Silver layer 200 nm thick	785	–	325
Glucose	Silver layer 200 nm thick on the surface of polystyrene nanospheres (d = 390 nm)	532 633	$\sim 10^{-3}$	326
Phenylalanine Glycoprotein	Porous (pore diameter d = 50 nm) ceramic material ($CaO-TiO_2-P_2O_5$) coated with 5-nm layer of silver nanoparticles	633	$\sim 10^{-3}$	327
Bovine serum albumin	Gold nanorods (d = 100 – 180 nm, l = 50 nm)	633	10^{-6}	328
Bovine ribonuclease A	A 100-nm layer of gold particles (d = 80 – 100 nm)	830	7×10^{-6}	330
Insulin	Silver layer 10 – 13 nm thick	568	10^{-6}	329
Lysozyme	A 100-nm layer of gold particles (d = 80 – 100 nm)	830	7×10^{-6}	330
Ribonuclease B	The same	830	7×10^{-6}	330
Myoglobin	"	830	7×10^{-6}	330
Haemoglobin	Au@Ag nanoparticles ($d \approx$ 50 nm)	633	1×10^{-9}	331
Myoglobin	The same	633	1×10^{-9}	331
Cytochrome *c*	A 20-nm gold layer supported on Ag electrode	514 568	– –	332 332
	Detection of living cells and recognition of bacteria			
Human keratinocytes	A probe coated with a 20-nm silver layer	532	–	333
Erythrocytes	Colloidal silver nanoparticles [b]	514	–	22
	$Ag@SiO_2$ colloidosomes (d_{Ag} = 10 – 20 nm; d_{SiO_2} = 250 – 300 nm)	514	–	91
	Detection and structure elucidation of living cells and bacteria			
Bacillus subtilis	Colloidal silver nanoparticles ($d \approx$ 30 nm)	785	–	334
Escherichia coli	The same	785	–	334
Staphylococcus aureus	"	785	–	334
Bacillus cereus	Colloidal gold nanoparticles ($d \approx$ 80 nm)	785	–	335
Bacillus subtilis	The same	785	–	335
Bacillus anthracis	"	785	–	335
Bacillus thuringiensis	"	785	–	335
Escherichia coliand	"	785	–	335
Salmonella typhimurium	"	785	–	335
Macrophages	Colloidal gold nanoparticles ($d \approx$ 50 nm)	785	–	336
Human respiratory syncytial virus	Silver nanorods (d = 100 nm, l = 870 nm)	785	$\sim 10^{-7}$	337
Rhinoviruses	The same	785	$\sim 10^{-7}$	337
Human adenoviruses	"	785	$\sim 10^{-7}$	337
Human immunodeficiency virus	"	785	$\sim 10^{-7}$	337
Influenza virus	"	785	$\sim 10^{-7}$	337
Mitichondria isolated from lung cancer cells	Colloidal gold nanoparticles ($d \approx$ 13 nm)	830	–	338
Normal and cancerous human esophageal tissues	Colloidal silver nanoparticles (d = 35 nm)	785	–	339

[a] Here and in other Tables λ_{ex} is the excitation wavelength and c_{min} is the minimum concentration studied by the authors. [b] The nanoparticle size was not determined; the presence of nanoparticles was confirmed by the plasmon resonance peak in the absorption spectra.

wide application due to the possibility to produce enhanced SERS signals and good biocompatibility.[342] For instance, SERS was used for simultaneous detection of two antigenic species in a mixture of rabbit and rat immunoglobulins *G*.[343] In the first step, two types of antibodies were immobilized on the surface of colloidal gold particles on a glass substrate. The second step involved the formation of specific complexes with the analyte molecules. In the third step, the labeled antibodies captured antigens from solution and then the SERS signal of the reporter was detected. Each of the two types of immune complexes corresponded to one SERS-active reporter (4-mercaptobenzoic acid, naphthalene-2-thiol or thiophenol).[343] Being rather advantageous, the approach has certain drawbacks, namely, it requires repeated purification, separation of antibodies and proteins, as well as prolonged incubation for specific antigen – antibody binding to occur.[94]

The use of Raman labels in combination with composite materials based on microparticles (microspheres) and metal nanoparticles offers prospects for 'controlled' immunoassay for highly sensitive detection of biomolecules.[344 – 347] In this method composite microparticles selectively bind the target bioanalyte to give an immune complex. Having concentrated the sample, mixing, conducting the reaction and washing products, SERS can be used to determine the amount of molecules attached to the nanoparticle in the immune complexes. In particular, alpha-fetoprotein (an oncomarker) can be detected quantitatively in a ~500-nlitre sample droplet with a low LOD (0.1 ng ml^{-1}) within 5 min.[341] It was proposed to utilize a highly specific complex enzyme(protein) – substrate for selective detection and subsequent quantitative determination of certain biologically active molecules with either high (proteins, enzymes) or low molecular mass. Practical implementation of this approach requires that the substrate of enzymatic reaction or the product of indicator test produce a strong SERS or SERRS signal.[348, 349]

The design of chemically modified biosensors that enable quantitative (or semiquantitative) determination of analytes plays a significant role.[302, 303] Often, silver nanoparticles chemically or physically deposited on silica or polystyrene microparticles immobilized on the substrate surface are used as SERS-active material. This allows one to increase the surface area of the contact between the analytes and the SERS-active material and creates prerequisites for increasing the number of hot spots in the silver layer on the surface of microspheres. Chemical modification of the surface of plasmonic particles (most often, with a monolayer of appropriately functionalized thiol) is used for subsequent selective sorption of analytes and to ensure pre-concentration and proximity of analyte molecules to the noble-metal nanostructure. The approach was used to perform a real-time analysis of glucose present at concentrations from 0 to 25 mmol $litre^{-1}$.[302] The latter value is close to a typical concentration of glucose in certain physiological fluids (also, in the presence of model plasma proteins, *e.g.*, bovine serum albumin). The functional characteristics of the sensor remain unchanged upon prolonged contact (to 72 h) with electrolytes at 'physiological' concentrations. This type of SERS sensors demonstrated sufficiently high accuracy and reproducibility of results at least two weeks after subcutaneous implantation in laboratory animals,[303] which is indicative of great prospects for application of such sensors for *in situ* monitoring of the state of living organisms.

3.1.2. Living cell studies

Since SERS is a nondestructive method of investigation of living objects (see above), it is used for analysis of living cells, tissues, spores, bacteria, viruses and single biomolecules (see Table 2).[36, 350, 351] Traditionally, SERS studies are carried out using colloidal silver or gold nanoparticles; however, a recent general trend has been to utilize nanostructured coatings. The application of colloidal solutions is not free from drawbacks which include toxic action of colloidal solutions on cells of side products of nanoparticle synthesis, hyposmotic effect of a colloidal solution and hardly controlled nanoparticle aggregation resulting in aggregates of different morphology, which significantly influences the enhancement factor of Raman signals from the molecules under study.

An alternative method for nanoparticle delivery to cells is to synthesize them *in vivo* by reduction of silver or gold cations from appropriate salt solutions.[352] In 2007, the formation of gold nanoparticles inside MCF10 human cells in 1 mM $HAuCl_4$ solution was used to detect the SERS spectra of intracellular constituents.[353] The SERS spectra of analyte molecules on bacterial cells, enhanced by intracellular nanoparticles, were detected in 2008.[354] Experiments with dissimilatory bacteria *Geobacter sulfurreducens* that reduce Fe^{III} revealed the formation of intracellular gold nanoparticles in Au^{III} salt solutions (within the cytoplasm close to the inner cell membrane) and extracellular silver nanoparticles (near the outer cell membrane) in silver salt solutions.

In studies of biological objects, preference should be given to nanostructured surfaces since they provide reproducible values of the enhancement factor of spectral signals and allow one to integrate SERS-active materials into 'lab-on-a-chip' and microfluidic devices. However, nanostructured coatings are not versatile because they cannot penetrate into cells and produce enhanced Raman signals from molecules in the cytoplasm and nucleus.[338, 339, 355 – 367]

Nanostructures for studies of biological objects should be nontoxic to cells, retain their chemical properties and morphology in biological fluids and solutions, provide a maximum and stable enhancement of the Raman signal and influence no intracellular processes and conformations of the cellular molecules involved in the contact.

Living cells were analyzed for the first time by SERS in the early 1990s. At that time, SERS investigations implied the introduction of nanoparticles into the living cells. One of the first publications[358] was devoted to studies of the interaction of doxorubicin (an antibiotic) with DNA and involved the internalization of colloidal nanoparticles into cells by endocytosis. At the present, endosomal internalization of nanoparticles into cells still remains the most widely used technique. Improvement of methods for nanoparticle modification has made it possible to functionalize them with specific ligands to cell receptors, antibodies, amino acid sequence of the nuclear localization signal for penetration of nanoparticles into

cellular nuclei and in many other ways. Nanoparticles are often stabilized with polymers, proteins or silica shells to increase the operating life and to prevent nonspecific binding to the cell molecules.

Detection of SERS signals from thyroid cancer cells and healthy thyroid cells adsorbed on the surface of silver nanoparticles was reported.[359] It was assumed that SERS can find application in diagnosis of thyroid cancer since the SERS spectra of the cancer and healthy cells are different. A similar study of large intestine cells was carried out earlier.[360] A method[361] proposed to detect circulating tumour cells is based on the SERS effect facilitated by gold nanoparticles modified with thiolated poly(ethylene glycol). Namely, the SERS spectrum of blood samples containing tumour cells changes compared to that of blood samples of healthy persons. This can underlie an rapid screening technique.

Nanostructures can be modified with reporter molecules having a characteristic intense SERS spectrum. When these molecules interact with the biological object under study, their conformation and, therefore, the SERS spectrum changes. This type of SERS sensors is highly specific, *i.e.*, these devices can be efficiently used only for a single type of molecules. Examples are provided by intracellular 'pH-metres' based on nanoparticles.[362, 363] Gold nanoparticles were coated with 4-mercaptobenzoic acid while silver nanoparticles were modified with 2-aminobenzene-1-thiol because these modifiers exhibit intense Raman and SERS spectra that depend on the pH of the medium. Incubation of NIH/3*T*3 cells or human carcinoma cells with the modified particles led to endocytosis of the nanoparticles which accumulated in the early or late endosomes or lysosomes depending on the incubation time. The pH of vesicles was determined using the SERS spectra of 4-mercaptobenzoic acid or 2-aminobenzene-1-thiol as lysosomes matured. The limitation of the approach is that the modified nanoparticles allow one to determine the pH value of only endosomes and lysosomes rather than the cytoplasm because they cannot escape from the vesicles.

The SERS sensors are also suitable for measuring the intracellular redox potential. A method for studying oxidative stress in cells using gold nanospheres with various quinone molecules as redox-sensitive reporter molecules[364] allows one to evaluate the cellular redox potential in a wider range (from −400 to 100 mV) compared to modern fluorescent probes. Yet another example of application of specific SERS sensors (highly selective hybrid nanosensor 'silver nanoparticles coated with cytochrome *c*') to study oxidative stress is the detection of superoxide radical anion.[365] The corresponding LOD is 10 nmol litre^{-1}. The technique is based on the shift of the SERS spectral band characteristic of oxidized cytochrome *c* to the position characteristic of reduced cytochrome *c* upon transfer of an electron from superoxide radical anion to cytochrome *c*.[365]

Yet another approach to the SERS of living organisms is to use nanostructures modified with molecules producing no SERS spectrum but capable of selective binding to the biological object whose SERS spectrum is detected. An example is provided by the sensor for highly sensitive detection of bacteria in blood.[366] Gold or composite silver-gold nanostructured surfaces were coated with vancomycin, an antibiotic that specifically binds Gram-positive bacteria. This technique for the design of multifunctional biochips seems to be promising because vancomycin can be replaced by other glycopeptides to detect a wide range of microorganisms and viruses.

An analysis of cell composition and monitoring the dynamics of its changes requires nonspecific SERS sensors capable of enhancing the Raman signal of a large number of molecules located near nanoparticles, *e.g.*, proteins, lipids, nucleic acids, haemes, *etc*. For instance, SERS-active nanoparticles were fabricated and a method for studying processes accompanying apoptosis (DNA fragmentation and denaturation of proteins) was developed.[367] Poly(ethylene glycol)-stabilized gold nanospheres coated with the peptide arginine-glycine-aspartate and a signal peptide for targeted delivery to cell nuclei were synthesized. The nanoparticles were placed into the culture medium and apoptosis was initiated by adding hydrogen peroxide upon endocytosis. Observation of real-time dynamics of apoptosis and detection of the SERS spectra revealed the appearance of peaks characteristic of denaturated proteins and fragmented DNA molecules.

Glass micropipettes coated with gold nanoparticles were introduced into cells.[368] Depending on the intracellular localization of the pipette, enhancement of the signal from cell nucleus constituents or the cytoplasm was detected and the spectral pattern depended on the functional state of cells.[368] A method based on SERS using coatings decorated with gold nanoparticles[369] is aimed to detect the secondary messenger, an intracellular molecule released in response to stimulation of receptors and activation of primary effector proteins in Ca^{2+}-signaling of NADP. Nanomaterials based on gold and a new methodology of highly sensitive determination of changes in the molecular conformations of nucleic acids and proteins and *in vivo* visualization of cells were developed.[52] Functionalized gold nanoparticles for discrimination of different-type lymphocytes and detection of leukemia cells were proposed.[370]

Analysis of the conformation and state of haemoglobin molecules in living erythrocytes is an important, high-potential task for biomedical diagnostics,[371 – 373] because various pathologies including cardiovascular diseases, inherited disorders (thalassemia, haemoglobinopathy, *etc.*),[374 – 376] intoxication and functioning of the human body under extreme conditions[377, 378] can cause specific changes in the state of haemoglobin molecules. The SERS studies of isolated haemoglobin face a number of issues. For instance, haemolysis forces haemoglobin to interact with colloidal nanoparticles that usually are involved in chemical interaction with haeme through reactions with tryptophan residues, amides or aromatic amines. As a result, the molecular conformation of haemoglobin changes and information on its native state is lost.[373, 379] This example demonstrates the need for the development of novel noninvasive methods for structure elucidation of haemoglobin molecules in living cells.

There are two types of haemoglobin molecules in erythrocytes, namely, cytoplasmic haemoglobin (Hb_c) and submembrane haemoglobin (Hb_{sm}).[92, 372] Conventional Raman spectroscopy studies of blood cells allow one to record the spectra of Hb_c since the contribution of

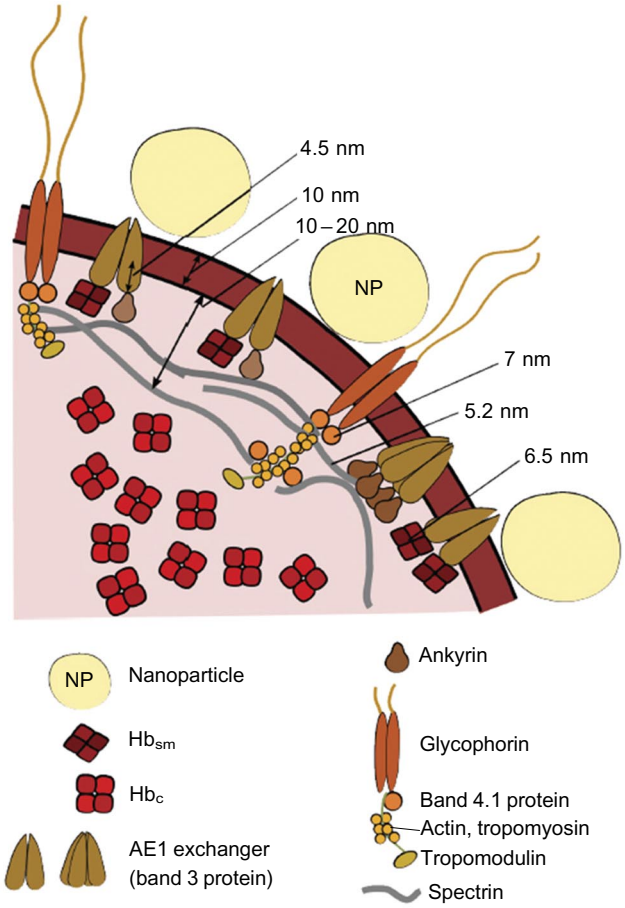


Figure 2. Erythrocytes contacting nanoparticles: a schematic structure.[92]

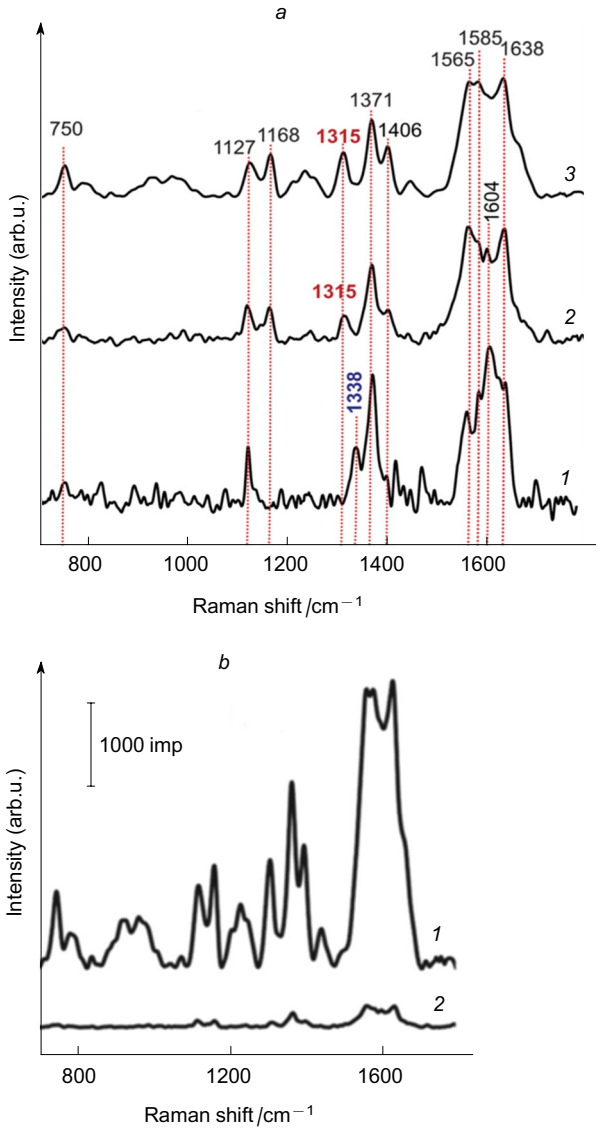


Figure 3. SERS spectra of erythrocytes (*1*) and mitochondria (*2*, *3*) recorded using $Ag@SiO_2$ colloidosomes.[248]
Normalized spectra (*a*) and changes in the intensity of spectral lines of mitochondria upon laser excitation at 532 (*1*) and 514 nm (*2*) (*b*); 'imp' stands for a scale bar.

Hb_{sm} is small because of a very low concentration of Hb_{sm} (less than 0.5% of the concentration of Hb_c). In the case of SERS, enhancement of Raman signal occurs from those Hb_{sm} molecules that are located in the immediate vicinity of the silver nanostructures (Fig. 2). Studies on the functional state and conformations of Hb_{sm} are of great importance for understanding processes occurring in erythrocytes and can serve as a basis for medical diagnosis in the future. Submembrane haemoglobin can be studied using colloidal silver nanoparticles, heterocomposite colloidosomes[248] or nanostructured coatings (Fig. 3).[21, 92, 288]

Methodological requirements of applied studies include very high reproducibility of the SERS spectra of the biological objects in hand. Any changes in the plasmon properties of nanostructures resulting from their storage or aggregation in biological solutions will influence the enhancement of Raman scattering of biomolecules and introduce artifacts into the spectra. For instance, solutions of identically prepared silver nanospheres can contain different relative numbers of nanoparticles whose size is less than 10 nm and larger than 50 nm; as a consequence, different-type aggregates are formed on the surface of erythrocytes and enhancement of the Raman scattering of Hb_{sm} becomes nonuniform.[21] Most likely, significant differences between the enhancement Raman scattering from intracellular molecules using nanoparticles of different diameter are due to different ability of the 'large' and 'small' nanoparticles to penetrate into the folds of the plasma membrane.[21] Therefore, fabrication of nanostructures with controlled morphology is crucial to biomedical studies.

The development of appropriate planar nanostructured materials and $Ag@SiO_2$ nanocomposites[248] made it possible to obtain a great, highly reproducible and selective enhancement of the Raman scattering signal of cytochrome *c* from the respiratory (electron transport) chain of intact living mitochondria. Using this technique, the redox state of cytochrome *c* in the intact mitochondria under modulation of the respiratory activity was studied for the first time and changes in the redox state and haem conformation of cytochrome *c* upon impair-

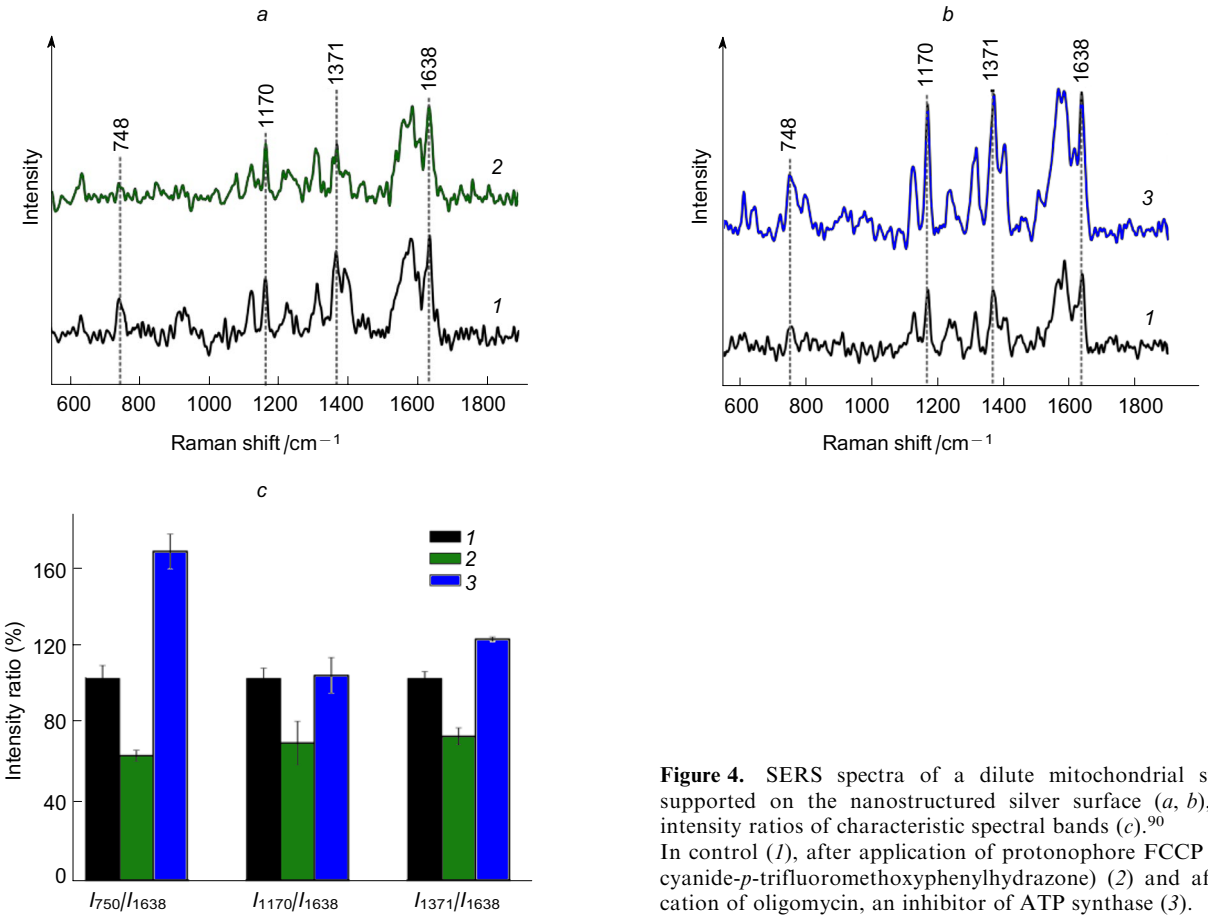


Figure 4. SERS spectra of a dilute mitochondrial suspension supported on the nanostructured silver surface (*a*, *b*), and the intensity ratios of characteristic spectral bands (*c*).[90]
In control (*1*), after application of protonophore FCCP (carbonyl cyanide-*p*-trifluoromethoxyphenylhydrazone) (*2*) and after application of oligomycin, an inhibitor of ATP synthase (*3*).

ment of respiration/electron transport chain and ATP synthesis, and upon inhibition of ATP synthesis by ATP synthase were demonstrated (Fig. 4).[90, 246, 380, 381] The SERS spectra of mitochondria allow one to evaluate changes in the relative content of reduced cytochrome *c* and the conformational mobility of cytochrome *c* haem (Fig. 4 *c*). In particular, taking intact mitochondria as an example, it was established for the first time that the addition of protonophore FCCP, which uncouples the ATP synthesis and the electron transport chain, decreases not only the relative amount of reduced cytochrome *c*, but also the conformational flexibility of haem methine bridges (see Fig. 4). On the contrary, oligomycin causes an increase in the conformational flexibility of the haem methine bridges and in the relative amount of reduced cytochrome *c* in mitochondria. This can be explained by slowing down electron transport in the mitochondrial respiratory chain and by accumulation of reduced charge carriers. The methodology seems to be promising for further studies of the function of the electron transport chain in intact mitochondria.

In conclusion, mention may be made that successful application of SERS-active nanostructures in biomedicine requires further interdisciplinary investigations aimed at determining the effect of nanostructures on the systems under study and involving the following:

— assessment of changes in the properties of nanostructures in biological fluids and upon contact with cells;

— synthesis of nanostructures that produce stable enhancement of the Raman signal with a reproducible spectral pattern due to reproducibility of the nanoparticle size, anisotropy and the aggregate structure or by uniformity of nanostructured coatings;

— detection of SERS spectra with peaks consistent with known characteristic vibrations.

As a consequence, this will provide unique information inaccessible to other instrumental methods of analysis and step up elaboration of methods for analysis of this information in order to integrate nanostructures in 'labs-on-chip' devices.

3.1.3. Detection of prohibited substances and quality control of pharmaceuticals

Detection and quantitative determination of pharmaceuticals and drugs is a challenge to biomedicine. In this connection, an undoubtful advantage of SERS is the possibility to establish the molecular structure. In some cases, the mechanism of binding of pharmaceuticals at active sites can be established by analyzing changes in the SERS spectra before and after interaction. SERS is mostly used in studies of anticancer drugs to determine their action mechanism, as well as to detect antiviral and antiretroviral drugs and diuretics. A DNA complex with doxorubicin in a silver hydrosol solution was studied.[382] Among various anticancer drugs studied by SERS, mention may be made of intoplicine. The SERS spectra of intoplicine and its complexes with DNA are available.[383]

Antiviral drug amantadine, which is also used in therapy of Parkinson's disease, interacts with colloidal silver particles.[384]

The detection of drugs by SERS was reported.[385 – 387] Key analytes include cocaine, amphetamine, methamphetamine, heroin, codeine, pemoline and many other compounds including prohibited substances (doping). Methods of *in situ* SERS detection of heroin, codeine and cocaine are available.[385] Yet another example is selective detection of cocaine in the presence of structurally similar compounds (benzocaine and lidocaine).[386] Compounds under study were adsorbed on colloidal silver particles and the analyte concentrations were of about 1 mg ml^{-1}. Silver and gold films proved themselves in SERS detection of amphetamine and a semi-quantitative method for the determination of this

Table 4. Main pharmaceuticals detected by SERS.

Analyte	SERS-Active surface	λ_{ex} /nm	c_{min} /mol litre^{-1}	Ref
	Anticancer drugs			
Emodin	Colloidal silver nanoparticles [a]	514	4×10^{-5}	388
Mitoxantrone	Colloidal silver nanoparticles coated with poly(ethylene glycol) (d = 10 – 20 nm)	488	10^{-6}	239
6-Mercaptopurine	Colloidal gold nanoparticles (d = 20 nm)	785	10^{-5}	389
6-Thioguanine (in human cancer cells)	The same	785	10^{-5}	389
Topotecan	"	–	2×10^{-4}	390
6-Thioguanine (in cells)	"	633	10^{-7}	391
Gemcitabine (in cells)	"	633	10^{-6}	391
Fadrozole (in cells)		633	10^{-6}	391
9-Aminoacridine	Colloidal silver nanoparticles [a]	1064	5×10^{-5}	392
		647	5×10^{-5}	392
		458	5×10^{-5}	392
	Antiviral and antiretroviral drugs			
Hypericin	Colloidal silver nanoparticles [a]	514	10^{-6}	393
Aciclovir	Colloidal gold nanoparticles (d = 20 nm)	633	10^{-5}	391
Quinacrine	Colloidal silver nanoparticles [a]	1064	10^{-7}	392
		647	10^{-7}	392
		458	10^{-7}	392
Pyrazinamide	Colloidal silver nanoparticles [a] (λ_{max} = 395 – 400 nm)	488	10^{-5}	394
Isoniazid	The same	488	10^{-5}	394
Isonicotinamide	"	488	2×10^{-5}	394
	Prohibited substances (doping)			
Aminoglutethimide	Colloidal silver nanoparticles (triangular nanoprisms l = 30 – 40 nm, 6.0 – 7.5 nm thick) and gold nanoparticles (d = 30 – 40 nm)	633	$10^{-9} – 10^{-8}$	311
Clenbuterol	Colloidal gold nanoparticles (d = 15 nm)	785	10^{-7}	395
Terbutaline	The same	785	2×10^{-7}	395
Salbutamol	"	785	3×10^{-6}	395
	Drugs			
Amphetamine	Colloidal silver nanoparticles [a]	514	3×10^{-3}	396
		633	3×10^{-3}	396
Cocaine	Klarite™ (see [b])	785	10^{-5}	397
Cocaine (in saliva)	Colloidal gold nanoparticles [a]	785	2×10^{-7}	398
Phencyclidine (in saliva)	The same	785	4×10^{-6}	398

[a] The nanoparticle size was not determined; the presence of nanoparticles was confirmed by the plasmon resonance peak in the absorption spectra.
[b] See Section 4.

compound using gold nanoparticles was proposed.[387] Certain anticancer, antiviral, prohibited substances (doping) and drugs that can be detected by SERS are listed in Table 4.

To design SERS sensors for monitoring the diffusion of pharmaceuticals and to assess how they penetrate through the cell membrane, silver-decorated silica microspheres were proposed.[399] The advantages of these systems include the possibility to investigate the diffusion kinetics of substances through the cell membrane towards particular cell organelles and to detect pharmaceuticals at lower concentrations compared to those detected by the fluorescence methods and, eventually, a lesser damage to cells. Usually, composites $Ag@SiO_2$ are prepared by modifying the surface of silica microspheres with amino groups using 3-aminopropyltrimethoxysilane. Then, the modified particles are mixed with a colloidal silver solution. The $Ag@SiO_2$ microspheres are consecutively incubated with U87-MG cancer cells and emodin (1,3,8-trihydroxy-6-methylanthraquinone, a potential anticancer drug); the undiffused emodin is removed and the SERS spectra are detected. The results of the SERS experiments are comparable with those obtained by fluorescence spectroscopy and allow emodin to be detected at concentrations in the range of 10^{-7}–10^{-5} mol litre^{-1}. Usually, qualitative analysis of samples for pharmaceuticals is insufficient, so quantitative determination is necessary. Although there is considerable literature on SERS detection of pharmaceuticals, detailed descriptions of particular methods for their quantitative determination in real samples are reported rarely.

3.2. Analysis of food and food additives

Surface-enhanced Raman spectroscopy finds application in quality control of food and food additives. High sensitivity and selectivity, as well as relatively simple sample preparation make the method suitable for routine analyses of food for toxic impurities. It can be used to detect pathogens (bacteria, spores, viruses), antibiotics (enrofloxacin, ciprofloxacin, chloramphenicol, *etc.*), drugs and prohibited substances (clenbuterol, sulfamerazine, ractopamine, theophylline, *etc.*), hormones (estrone, estradiol, estriol, bisphenol *A*, *etc.*), food additives, impurities (*e.g.*, pesticides).[400] The detection of toxic impurities in food using SERS was demonstrated taking melamine as an example.[307, 401, 402] Joint use of data obtained by different methods (most often, different versions of chromatography) can provide fast and effective monitoring of melamine impurities in bulk quantities of food and animal feed. To detect water-insoluble dyes, nanoparticles are modified with nonpolar compounds.[403] Table 5 presents the list of most important toxic compounds detected by SERS.

Table 5. Selected compounds detected in food by SERS.

Analyte	SERS-Active surface	λ_{ex} /nm	c_{min} /mol litre^{-1}	Object	Ref.
		Food additives			
Benzoic acid	Colloidal gold nanoparticles ($d \approx 13$ nm)	633	–	–	404
Phthalic acid (E)	The same	633	–	–	404
Butylhydroxy-anisole (E320)	Colloidal gold nanoparticles ($\lambda_{max} = 530$ nm, $d \approx 50$ nm)	785	5×10^{-5}	–	130
Thiabendazole (E233)	Colloidal silver nanoparticles	532	10^{-5}	–	405
	($d \approx 10-50$ nm)	1064	10^{-5}	–	405
Sodium benzoate (E211)	Colloidal silver nanoparticles	–	10^{-7}	–	406
	($\lambda_{max} = 430$ nm, $d \approx 20$ nm)				
Aspartame (E951)	Silver nanoparticle island films with	488	10^{-2}	–	407
	a surface roughness of 2.9 Å	514	10^{-2}	–	407
Monosodium glutamate (E621)	Colloidal silver nanoparticles ($\lambda_{max} = 530$ nm, $d \approx 50$ nm)	514	7×10^{-5}	–	408
4-Arsanilic acid	Ag/polydimethylsiloxane 20 ± 2 nm thick	633	10^{-4}	–	409
Roxarsone	The same	633	10^{-4}	–	409
Acetarsone	"	633	10^{-4}	–	409
L-Carnitine	Silver nanoparticle sol	514	10^{-4}	–	410
Creatine	The same	514	10^{-4}	–	410
		Pesticides			
Methamidophos	Colloidal silver nanoparticles ($\lambda_{max} = 408$ nm, $d \approx 50$ nm)	785	7×10^{-9}	African firefinch, Brussels sprout, leek	134
Chlorpyrifos	Aluminium foil (Raman spectra)	780	48 mg kg^{-1}	Apple surface	411
Azinphos methyl	Q-SERS^{TM} G1 (see [a])	–	5×10^{-7}	Apples, tomatoes	412

Table 5 (continued).

Analyte	SERS-Active surface	λ_{ex} /nm	c_{min} /mol litre^{-1}	Object	Ref.
		Pesticides			
Azinphos methyl	Q-SERS^{TM} G1 (see [a])	–	5×10^{-7}	The same	412
Carbaryl	The same	–	5×10^{-7}	"	412
		Nutritional supplements			
Dimethoate	Silver nanoparticle sol	514	10^{-5}	–	413
		633	10^{-5}	–	413
		785	10^{-5}	–	413
Omethoate	The same	–	10^{-5}	–	413
Tricyclazole	Colloidal silver nanoparticles [b]	785	10^{-8}	Rice grains	129
		Antibiotics and prohibited substances			
Furadantin	Colloidal gold nanoparticles (red, $d \approx 50$ nm)	785	2×10^{-5}	–	414
Furaltadone	The same	785	2×10^{-5}	–	414
Tetracycline	Nickel microspheres coated with gold nanoparticles ($d \approx 5$ nm)	785	2×10^{-7}	–	415
Ciprofloxacin	Silver dendrites ($d \approx 5$ nm)	785	6×10^{-5}	–	127
Enrofloxacin	The same	785	6×10^{-5}	–	127
Chloramphenicol	"	785	6×10^{-5}	–	127
Enrofloxacin	Klarite^{TM} (see [a])	785	10^{-2}	–	416
Chloramphenicol	Klarite^{TM} (see [a])	785	2×10^{-7}	–	417
Furazolidone	Q-SERS^{TM} (see [a])	785	4×10^{-6}	Fish (tilapia fillet)	416
		Prohibited dyes			
Sudan-I	Colloidal silver nanoparticles [b]	785	10^{-4}	Paprica	122
	Gold nanoparticles on silicon substrate (MaRS Technology Co., Ltd)	785	–	–	418
Sudan-III	Silver nanoparticles ($d \approx 30-60$ nm)	488	9×10^{-6}	Paprica	403
Rhodamine B	The same	785	–	–	418
Malachite green	"	785	–	–	418
Sudan-II	ZnO/Ag nanostructure ($d_{Ag} \approx 30-60$ nm)	514	10^{-12}	–	419
Sudan-IV	The same	514	10^{-12}	–	419
Brilliant yellow (E142)	200-nm silver films supported on silica gel ($d \approx 470$ nm) or polystyrene nanospheres ($d \approx 533$ nm)	514	10^{-6}	–	420
Crystal violet	Q-SERS^{TM} (see [a])	780	5×10^{-8}	–	417
Tetrazine (E102)	Colloidal gold nanoparticles [b]	514	5×10^{-10}	–	421
		Mycotoxins and other toxins			
Aflatoxin B1	Silver nanorods ($l = 870$ nm, $d = 100$ nm)	785	5×10^{-5}	–	129
Aflatoxin B2	The same	785	10^{-4}	–	129
Aflatoxin G1	"	785	5×10^{-6}	–	129
Aflatoxin G2	"	785	5×10^{-6}	–	129
Saxitoxin	Colloidal silver nanoparticles [b]	–	2×10^{-9}	–	422

[a] See Section 4. [b] The nanoparticle size was not determined; the presence of nanoparticles was confirmed by the plasmon resonance peak in the absorption spectra.

3.3. Analysis of environmental objects

Using SERS, researchers can solve a wide range of issues in the studies of environmental objects including soils,[423 – 426] natural water;[309, 428 – 430] wastewater [431 – 435] and air;[436, 437] in environmental monitoring in the field [438] with minimum sample preparation,[439] as well as in improvement of industrial petroleum refining processes to reduce technogenic pollution.[440 – 442] The method is employed to investigate the structure and qualitative composition of soils; for highly sensitive detection and multiplex determination of organic and inorganic pollutants and pathogens;[443 – 445] in studies of plants, tissues of living organisms and microorganisms;[109, 446] these fields of application are almost inaccessible to other methods.[447, 448] The availability of portable Raman spectrometers makes SERS a rapid and user-friendly method.[112, 307, 449] However, to solve all problems, one should overcome certain constraints.[446]

Fluidic systems developed for SERS studies [450] were adapted for analysis of environmental objects.[429, 451 – 454] Quantitative SERS analysis of environmental objects is carried out using internal references (to normalize signals) or microfluidic cells [455] where the sample flows are turbulently mixed, which abruptly reduces the scatter of the results of different measurements and allows one to obtain reliable calibration curves for the determination of pesticides, nicotine, cyanides, parathion methyl, Saxitoxin,[456] dipicolinic acid (anthrax biomarker),[457] uranyl ions [458] and other compounds.[459]

3.3.1. Analysis of soils

Soil is difficult to analyze because its main components, *viz*., clays, inorganic oxides and humic substances, have large specific surface areas, which predetermines the adsorption of pollutant molecules. Using SERS, one can obtain information on the composition and structure of soil.[47, 460, 461] Most other methods cannot simultaneously solve both tasks and often require specific experimental conditions.

Humic substances, that is, organic compounds of complex structure are an important component of soil. They are responsible for soil productivity and acidity. Using SERS, one can determine their molecular structure and monitor how it changes upon interaction with various compounds (in particular, pollutants). Usually, analyte samples are obtained by extractive methods. SERS enables multiplex detection of compounds in extracts [460, 461] and the possibility to investigate adsorbates on the surface of humic substances.[47] Also, it was proposed to use the reductive properties of humic substances for the synthesis of gold nanoparticles directly in the course of the interaction of the analyte extract with a potassium tetrachloroaurate(III) solution; this allows one to detect an enhanced Raman signal of 2-sulfanylbenzothiazole, a widely used inorganic pollutant.[462] Usually, SERS detection of certain hazardous compounds involves a single, relatively short-term (10 min) extraction without further purification (as in some alternative methods).[463]

3.3.2. Analysis of water

At the present, SERS is most widely used for analysis of natural water and wastewater since it does not require preliminary sample preparation. Indeed, it is sufficient to mix a sample with a colloidal solution of SERS-active metal particles or to place a water aliquot on the surface of a plasmonic nanostructure. Most often, SERS is used to detect pesticides and factory waste (see Table 4).[47]

The possibility to detect different classes of inorganic compounds using a silver electrode as a SERS-active surface was studied. Humic substances present in natural water do not preclude the detection of many pollutants including aniline, benzene, phenol, benzothiophene, pyridine, indole, methanol, benzofuran, carbon tetrachloride, *etc*.[428] To detect pyridine, nicotinic acid and pesticides (carbendazim and metazachlor) in aqueous solutions, a combination of flow injection analysis with SERS was proposed.[429] Trace amounts of these pollutants were detected using the surface of electrolytically deposited silver as a SERS-active surface. Besides, an optical sensor based on Ag nanoparticles for water quality assessment was developed.[306] The indicator system of the sensor contains a polycarbonate membrane for pre-concentration of analytes, which allows one to detect rather low concentrations of various nitrogen-containing organic compounds.

An important aspect in analysis of water is the SERS detection of nonpolar compounds bearing no functional groups facilitating chemisorption. These compounds are formed during production at the enterprises of chemical, petrochemical, metallurgic, pulp and paper and other industries and often represent technogenic pollutants (polyaromatic hydrocarbons, toxic substances). In this connection, there has been considerable research activity aimed at modifying SERS-active surfaces, in particular, through hydrophobization. Moreover, efficient operation of SERS sensors requires efficient selective binding of analytes and the formation of an intense analytical signal. Considering optical sensors, it seems promising to combine methods for selective isolation/separation of analytes with enhancement of the optical signal using nanostructured materials. Therefore, the design of a versatile sensor structure for the simultaneous concentration of analytes and formation of an intense analytical signal becomes a challenge. To solve this problem is urgent for chemistry and materials science.

Better adsorption of polyaromatic hydrocarbons on the surface of SERS sensors was attained using substrates fabricated as follows: quartz plates were functionalized with trimethoxy(3-mercaptopropyl)silane and then coated with a gold layer and a monolayer of self-assembling propane-1-thiol molecules.[464] The SERS-active surface thus fabricated enables the detection of pyrene, benz[*a*]pyrene and fluoranthene in natural water at concentrations of the order of 10^{-6} mol litre^{-1}. Polyaromatic hydrocarbons were also detected by SERS in sea water at concentrations of about 10^{-7} mol litre^{-1}.[465] A SERS sensor representing a quartz plate modified with trimethoxy(3-mercaptopropyl)silane and coated with gold nanoparticles 40 – 100 nm in diameter was designed to detect naphthalene and pyrene in sea water with LOD of about of 10^{-8} mol litre^{-1}.[466]

Extraction of nonpolar compounds from water is due to hydrophobic interactions, that is, polyaromatic hydrocarbons are adsorbed on the nonpolar sensor surface. It was proposed to detect them using gold nanoparticles hydrophobized with poly(glycidyl methacrylate-*co*-ethylene dimethacrylate); the LOD values for anthracene,

phenanthrene and pyrene used as model analytes were 10^{-7}, 5×10^{-7} and 10^{-8} mol litre^{-1}, respectively.[467] Besides, the detection of components of a complex mixture containing 18 different polyaromatic hydrocarbons was demonstrated using rough surface of a silver electrode as a SERS-active planar structure. The LOD values of the analytes differed considerably, being equal to 8×10^{-8} mol litre^{-1} for dibenzothiophene (DBT) and 10^{-15} mol litre^{-1} for azulene. This was explained by different mechanisms of signal enhancement, namely, electromagnetic enhancement in the case of DBT and by additional contribution of the 'chemical' mechanism in the latter case since azulene is characterized by charge separation in its structure (seven-membered ring bears a positive charge while the five-membered ring bears a negative charge).[468]

Yet another method of sorption of nonpolar pyrene and anthracene on the metal surface involves modification of gold nanoparticles with 6-deoxy-(6-thio)-β-cyclodextrin.[469] Polyaromatic hydrocarbon molecules enter the cyclodextrin cavity and form 'host – guest' complexes through hydrophobic interactions. The β-cyclodextrin cavity has the shape of a truncated cone with a height of 7.9 Å and a diameter of 6.4 Å; therefore, the SERS-active particles in question exhibit selectivity with respect to molecules less than 6.4 Å in size. The LOD values of pyrene and anthracene were 7.5×10^{-6} and 10^{-5} mol litre^{-1}, respectively. It is believed[471] that the limits of detection of polyaromatic hydrocarbons can vary depending on the stoichiometry of the 'host – guest' complexes. The method is suitable for detection of model analytes in their individual solutions in the concentration range from 10^{-6} to 10^{-8} mol litre^{-1}.[470] Using functionalized gold nanoparticles as SERS-active material, certain analytes can be detected at a level of 10^{-9} mol litre^{-1}.[470] The limits of detection of anthracene and pyrene on the surface of silver nanoparticles modified with decane-1-thiol were 5×10^{-9} and 1.4×10^{-8} mol litre^{-1}, respectively.[471]

Polyaromatic hydrocarbon molecules absorbing in the UV region (270 – 330 nm) give rather low enhancement factors because this wavelength range is far from that of surface plasmon resonance of silver or gold nanospheres (~380 – 450 nm and 500 – 550 nm, respectively). Therefore, polyaromatic hydrocarbons should be transformed into coloured compounds that absorb visible light, *i.e.*, in the longer-wavelength spectral region.[440] Polyaromatic hydrocarbons are efficient electron donors and can form charge-transfer complexes with π-acceptor molecules; these systems absorb in the visible region (450 – 750 nm).

Hydrophobic properties of nanostructured metal surfaces can be tuned or changed by coating with polymer layers having different properties.[472] This approach allows one to detect different aromatic compounds in complex nonpolar matrices and is thought to be promising for rapid analysis of petrochemical quality markers in motor fuel and in the environment.[486, 487] Besides, it is suitable for the detection of sulfur-containing heterocyclic compounds (DBT, its homologues and oxidized forms). These components of crude petroleum are difficult-to-remove by hydrodesulfurization while their maximum allowable content should meet the environmental regulations.[440]

3.3.3. Analysis of air

The design of gas sensors is a topical trend in applied research which extends the scope of SERS in analysis (Table 6). However, efficient gas-phase sorption of analytes on SERS-active surfaces requires much greater efforts compared to the process in water.[185] Analyte molecules bearing functional groups with high chemical affinity for gold or silver nanoparticle surfaces are adsorbed onto freshly prepared metallic films directly from the air sample.[47] Using different types of silver surfaces, one can perform multiplex analysis of aerosols for acridine, quinacrine, 4-nitrophenol and 4,6-dinitrophenol present at concentrations down to about 10^{-9} g.[475]

Table 6. Major environmental pollutants detected by SERS.

Analyte	SERS-active surface	λ_{ex} /nm	c_{min} /mol litre^{-1}	Object	Ref.
	Organic pollutants				
Thiophenol	Colloidal gold nanoparticles (λ_{max} = 520 nm, d = 30 – 60 nm)	633	10^{-5}	Soil	478
1-Aminonaphthalene	The same	633	10^{-5}	Soil	478
Pyridine	"	633	10^{-5}	Soil	478
4-Aminobenzoic acid	Silver nanoparticles [a] (layer thickness 19 nm)	633	3.5×10^{-8}	Wastewater	479
4-Hydroxybenzoic acid	The same	633	2.9×10^{-8}	The same	479
4-Chlorobenzoic acid	"	633	5.9×10^{-8}	"	479
Phenolphthalein	"	633	5.5×10^{-8}	"	479
Hexogen (cyclotrimethylenetrinitramine)	Colloidal gold nanoparticles (d = 90 – 100 nm)	785	7×10^{-7}	Groundwater	480
2,4,6-Trinitrotoluene	Colloidal gold nanoparticles (d = 30 nm)	670	~ 10^{-12}	–	481
Thiram	Colloidal gold nanoparticles (d = 43 – 65 nm)	785	4.4×10^{-8}	–	482

Table 6 (countinued).

Analyte	SERS-active surface	λ_{ex} /nm	c_{min} /mol litre^{-1}	Object	Ref.
	Polyaromatic hydrocarbons				
Fluoranthene	Silver nanoparticles (d = 50 – 70 nm) supported on copper foil	785	$\sim 10^{-6}$	–	483
Acenaphthene	The same	785	$\sim 10^{-6}$	–	483
Naphthalene	"	785	$\sim 10^{-6}$	–	483
	Polystyrene microspheres ($d \approx$ 800 nm) coated with gold nanoparticles ~10 – 15 nm thick	633	8×10^{-6}	–	484
	Fe_3O_4@Ag composite nanospheres (d = 30 – 70 nm) modified with pentane-1-thiol and coated with silver nanoparticles 15 nm thick	785	$\sim 10^{-6}$	–	485
Benzene	The same	785	$\sim 10^{-6}$	–	485
Anthracene	"	785	$\sim 10^{-6}$	–	485
Phenanthrene	"	785	$\sim 10^{-6}$	–	485
Pyrene	"	785	$\sim 10^{-6}$	–	485
Perylene	"	785	$\sim 10^{-6}$	–	485
Benz[*a*]pyrene	"	785	$\sim 10^{-6}$	–	485
Fluorene	"	785	$\sim 10^{-6}$	–	485
	Silver nanoparticles (d = 50 – 70 nm) supported on copper foil	785	$\sim 10^{-6}$	–	483
	Inorganic pollutants				
UO_2^{2+}	Sol – gel films with silver nanoparticles (d = 80 – 100 nm)	633	8.5×10^{-8}	–	458
NpO_2^+	The same	633	10^{-3}	–	458
Cr^{6+}	Fe_3O_4@Ag composite nanospheres (d = 30 – 70 nm) coated with silver nanoparticles	785	10^{-7}	Wastewater	486
UO_2^{2+}	Colloidal gold nanoparticles (d = 50 – 60 nm) modified with aminomethylphosphonic acid	785	8×10^{-7}	Water	487
Hg^{2+}	Tryptophan-modified gold nanoparticles (d = 40 – 60 nm)	670	3×10^{-8}	Wastewater	488
CN^-	Colloidal gold nanoparticles (d = 60 nm)	670	4×10^{-12}	–	489

[a] The nanoparticle size was not determined; the presence of nanoparticles was confirmed by the plasmon resonance peak in the absorption spectra.

However, most volatile pollutants are poorly adsorbed on metal surfaces and therefore the surfaces should be modified with some trapping agents.[47] For instance, the trapping concept is used to detect carcinogenic polyaromatic hydrocarbons in air. The sensitive layer of a sensor for the detection and identification of such compounds comprises silver nanoparticles bearing adsorbed n-decane-1-thiol. Owing to the presence of surface hydrophobic groups adsorption of polyaromatic hydrocarbons occurs quite rapidly and the response time of the sensor is at most 5 min.[471] The chemical affinity of sulfur for gold nanoparticles was used to detect naphthalene-2-thiol at a concentration of 4.4×10^{-11} mol litre^{-1} using a sensor with nanostructured gold surface; however, the process takes a long time, from 60 to 100 min.[490] To protect the SERS-active surface from degradation, systems for the detection of chlorine-containing solvents, aromatic compounds and methyl *tert*-butyl ether can be equipped with a thermoelectric cooler (temperature of analysis was 5 to 15 °C).[476] Multiplex detection of volatile compounds in air by SERS is also possible. In particular, ethanol and acetone vapours were detected using a planar sensor with the active layer made of nanorods; the corresponding LODs were equal to 1.7×10^{-12} and 3.7×10^{-12} g.[477]

4. New experimental approaches in the field of SERS sensorics

Wide use of SERS gave an impetus to manufacture ready-to-use standard SERS-active metal surfaces for studies of the enhancement mechanisms of SERS signal,[490] molecular imprinting,[491] quality control of pharmaceuticals[492] and food,[493,494] drinking water,[495] and

for comparison of the efficiency of the newly designed and commercially available SERS-active surfaces.[496] The most widely used commercially available SERS surfaces include Klarite™ (D3technologies, United Kingdom), Q-SERS™ G1 and SERS™ G0 (Nanova, USA). Standard samples represent glass plates with small areas (4 × 4 mm) coated with a SERS-active metal, mostly gold. Plates with a controlled contact angle are also available; this allows one to obtain better reproducibility of results and to use the Q-SERS™ G1 or SERS™ G0 surfaces depending on the hydrophilicity of the analyte sample.

From the standpoint of reducing the price of analysis it seems promising to design SERS sensors with a renewable or multiple-use surface. For instance, a nanostructured surface has been developed which remains SERS-active after more than ten adsorption – cleaning cycles. This was demonstrated taking the detection of two dyes, rhodamine 6G (10^{-12} mol litre^{-1}) and methylene blue (10^{-13} mol litre^{-1}), as examples; the enhancement factor was $10^7 - 10^8$. However, the authors[497] emphasized the need to study the possibility of combining sensors and portable Raman spectrometers. Since the enhancement factors of many commercially available SERS-active surfaces are not high, the need arises for the design of more efficient specific (aimed at solving particular tasks) and available SERS sensors.

In spite of all undisputed advantages of SERS in the detection of many important analytes, two main problems are still to be solved. One of them is the mismatch between the main UV absorption lines of many organic compounds and the plasmon resonance band (~410 nm for silver and 520 nm for gold).[498, 499] The other problem arises from low adsorption and insufficient pre-concentration of small nonpolar analyte molecules bearing no functional groups on the metal surfaces. Therefore, these molecules give low enhancement factors when using standard SERS-active materials. As mentioned above, this concerns many organic ecotoxicants, that is, polyaromatic hydrocarbons and heterocyclic sulfur compounds. The latter are the most difficult-to-remove from petrochemicals and can thus be treated as hydrocarbon fuel quality markers. These limitations preclude the use of SERS as a highly sensitive tool for the detection of certain important analytes.

The most expected solution to this problem is smart functionalization of metal surfaces.[500] A simple and efficient method[440] for the detection of polyaromatic heterocyclic compounds is based on transformation of π-donor compounds into charge-transfer complexes. For instance, solutions containing heterocyclic polyaromatic sulfur compounds [DBT, its oxidized forms DBTO and $DBTO_2$ and an alkyl derivative, 4,6-dimethyldibenzothiophene (4,6-DMDBT)] exhibit no strong signals in the SERS spectra recorded using silver nanoparticles as SERS-active material. Coating nanostructured silver surfaces with π-acceptors enables quantitative determination of these compounds. In particular, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and 7,7,8,8-tetracyanoquinodimethane (TCQM) are the most appropriate trapping agents for quantitative determination of heterocyclic polyaromatic sulfur compounds.

The formation of a charge-transfer complex is accompanied by the appearance of a new Benesi – Hildebrand

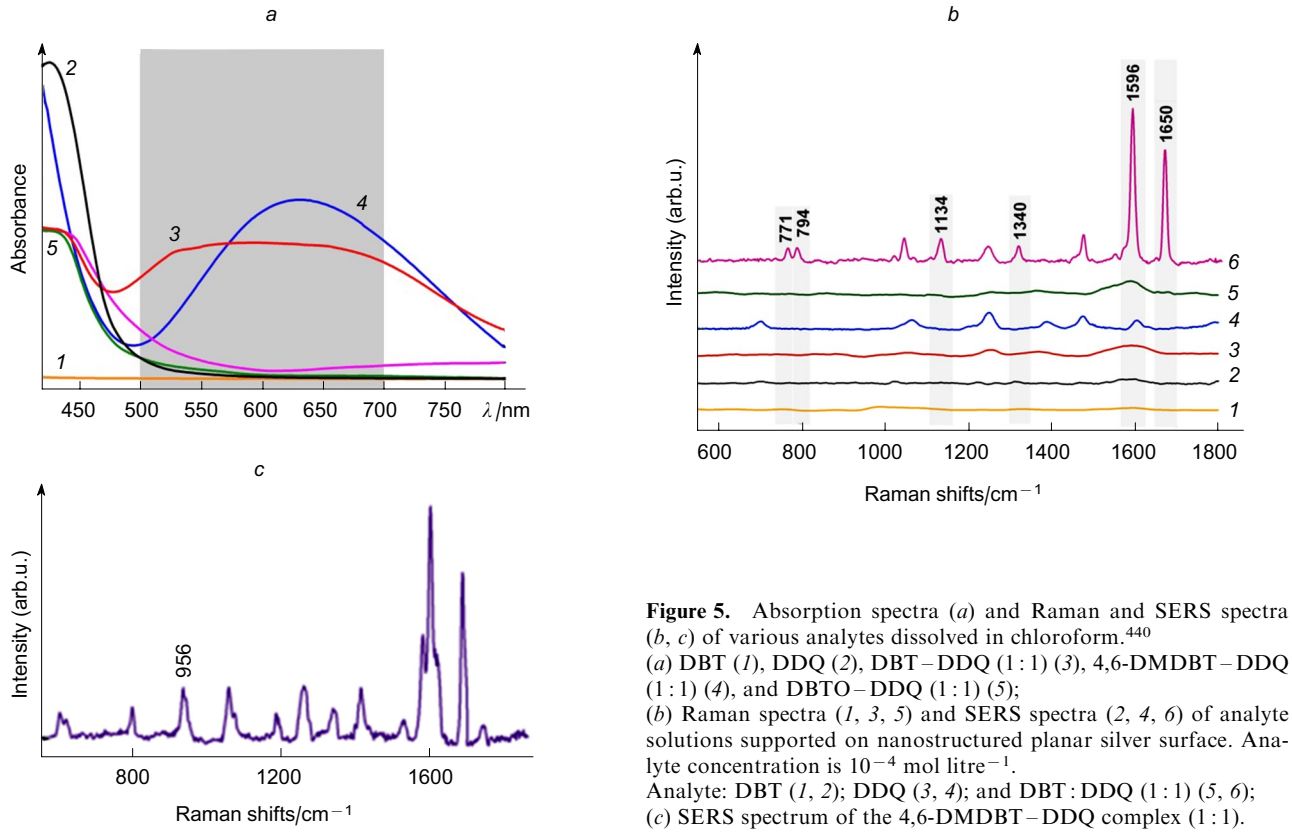


Figure 5. Absorption spectra (*a*) and Raman and SERS spectra (*b*, *c*) of various analytes dissolved in chloroform.[440]
(*a*) DBT (*1*), DDQ (*2*), DBT – DDQ (1 : 1) (*3*), 4,6-DMDBT – DDQ (1 : 1) (*4*), and DBTO – DDQ (1 : 1) (*5*);
(*b*) Raman spectra (*1*, *3*, *5*) and SERS spectra (*2*, *4*, *6*) of analyte solutions supported on nanostructured planar silver surface. Analyte concentration is 10^{-4} mol litre^{-1}.
Analyte: DBT (*1*, *2*); DDQ (*3*, *4*); and DBT : DDQ (1 : 1) (*5*, *6*);
(*c*) SERS spectrum of the 4,6-DMDBT – DDQ complex (1 : 1).

absorption band in the spectrum (see the 500 – 600 nm region in Fig. 5 *a*). The electronic system of such a complex supported on the nanostructured metal surface is at resonance with the electronic system of silver nanoparticles. Induced electronic excitation of the molecular structure influences the number and frequencies of vibrational modes of the charge-transfer complex. For instance, the appearance of new modes in the Raman spectra can be associated with the formation of new vibronic structures.[501] The intensities of the Raman signals of all compounds under study and their complexes present at the specified concentrations do not much exceed the background intensity (see Fig. 5 *b*, spectra *1* – *5*), except DDQ characterized by weak peaks (see Fig. 5 *b*, spectrum *4*). However, the SERS spectra of the charge-transfer complex exhibit strong characteristic peaks indicating that the complex is immobilized on the substrate. Positions of most characteristic peaks of DBT and DDQ are different; therefore, the SERS spectrum of the DBT – DDQ complex (1 : 1) corresponds to DBT as analyte immobilized in the charge-transfer complex. Besides, the method allows one to distinguish between certain alkyl derivatives of DBT. The strongest signals in the spectrum of the 4,6-DMDBT – DDQ charge-transfer complex (1 : 1), one of the most difficult-to-remove contaminants of petrochemicals, correspond to eigenmodes analogous to those of the DBT – DDQ complex (1 : 1). Certain additional bands in the experimental spectra (at 929 and 1567 cm^{-1}) can be assigned to the characteristic peaks of 4,6-DMDBT. The signal of DBT at 1674 cm^{-1} in the Raman spectra appeared to be weak (its intensity was only 12 – 14 times higher than the background intensity at a concentration of 10^{-3} mol $litre^{-1}$). The enhancement factor of the signal of DDQ at 1250 cm^{-1} at the same concentration is 25 – 30 (Table 7). At the same time, the enhancement factor calculated for the DBT – DDQ complex is 3×10^4. This offers prospects for elaboration of sensitive and selective methods for the detection of polyaromatic heterocyclic sulfur compounds.[440]

Table 7. Enhancement factors of systems studied by SERS.[440]

Concentration /mol $litre^{-1}$	Surface	Raman shift /cm^{-1}	EF [a]
	DBT as analyte		
10^{-3}	–	1674	–
10^{-4}	Silver nanoparticles	1674	3 – 4
	DDQ as analyte		
10^{-3}	–	1250	–
10^{-4}	Silver nanoparticles	1250	25 – 30
	DBT – DDQ as analyte		
10^{-3}	–	1674	–
10^{-4}	Silver nanoparticles	1674	30 000

[a] The enhancement factor (EF) is calculated as follows:

$$EF = \frac{I_{SERS}}{I_{Raman}} \frac{c_{Raman}}{c_{SERS}}$$

where I_{SERS} and I_{Raman} are the intensities of a chosen band in the SERS and Raman spectra, respectively, and c_{SERS} and c_{Raman} are the concentrations of the molecules producing the SERS and Raman signals, respectively.

Fabrication of chemically modified planar substrates for optical sensors for the detection of polyaromatic heterocyclic sulfur compounds enables multiplex analysis of a mixture of analytes owing to significant differences between the Raman spectra of analytes with different molecular structures. Therefore, the SERS spectra can be treated as a kind of spectral 'fingerprints' of analytes and it is of importance that they are sensitive not only to

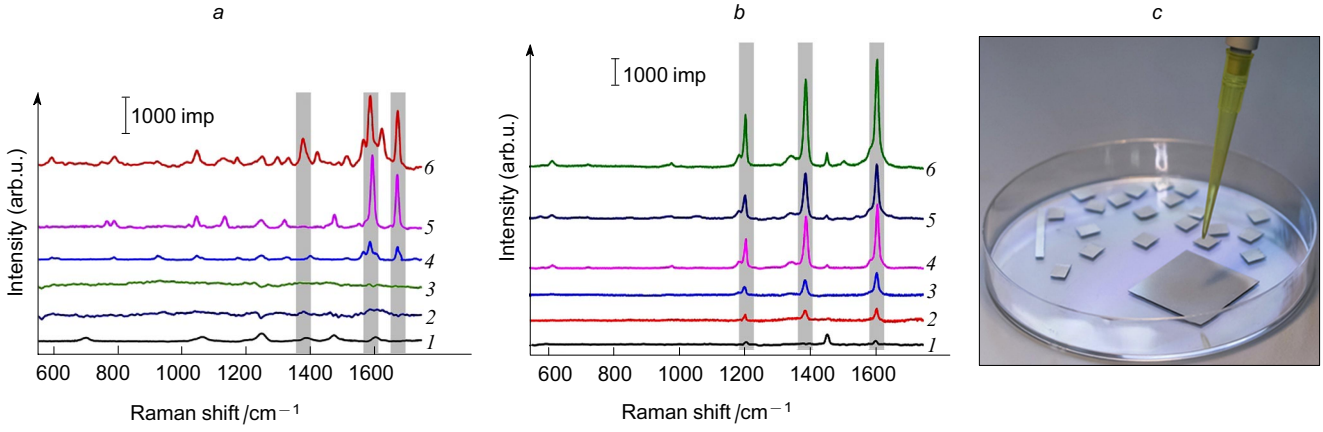


Figure 6. SERS spectra of compounds in model mixtures with DDQ (5 mmol $litre^{-1}$) (*a*) and TCQM (0.5 mmol $litre^{-1}$) (*b*) supported on planar nanostructured silver surface.[131]
(*a*) No analyte (*1*), $DBTO_2$ (*2*), DBTO (*3*), 4,6-DMDBT (*4*), DBT (*5*), a model mixture DBT – 4,6-DMDBT – DBTO (1 : 10 : 9) (*6*);
(*b*) no analyte (*1*), DBT (*2*), 4,6-DMDBT (*3*), $DBTO_2$ (*4*), a model mixture 4,6-DMDBT – DBTO (*5*), DBTO (*6*);
(*c*) planar surface synthesised represented a large square sheet (24 × 24 mm) cut into small squares (4 × 4 mm); mixtures under study were placed on the small squares using a dosing unit.

significant changes in the reporter structure, but also to the conformation of the analyte molecules.

The SERS spectra shown in Fig. 6 were obtained in a study of the possibility of multiplex detection of compounds in model multicomponent mixtures DBT – 4,6-DMDBT – DBTO at a concentration ratio of 1 : 10 : 9 using DDQ and TCQM as acceptors. The spectra of this three-component mixture recorded in the presence of DDQ exhibit characteristic signals corresponding to vibrations of structural fragments of DBT and 4,6-DMDBT molecules at 1134 cm^{-1}, thiophene ring at 1584 – 1627 cm^{-1}, and C=C aromatic bonds. Contrary to this, the spectrum recorded using the TCQM-modified SERS-active surface demonstrated selectivity to the oxidized form DBTO. Using different acceptors, one can implement multiplex detection of structurally similar compounds owing to effective measurement of spectra and selective formation of corresponding charge-transfer complexes.[131]

By varying substituents at the aromatic ring of the π-acceptor one can control the stability of the complexes, extend the range of analytes to be detected and improve the selectivity. The approach using charge-transfer complexes is unique and can be successfully employed to detect other important analytes, in particular, nonpolar organic molecules bearing no functional groups. This extends the scope of SERS in the field of environmental monitoring of water, air and soil, as well as petrochemical quality control.

Rapid analysis of fuel quality and environmental monitoring using commercially available portable equipment opens up new horizons for SERS. A comparison of characteristics of different physicochemical methods of analysis is presented in Fig. 7 taking the detection of hydrocarbons and heterocyclic compounds in petroleum and petrochemicals as examples.

The approach involving optimization of methods for fabrication of nanostructures and targeted modification of their surface can make SERS highly competitive with the related methods in availability, rapidity, simplicity of sample preparation, sensitivity and selectivity. Considering routine experiments, SERS is about ten orders of magnitude more sensitive than IR spectroscopy, which is physically the closest related optical method of analysis. Indeed, SERS allows one to detect mixture component concentrations of about 10^{-9} molar per cent *vs.* a few molar per cent for IR. In some cases, detection of single molecules is possible. This is comparable with the sensitivity of gas chromatography with mass spectrometric detection and ion-cyclotron resonance mass spectrometry and much exceeds that of X-ray fluorescence spectroscopy. In addition, SERS is characterized by the best rapidity of analysis, *viz.*, detection of the analytical signal takes fractions of a minute, which is comparable with rapidity of IR spectroscopy; *i.e.*, both methods enable high-performance screening. As to other methods, analyses take a few minutes (or tens of minutes) for chromatography and up to 3 – 5 min for X-ray fluorescence spectroscopy to acquire high-quality data.

Besides, SERS experiments almost do not require sample preparation; usually, no optical cells are needed for nondestructive (noninvasive) analysis of small samples (5 – 10 μlitre) provided that a microscope accessory is available and large surface areas provided that a fibre optic channel is available. Taking account of a long operating life of excitation lasers, a single analysis becomes cheap.

X-Ray fluorescence spectroscopy experiments require expensive optical cells transparent to characteristic X-ray radiation. Usually, sample cells are also needed for IR spectroscopy which is also sensitive to polar molecules (in particular, water) that form hydrogen bonds in samples. This makes the method of limited use in analysis of biological samples containing low concentrations of analyte molecules.

As to chromatographic methods, the column unit requires thorough sample preparation to provide long operating life. These methods are also characterized by long time of analyses and rather high cost of single analysis. IR spectroscopy ranks first in availability of equipment, being followed by SERS. However, expensive (including chromatographic) equipment enables multiplex detection of analytes. In this respect, ion-cyclotron resonance mass spectrometry is undoubted leader. The next is gas chromatography with mass spectrometric detection. Both IR spectroscopy and SERS allow one to simultaneously detect about ten analytes in a mixture, but SERS has a higher selectivity if the SERS-active surface is modified with molecular traps that selectively bind the target analytes. A feature of X-ray fluorescence spectroscopy is the risk of significant distortion of the analytical signal due to the matrix effects manifested in the presence of impurities since their characteristic radiation is overlapped with the signal of the target analyte.

Unfortunately, the problem of relatively low reproducibility of line intensities in the SERS spectra is still to be solved, although a spectral resolution 1 – 2 cm^{-1} is achieved reproducibly and allows SERS to compete with IR spectroscopy in multiplexity of analysis. At the same time, the data in Table 1 show that 'irreproducibility' of results is a tentative problem which will undoubtedly be resolved with advances in the design of novel materials for SERS and further improvement of the SERS methodology and experimental techniques. Recent considerable improvement of the reproducibility of SERS data is to a great extent related to fabrication of specific nanostructured materials (see references in Table 1). In this respect SERS now approaches IR spectroscopy and X-ray fluorescence spectroscopy, being, however, less efficient than gas chromatography with mass spectrometric detection and especially ion-cyclotron resonance mass spectrometry.

Thus, the approach involving optimization of methods for fabrication of nanostructures and targeted modification of their surface makes SERS highly competitive with the related methods in availability, rapidity of analysis, simplicity of sample preparation (or the absence of this step), sensitivity and selectivity. One should expect further progress and improvement of SERS through extension of the range of analytes, improvement of metrological characteristics of the available analytical procedures and elaboration of new techniques that should provide multiplex detection of target analytes in complex sample matrices with metrological characteristics necessary to solve particular problems. This will enable SERS to occupy its rightful place among the methods of chemical analysis used in critical areas including modern medical diagnosis.[502]

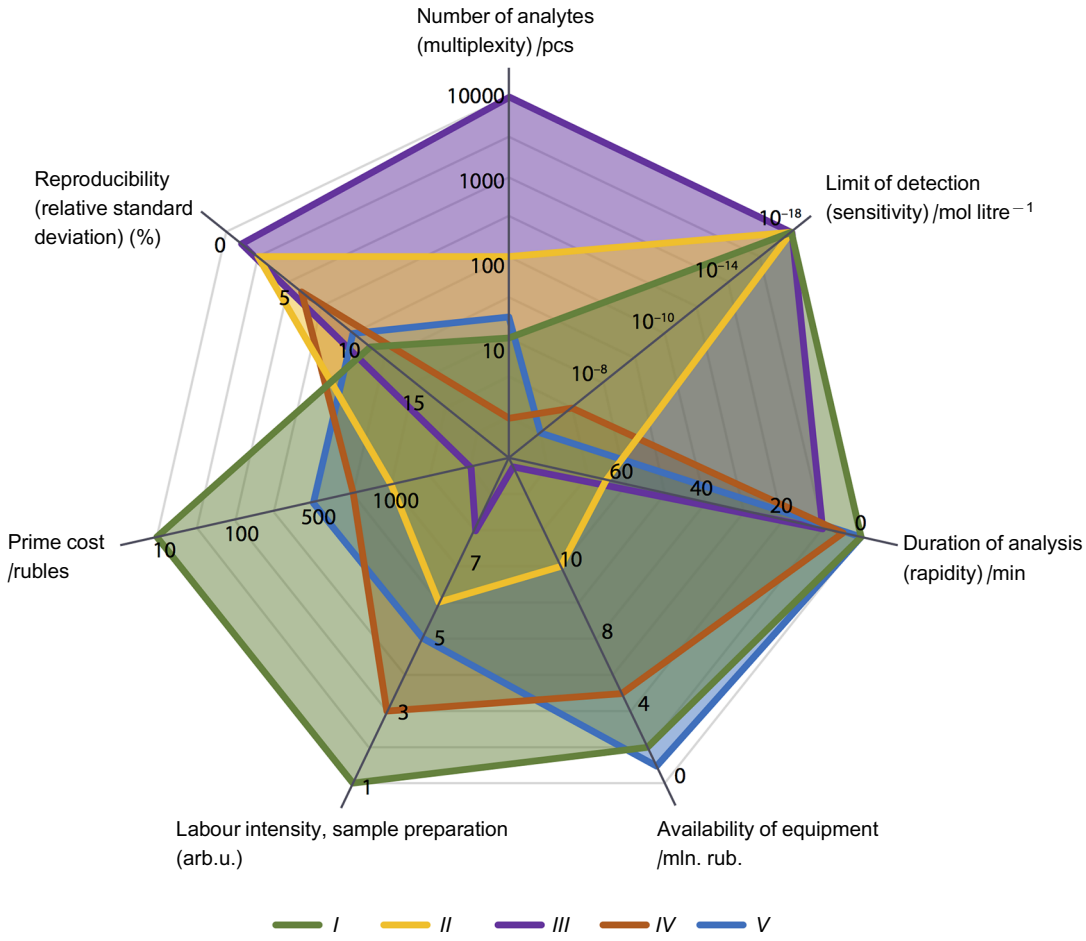


Figure 7. Comparison of different physicochemical methods of analysis taking the determination of polyaromatic hydrocarbons and heterocyclic sulfur compounds in petroleum and petrochemicals as examples.
SERS (*I*), gas chromatography with mass spectrometric detection (*II*), ion-cyclotron resonance mass spectrometry (*III*), X-ray fluorescence spectroscopy (*IV*) and IR spectroscopy (*V*).

5. Conclusion

Surface-enhanced Raman spectroscopy has a great potential as a method for analysis of samples present in complex matrices sometimes of unpredictable composition. The method is characterized by high sensitivity and selectivity, requires minimum sample preparation and enables multiplex analysis. The feasibility of SERS for being used in various fields including medicine, pharmaceutical industry, ecology, fuel and energy area, *etc*. has been demonstrated. However, in spite of extensive development of theory of the method and successful practical implementation in studies of real samples of different chemical composition and physicochemical properties, the key problems in SERS still include a relatively narrow range of analytes and inappropriate metrological characteristics in the case of analysis of certain samples. These drawbacks limit practical application of SERS in chemical analysis. Besides, wide use of SERS-active nanostructures in future biomedical studies require not only enhancement of SERS signals from single biomolecules, but also a novel interdisciplinary research into the influence of these nanostructures on biological samples and assessment of changes in the properties of the nanostructures contacting biological fluids and cells.

The title method has been successfully used in environmental analysis including the detection of technogenic pollutants and ecotoxicants; however, information on its application in analysis of systems with complex nonpolar matrices is scarce. For instance, most studies on important nonpolar pollutants like polyaromatic hydrocarbons and sulfur-containing aromatic heterocyclic compounds are carried out in polar media, whereas their detection in nonpolar media still requires more complicated and expensive chromatographic methods. In this connection the design of simple fast multiplex sensor systems for the SERS detection of various technogenic pollutants in nonpolar matrices remains a topical task in modern chemical analysis.

Prospective methods to solve the problems posed first of all include targeted synthesis and smart functionalization of metal surfaces to take into account actual conditions (*in vitro*, *ex vivo* or *in vivo* analyses of biological samples), complex chemical composition and phase state of samples, character (polar or nonpolar) of matrices containing technogenic pollutants in the case of environ-

mental monitoring and extension of SERS and its versions to a wide range of important analytes and new objects. This will allow SERS to find a place among other modern methods of chemical analysis.

This review has been written with the financial support from the Russian Science Foundation (Project No. 14-13-00871-P).

References

1. K.Kneipp, Y.Wang, H.Kneipp, L.T.Perelman, I.Itzkan, R.R.Dasari, M.Feld. *Phys. Rev. Lett.*, **78**, 1667 (1997)
2. I.R.Nabiev, P.G.Efremov, G.D.Chumanov. *Sov. Phys. Usp.*, **31**, 241 (1988)
3. A.Yu.Olenin, G.V.Lisichkin. *Russ. Chem. Rev.*, **80**, 605 (2011)
4. G.McNay, D.Eustace, W.Ewensmith, K.Faulds, D.Graham. *Appl. Spectrosc.*, **65**, 825 (2011)
5. Yu.A.Krutyakov, A.A.Kudrinsky, A.Yu.Olenin, G.V.Lisichkin. *Russ. Chem. Rev.*, **77**, 233 (2008)
6. W.Xie, P.Qiua, C.Mao. *J. Mater. Chem.*, **21**, 5190 (2011)
7. M.E.Stewart, C.R.Anderton, L.B.Thompson, J.Maria, S.K.Gray, J.A.Rogers, R.G.Nuzzo. *Chem. Rev.*, **108**, 494 (2008)
8. D.Cialla, A.März, R.Böhme, F.Theil, K.Weber, M.Schmitt, J.Popp. *Anal. Bioanal. Chem.*, **403**, 27 (2012)
9. Y.F.Yuan, Y.N.Lin, B.B.Gu, N.Panwar, S.C.Tjin, J.Song, J.L.Qu, K.-T.Yong. *Coord. Chem. Rev.*, **339**, 138 (2017)
10. Y.Zhang, S.Zhao, J.Zheng, L.He. *TRAC: Trends Anal. Chem.*, **90**, 1 (2017)
11. Y.Wang, B.Yan, L.Chen. *Chem. Rev.*, **113**, 1391 (2013)
12. Y.Yuan, N.Panwar, S.H.K.Yap, Q.Wu, S.Zeng, J.Xu, S.C.Tjin, J.Song, J.Qu, K.-T.Yong. *Coord. Chem. Rev.*, **337**, 1 (2017)
13. N.L.Gruenke, M.F.Cardinal, M.O.McAnally, R.R.Frontiera, G.C.Schatz, R.P.Van Duyne. *Chem. Soc. Rev.*, **45**, 2263 (2016)
14. S.Kawata, T.Ichimura, A.Taguchi, Y.Kumamoto. *Chem. Rev.*, **117**, 4983 (2017)
15. S.Laing, K.Gracie, K.Faulds. *Chem. Soc. Rev.*, **45**, 1901 (2016)
16. D.Radziuk, H.Moehwald. *Phys. Chem. Chem. Phys.*, **17**, 21072 (2015)
17. J.Kneipp, H.Kneipp, B.Wittig, K.Kneipp. *Nano Lett.*, **7**, 2819 (2007)
18. M.Chen, L.Zhang, M.Gao, X.Zhang. *Talanta*, **172**, 176 (2017)
19. D.Drescher, J.Kneipp. *Chem. Soc. Rev.*, **41**, 5780 (2012)
20. B.R.Wood, P.Caspers, G.J.Puppels, S.Pandiancherri, D.McNaughton. *Anal. Bioanal. Chem.*, **387**, 1691 (2007)
21. N.A.Brazhe, E.Y.Parshina, V.V.Khabatova, A.A.Semenova, A.R.Brazhe, A.I.Yusipovich, A.S.Sarycheva, A.A.Churin, E.A.Goodilin, G.V.Maksimov, O.V.Sosnovtseva. *J. Raman Spectrosc.*, **44**, 686 (2013)
22. A.A.Semenova, N.A.Brazhe, E.Y.Parshina, V.K.Ivanov, G.V.Maksimov, E.A.Goodilin. *Plasmonics*, **9**, 227 (2013)
23. A.A.Semenova, N.A.Brazhe, E.Y.Parshina, A.S.Sarycheva, G.V.Maksimov, E.A.Goodilin. *RSC Adv.*, **6**, 85156 (2016)
24. R.M.Jarvis, R.Goodacre. *Chem. Soc. Rev.*, **37**, 931 (2008)
25. P.Wang, S.Pang, J.Chen, L.McLandsborough, S.R.Nugen, M.Fan, L.He. *Analyst*, **141**, 1356 (2016)
26. J.H.Granger, N.E.Schlotter, A.C.Crawford, M.D.Porter. *Chem. Soc. Rev.*, **45**, 3865 (2016)
27. S.Efrima, L.Zeiri. *J. Raman Spectrosc.*, **40**, 277 (2009)
28. H.-W.Cheng, S.-Y.Huan, R.-Q.Yu. *Analyst*, **137**, 3601 (2012)
29. V.Hoang, R.A.Tripp, P.Rota, R.A.Dluhy. *Analyst*, **135**, 3103 (2010)
30. N.N.Durmanov, R.R.Guliev, A.V.Eremenko, I.A.Boginskaya, I.A.Ryzhikov, E.A.Trifonova, E.V.Putlyaev, A.N.Mukhin, S.L.Kalnov, M.V.Balandina, A.P.Tkachuk, V.A.Gushchin, A.K.Sarychev, A.N.Lagarkov, I.A.Rodionov, A.R.Gabidullin, I.N.Kurochkin. *Sens. Actuators, B*, **257**, 37 (2018)
31. W.A.El-Said, S.U.Kim, J.-W.Choi. *J. Mater. Chem. C*, **3**, 3848 (2015)
32. W.Xie, S.Schlücker. *Phys. Chem. Chem. Phys.*, **15**, 5329 (2013)
33. M.M.Harper, K.S.McKeating, K.Faulds. *Phys. Chem. Chem. Phys.*, **15**, 5312 (2013)
34. J.Han, X.Qian, Q.Wu, R.Jha, J.Duan, Z.Yang, K.O.Maher, S.Nie, C.Xu. *Biomaterials*, **105**, 66 (2016)
35. P.D.Howes, S.Rana, M.M.Stevens. *Chem. Soc. Rev.*, **43**, 3835 (2014)
36. J.Taylor, A.Huefner, L.Li, J.Wingfield, S.Mahajan. *Analyst*, **141**, 5037 (2016)
37. G.Clemens, J.R.Hands, K.M.Dorling, M.J.Baker. *Analyst*, **139**, 4411 (2014)
38. S.McAughtrie, K.Faulds, D.Graham. *J. Photochem. Photobiol., C*, **21**, 40 (2014)
39. G.J.Puppels, F.F.M.de Mul, C.Otto, J.Greve, M.Robert-Nicoud, D.J.Arndt-Jovin, T.M.Jovin. *Nature (London)*, **347**, 301 (1990)
40. R.A.Alvarez-Puebla, L.M.Liz-Marzán. *Small*, **6**, 604 (2010)
41. A.März, B.Mönch, P.Rösch, M.Kiehntopf, T.Henkel, J.Popp. *Anal. Bioanal. Chem.*, **400**, 2755 (2011)
42. L.He. *Food Chem. Hazard Detect.*, **3**, 191 (2014)
43. I.J.Jahn, O.Žukovskaja, X.-S.Zheng, K.Weber, T.W.Bocklitz, D.Cialla-May, J.Popp. *Analyst*, **142**, 1022 (2017)
44. R.Hou, S.Pang, L.He. *Anal. Methods*, **7**, 6325 (2015)
45. N.Duan, S.Wu, S.Dai, H.Gu, L.Hao, H.Ye, Z.Wang. *Analyst*, **141**, 3942 (2016)
46. S.Kumar, P.Goel, J.P.Singh. *Sens. Actuators, B*, **241**, 577 (2017)
47. R.A.Alvarez-Puebla, L.M.Liz-Marzán. *Energy Environ. Sci.*, **3**, 1011 (2010)
48. M.Potara, C.Farcau, I.Botiz, S.Astilean, in *Advanced Environmental Analysis: Applications of Nanomaterials.* (Eds C.M.Hussain, B.Kharisov). (London: Royal Society of Chemistry, 2017). P. 534
49. X.Huang, Q.Liu, S.Yao, G.Jiang. *Anal. Methods*, **9**, 2768 (2017)
50. H.Wei, S.M.H.Abtahi, P.J.Vikesland. *Environ. Sci.: Nano*, **2**, 120 (2015)
51. K.C.Bantz, A.F.Meyer, N.J.Wittenberg, H.Im, Ö.Kurtuluş, S.H.Lee, N.C.Lindquist, S.-H.Oh, C.L.Haynes. *Phys. Chem. Chem. Phys.*, **13**, 11551 (2011)
52. J.Chao, W.Cao, S.Su, L.Weng, S.Song, C.Fan, L.Wang. *J. Mater. Chem. B*, **4**, 1757 (2016)

53. J.-H.Kim, H.Kang, S.Kim, B.-H.Jun, T.Kang, J.Chae, S.Jeong, J.Kim, D.H.Jeong, Y.-S.Lee. *Chem. Commun.*, **47**, 2306 (2011)
54. A.J.Driscoll, M.H.Harpster, P.A.Johnson. *Phys. Chem. Chem. Phys.*, **15**, 20415 (2013)
55. K.Gracie, D.Lindsay, D.Graham, K.Faulds. *Anal. Methods*, **7**, 1269 (2015)
56. A.Torres-Nuñez, K.Faulds, D.Graham, R.A.Alvarez-Puebla, L.Guerrini. *Analyst*, **141**, 5170 (2016)
57. I.A.Veselova, E.A.Sergeeva, V/I/Makedonskaya, O.E.Eremina, S.N.Kalmykov, T.N.Shekhovtsova. *J. Anal. Chem.*, **71**, 1235 (2016)
58. L.Polavarapu, J.Perez-Juste, Q.Xu, L.M.Liz-Marzán. *J. Mater. Chem. C*, **2**, 7460 (2014)
59. W.Zhou, X.Gao, D.Liu, X.Chen. *Chem. Rev.*, **115**, 10575 (2015)
60. T.Demeritte, R.Kanchanapally, Z.Fan, A.K.Singh, D.Senapati, M.Dubey, E.Zakar, P.C.Ray. *Analyst*, **137**, 5041 (2012)
61. S.Fateixa, H.I.S.Nogueira, T.Trindade. *Phys. Chem. Chem. Phys.*, **17**, 21046 (2015)
62. L.Guerrini, D.Graham. *Chem. Soc. Rev.*, **41**, 7085 (2012)
63. S.Emamian, A.Eshkeiti, B.B.Narakathu, S.G.R.Avuthu, M.Z.Atashbar. *Sens. Actuators, B*, **217**, 129 (2015)
64. A.Hakonen, P.O.Andersson, M.S.Schmidt, T.Rindzevicius, M.Kaell. *Anal. Chim. Acta*, **893**, 1 (2015)
65. L.Jing, Y.Shi, J.Cui, X.Zhang, J.Zhan. *RSC Adv.*, **5**, 13443 (2015)
66. J.Docherty, S.Mabbott, E.Smith, K.Faulds, C.Davidson, J.Reglinski, D.Graham. *Analyst*, **141**, 5857 (2016)
67. W.A.Hassanain, E.L.Izake, M.S.Schmidt, G.A.Ayoko. *Biosens. Bioelectron.*, **91**, 664 (2017)
68. A.Dhillon, M.Nair, D.Kumar. *Anal. Methods*, **7**, 10088 (2015)
69. L.Xiao, M.Zhang, Z.Liu, W.Bian, X.Zhang, J.Zhan. *Anal. Methods*, **9**, 1816 (2017)
70. S.Pang, T.Yang, L.He. *TRAC: Trends Anal. Chem.*, **85**, 73 (2016)
71. M.Fleischmann, P.J.Hendra, A.J.McQuillan. *Chem. Phys. Lett.*, **26**, 163 (1974)
72. M.Jahn, S.Patze, I.J.Hidi, R.Knipper, A.I.Radu, A.Mühlig, S.Yüksel, V.Peksa, K.Weber, T.Mayerhöfer, D.Cialla-May, J.Popp. *Analyst*, **141**, 756 (2016)
73. M.Fan, G.F.S.Andrade, A.G.Brolo. *Anal. Chim. Acta*, **693**, 7 (2011)
74. S.Wachsmann-Hogiu, T.Weeks, T.Huser. *Curr. Opin. Biotechnol.*, **20**, 63 (2009)
75. S.H.Yazdi, I.M.White. *Biomicrofluidics*, **6**, 14105 (2012)
76. T.Itoh. *Front. Surf.-Enhanc. Raman Scatter.*, **1**, 59 (2014)
77. Y.S.Yamamoto, Y.Ozaki, T.Itoh. *J. Photochem. Photobiol., C*, **21**, 81 (2014)
78. Z.D.Schultz, J.M.Marr, H.Wang, A.Lewis. *Nanophotonics*, **3**, 91 (2014)
79. P.L.Stiles, J.A.Dieringer, N.C.Shah, R.P.Van Duyne. *Annu. Rev. Anal. Chem.*, **1**, 601 (2008)
80. Y.S.Yamamoto, T.Itoh, *J. Raman Spectrosc.*, **47**, 78 (2016)
81. A.Shiohara, Y.Wanga, L.M.Liz-Marzán. *J. Photochem. Photobiol., C*, **21**, 2 (2014)
82. X.Xu, K.Kim, C.Liu, D.Fan. *Sensors*, **15**, 10422 (2015)
83. J.Wackerlig, P.A.Lieberzeit. *Sens. Actuators, B*, **207**, 144 (2015)
84. S.J.Barcelo, W.Wu, X.Li, Z.Li, R.S.Williams, R.Stanley. *Appl. Phys. A: Mater. Sci. Proc.*, **121**, 443 (2015)
85. Z.Fan, X.Huang, C.Tan, H.Zhang. *Chem. Sci.*, **6**, 95 (2015)
86. W.Xu, N.Mao, J.Zhang. *Small*, **9**, 1206 (2013)
87. B.Sharma, R.R.Frontiera, A.I.Henry, E.Ringe, R.P.Van Duyne. *Mater. Today*, **15**, 16 (2012)
88. A.X.Wang, X.Kong. *Materials*, **8**, 3024 (2015)
89. U.Y.Qazi, R.Javaid. *Adv. Nanopart.*, **5**, 27 (2016)
90. N.A.Brazhe, A.B.Evlyukhin, E.A.Goodilin, A.A.Semenova, S.M.Novikov, S.I.Bozhevolnyi, B.N.Chichkov, A.S.Sarycheva, A.A.Baizhumanov, E.I.Nikelshparg, L.I.Deev, E.G.Maksimov, G.V.Maksimov, O.Sosnovtseva. *Sci. Rep.*, **5**, 13793 (2015)
91. A.S.Sarycheva, A.A.Semenova, E.Y.Parshina, N.A.Brazhe, A.Y.Polyakov, A.Y.Kozmenkova, A.V.Grigorieva, G.V.Maksimov, E.A.Goodilin. *Mater. Lett.*, **121**, 66 (2014)
92. N.A.Brazhe, S.Abdali, A.R.Brazhe, O.G.Luneva, N.Y.Bryzgalova, E.Y.Parshina, O.V.Sosnovtseva, G.V.Maksimov. *Biophys. J.*, **97**, 3206 (2009)
93. S.Schluecker. *Angew. Chem., Int. Ed.*, **53**, 4756 (2014)
94. A.Bonifacio, S.Cervo, V.Sergo. *Anal. Bioanal. Chem.*, **407**, 8265 (2015)
95. Z.A.Nima, A.Biswas, I.S.Bayer, F.D.Hardcastle, D.Perry, A.Ghosh, E.Dervishi, A.S.Biris. *Drug Metab. Rev.*, **46**, 155 (2014)
96. A.Samanta, S.Jana, R.K.Das, Y.T.Chang. *Nanomedicine (London)*, **9**, 523 (2014)
97. S.Ye, Y.Mao, Y.Guo, S.Zhang. *TRAC: Trends Anal. Chem.*, **55**, 43 (2014)
98. W.R.Premasiri, P.Lemler, Y.Chen, Y.Gebregziabher, L.D.Ziegler. *Front. Surf.-Enhanc. Raman Scatter.*, **1**, 257 (2014)
99. J.Kneipp, D.Drescher. *Front. Surf.-Enhanc. Raman Scatter.*, **1**, 285 (2014)
100. P.Negri, R.A.Dluhy. *J. Biophotonics*, **6**, 20 (2013)
101. L.Chen, L.Cai, W.Ruan, B.Zhao in *Encyclopedia of Analytical Chemistry, Surface-Enhanced Raman Spectroscopy (SERS): Protein Application. Encyclopedia of Analytical Chemistry*. (New York: Wiley, 2014). P. 23
102. H.W.Cheng, J.Luo, C.J.Zhong. *Front. Chem. Sci. Eng.*, **9**, 428 (2015)
103. L.A.Lane, X.Qian, S.Nie. *Chem. Rev.*, **115**, 10489 (2015)
104. S.Cherukulappurath. *Sens. Transduc. J.*, **197**, 1 (2016)
105. S.Uskoković-Marković, V.Kuntić, D.Bajuk-Bogdanović, I.Holclajtner-Antunović, in *Reference Module in Chemistry, Molecular Sciences and Chemical Engineering from Encyclopedia of Spectroscopy and Spectrometry*. (3rd Edition), (Elsevier, 2017). P. 383
106. J.Zheng, L.He. *Compr. Rev. Food Sci. Food Saf.*, **13**, 317 (2014)
107. W.Liao, X.N.Lu. *Trends Food Sci. Technol.*, **54**, 103 (2016)
108. T.Vankeirsbilck, A.Vercauteren, W.Baeyens, G.Van der Weken, F.Verpoort, G.Vergote, J.P.Remon. *TRAC: Trends Anal. Chem.*, **21**, 869 (2002)
109. L.M.Liz-Marzán, R.A.Álvarez-Puebla. *Energy Environ. Sci.*, **3**, 981 (2010)
110. D.W.Li, W.L.Zhai, Y.T.Li, Y.T.Long. *Microchim. Acta*, **181**, 23 (2014)
111. C.Muehlethaler, M.Leona, J.R.Lombardi. *Anal. Chem.*, **88**, 152 (2016)
112. J.F.Betz, W.W.Yu, Y.Cheng, I.M.White, G.W.Rubloff. *Phys. Chem. Chem. Phys.*, **16**, 2224 (2014)

113. P.A.Mosier-Boss, M.D.Putnam. *Anal. Chem. Insig.*, **8**, 83 (2013)
114. L.Sun, M.Zhang, V.Natarajan, X.Yu, X.Zhang, J.Zhan. *RSC Adv.*, **7**, 23866 (2017)
115. Y.Zhao, J.-A.Huang, Z.Zhang, X.Chen, W.Zhang. *J. Mater. Chem., A*, **2**, 10218 (2014)
116. S.Kasera, F.Biedermann, J.J.Baumberg, O.A.Scherman, S.Mahajan. *Nano Lett.*, **12**, 5924 (2012)
117. C.Leordean, A.-M.Gabudean, V.Canpean, S.Astilean. *Analyst*, **138**, 4975 (2013)
118. X.Zhang, Y.Zheng, X.Liu, W.Lu, J.Dai, D.Y.Lei, D.R.MacFarlane. *Adv. Mater.*, **27**, 1090 (2015)
119. M.Sackmann, A.Materny. *J. Raman Spectrosc.*, **37**, 305 (2006)
120. D.L.Stokes, T.Vo-Dinh. *Sens. Actuators, B*, **69**, 28 (2000)
121. Z.Y.Bao, X.Liu, Y.Chen, Y.C.Wu, H.L.W.Chan, J.Y.Dai, D.Y.Lei. *J. Hazard. Mater.*, **280**, 706 (2014)
122. W.Cheung, I.T.Shadi, Y.Xu, R.Goodacre. *J. Phys. Chem. C*, **114**, 7285 (2010)
123. X.T.Wang, W.S.Shi, G.W.She, L.X.Mu, S.T.Lee. *Appl. Phys. Lett.*, **96**, 053104-1 (2010)
124. K.R.Strehle, D.Cialla, P.Rösch, T.Henkel, M.Köhler, J.Popp. *Anal. Chem.*, **79**, 1542 (2007)
125. K.K.Strelau, T.Schüler, R.Möller, W.Fritzsche, J.Popp. *ChemPhysChem*, **11**, 394 (2010)
126. G.H.Gu, J.S.Suh. *J. Raman Spectrosc.*, **41**, 624 (2010)
127. L.He, M.Lin, H.Li, N.-J.Kim. *J. Raman Spectrosc.*, **41**, 739 (2010)
128. P.H.Hsu, H.K.Chiang. *J. Raman Spectrosc.*, **41**, 1610 (2010)
129. H.Tang, D.Fang, Q.Li, P.Cao, J.Geng, T.Sui, X.Wang, J.Iqbal, Y.Du. *J. Food Sci.*, **77**, T105 (2012)
130. Y.Xie, G.Mukamurezi, Y.Sun, H.Wang, H.Qian, W.Yao. *Eur. Food Res. Technol.*, **234**, 1091 (2012)
131. O.E.Eremina, A.V.Sidorov, T.N.Shekhovtsova, E.A.Goodilin, I.A.Veselova. *ACS Appl. Mater. Interfaces*, **9**, 15058 (2017)
132. S.E.J.Bell, J.N.Mackle, N.M.S.Sirimuthu. *Analyst*, **130**, 545 (2005)
133. J.H.Jung, J.Choo, D.J.Kim, S.Lee. *Bull. Korean Chem. Soc.*, **27**, 277 (2006)
134. X.Wu, S.Gao, J.S.Wang, H.Wang, Y.W.Huang, Y.Zhao. *Analyst*, **137**, 4226 (2012)
135. W.Yao, Y.Sun, Y.Xie, S.Wang, L.Ji, H.Wang, H.Qian. *Eur. Food Res. Technol.*, **233**, 835 (2011)
136. L.Zhang, Q.Li, W.Tao, B.Yu, Y.Du. *Anal. Bioanal. Chem.*, **398**, 1827 (2010)
137. N.Nechaeva, T.Prokopkina, G.Makhaeva, E.Rudakova, N.Boltneva, C.Dishovsky, A.Eremenko, I.Kurochkin. *Sens. Actuators, B*, **259**, 75 (2018)
138. F.Gao, E.Grant, X.Lu. *Anal. Chim. Acta*, **901**, 68 (2015)
139. S.Song, L.Wang, J.Li, J.Zhao, C.Fan. *TRAC: Trends Anal. Chem.*, **27**, 108 (2008)
140. J.H.Lee, J.M.Nam, K.S.Jeon, D.K.Lim, H.Kim, S.Kwon, H.Lee, Y.D.Suh. *ACS Nano*, **6**, 9574 (2012)
141. G.Haran. *Acc. Chem. Res.*, **43**, 1135 (2010)
142. K.Li, M.I.Stockman, D.Bergman. *J. Phys. Rev. Lett.*, **91**, 227402 (2003)
143. H.Wei, H.Xu. *Nanoscale*, **5**, 10794 (2013)
144. P.Verma. *Chem. Rev.*, **117**, 6447 (2017)
145. J.F.Li, Y.F.Huang, Y.Ding, Z.L.Yang, S.B.Li, X.S.Zhou, F.R.Fan, W.Zhang, Z.Y.Zhou, D.Y.Wu, B.Ren, Z.L.Wang, Z.Q.Tian. *Nature (London)*, **464**, 392 (2010)
146. A.B.Zrimsek, N.L.Wong, R.P.Van Duyne. *J. Phys. Chem. C*, **120**, 5133 (2016)
147. H.M.Lee, S.M.Jin, H.M.Kim, Y.D.Suh. *Phys. Chem. Chem. Phys.*, **15**, 5276 (2013)
148. E.C.Le Ru, M.Meyer, P.G.Etchegoin. *J. Phys. Chem. B*, **110**, 1944 (2006)
149. S.Nie, L.A.Lipscomb, N.-T.Yu. *Appl. Spectrosc. Rev.*, **26**, 203 (1991)
150. X.Wang, S.-C.Huang, T.-X.Huang, H.-S.Su, J.-H.Zhong, Z.-C.Zeng, M.-H.Lia, B.Ren. *Chem. Soc. Rev.*, **46**, 4020 (2017)
151. J.Wessel. *J. Opt. Soc. Am. B*, **2**, 1538 (1985)
152. H.Xu, J.Aizpurua, M.Käll, P.Apell. *Phys. Rev. E*, **62**, 4318 (2000)
153. R.C.Maher, in *Raman Spectroscopy for Nanomaterials Characterization*. (Ed. C.S.S.R.Kumar). (Berlin: Springer-Verlag, 2012). P. 645
154. P.G.Etchegoin, E.C.Le Ru. *Phys. Chem. Chem. Phys.*, **10**, 6079 (2008)
155. C.Zheng, W.Shao, S.K.Paidi, B.Han, T.Fu, D.Wu, L.Bi, W.Xu, Z.Fan, I.Barman. *Nanoscale*, **7**, 16960 (2015)
156. B.-Y.Wen, X.Jin, Y.Li, Y.-H.Wang, C.-Y.Li, M.-M.Liang, R.Panneerselvam, Q.-C.Xu, D.-Y.Wu, Z.-L.Yang, J.-F.Li, Z.-Q.Tian. *Analyst*, **141**, 3731 (2016)
157. K.Qian, H.Liu, L.Yang, J.Liu. *Analyst*, **137**, 4644 (2012)
158. Y.Zhu, J.Wu, H.Gao, G.Liu, Z.Tian, J.Feng, L.Guo, J.Xie. *RSC Adv.*, **6**, 59919 (2016)
159. E.T.J.Nibbering, H.Fidder, E.Pines. *Annu. Rev. Phys. Chem.*, **56**, 337 (2005)
160. S.T.Kochuveedu, Y.H.Jang, D.H.Kim. *Chem. Soc. Rev.*, **42**, 8467 (2013)
161. P.Christopher, H.Xin, A.Marimuthu, S.Linic. *Nat. Mater.*, **11**, 1044 (2012)
162. Z.Zhang, T.Deckert-Gaudig, V.Deckert. *Analyst*, **140**, 4325 (2015)
163. S.Mukherjee, L.Zhou, A.M.Goodman, N.Large, C.Ayala-Orozco, Y.Zhang, P.Nordlander, N.J.Halas. *J. Am. Chem. Soc.*, **136**, 64 (2014)
164. D.Graham, K.Faulds. *Chem. Soc. Rev.*, **37**, 1042 (2008)
165. A.McLintock, H.J.Lee, A.W.Wark. *Phys. Chem. Chem. Phys.*, **15**, 18835 (2013)
166. D.Song, R.Yang, H.Wang, W.Li, H.Wang, H.Long, F.Long. *Anal. Methods*, **9**, 154 (2017)
167. T.R.Nayak, C.Andreou, A.Oseledchyk, W.D.Marcus, H.C.Wong, J.Massagué, M.F.Kircher. *Nanoscale*, **9**, 1110 (2017)
168. T.Itoh, M.Iga, H.Tamaru, K.Yoshida, V.Biju, M.Ishikawa. *J. Chem. Phys.*, **136**, 024703 (2012)
169. D.A.Weitz, S.Garoff, J.I.Gersten, A.Nitzan. *J. Chem. Phys.*, **78**, 5324 (1983)
170. D.Cunningham, R.E.Littleford, W.E.Smith, P.J.Lundahl, I.Khan, D.W.McComb, D.Graham, N.Laforest. *Faraday Discuss.*, **132**, 135 (2006)
171. K.Kneipp, H.Kneipp, J.Kneipp. *Acc. Chem. Res.*, **39**, 443 (2006)
172. D.V.Murphy, K.U.Von Raben, R.K.Chang, P.B.Dorain. *Chem. Phys. Lett.*, **85**, 43 (1982)
173. J.T.Golab, J.R.Sprague, K.T.Carron, G.C.Schatz, R.P.Van Duyne. *J. Chem. Phys.*, **88**, 7942 (1988)

174. K.Kneipp, H.Kneipp. *Beilstein J. Nanotechnol.*, **4**, 834 (2013)
175. A.M.Polubotko. *Chem. Phys. Lett.*, **519** – **520**, 110 (2012)
176. K.C.Brown, E.J.Hurd, J.C.Holtgrave, G.P.Perram. *Opt. Commun.*, **309**, 21 (2013)
177. C.Herrero-Latorre, J.Álvarez-Méndez, J.Barciela-García, S.García-Martín, R.M.Peña-Crecente. *Anal. Chim. Acta*, **853**, 77 (2015)
178. N.S.Green, M.L.Norton. *Anal. Chim. Acta*, **853**, 127 (2015)
179. M.J.Banholzer, J.E.Millstone, L.Qin, C.A.Mirkin. *Chem. Soc. Rev.*, **37**, 885 (2008)
180. R.A.Tripp, R.A.Dluhy, Y.Zhao. *Nanotoday*, **3**, 31 (2008)
181. Y.Liu, H.Yuan, F.R.Kersey, J.K.Register, M.C.Parrott, T.Vo-Dinh. *Sensors*, **15**, 3706 (2015)
182. D.-Y.Wu, M.Zhang, L.-B.Zhao, Y.-F.Huang, B.Ren, Z.-Q.Tian. *Sci. China: Chem.*, **58**, 574 (2015)
183. L.Nie, F.Liu, P.Ma, X.Xiao. *J. Biomed. Nanotechnol.*, **10**, 2700 (2014)
184. Z.Zhang, T.Deckert-Gaudig, V.Decker. *Analyst (Cambridge, UK)*, **140**, 4325 (2015)
185. M.Moskovits. *Rev. Mod. Phys.*, **57**, 783 (1985)
186. G.C.Weaver, K.Norrod. *J. Chem. Ed.*, **57**, 621 (1998)
187. J.R.Lombardi, R.L.Birke. *J. Phys. Chem. C*, **112**, 5605 (2008)
188. A.Campion, P.Kambhampati. *Chem. Soc. Rev.*, **27**, 241 (1998)
189. M.J.Weaver, S.Zou, H.Y.H.Chan. *Anal. Chem.*, **72**, 38A (2000)
190. M.Fan, A.G.Brolo. *Phys. Chem. Chem. Phys.*, **11**, 7381 (2009)
191. J.M.Sequaris, E.Koglin. *Anal. Chem*, **321**, 758 (1985)
192. T.Vo-Dinh, M.Y.K.Hiromoto, G.M.Begun, R.L.Moody. *Anal. Chem.*, **56**, 1667 (1984)
193. C.D.Tran. *J. Chromatogr.*, **292**, 432 (1984)
194. V.K.Sharma, R.A.Yngard, Y.Lin. *Adv. Colloid Interface Sci.*, **145**, 83 **(**2009)
195. M.Ahamed, M.S.AlSalhi, M.K.J.Siddiqui. *Clin. Chim. Acta*, **411**, 1841 (2010)
196. K.M.M.Abou El-Nour, A.Eftaiha, A.Al-Warthan, R.A.A.Ammar. *Arabian J. Chem.*, **3**, 135 (2010)
197. L.S.Nair, C.T.Laurencin. *J. Biomed. Nanotechnol.*, **3**, 301 (2007)
198. B.Nowack, H.F.Krug, M.Height. *Environ. Sci. Technol.*, **45**, 1177 (2011)
199. J.N.Solanki, Z.V.P.Murthy. *Ind. Eng. Chem. Res.*, **50**, 12311 (2011)
200. K.Chaloupka, Y.Malam, A.M.Seifalian. *Trends Biotechnol.*, **28**, 580 (2010)
201. X.K.Meng, S.C.Tang, S.Vongehr. *J. Mater. Sci. Technol.*, **26**, 487 (2010)
202. D.Yu, V.W.W.Yam. *J. Phys. Chem. B*, **109**, 5497 (2005)
203. Y.Sun. *Science*, **298**, 2176 (2002)
204. A.Guerrero-Martínez, S.Barbosa, I.Pastoriza-Santos, L.M.Liz-Marzán. *Curr. Opin. Colloid Interface Sci.*, **16**, 118 (2011)
205. B.Lim, Y.Xia. *Angew. Chem., Int. Ed.*, **50**, 76 (2011)
206. P.R.Sajanlal, T.Pradeep. *Nano Res.*, **2**, 306 (2009)
207. J.Turkevich, P.C.Stevenson, J.Hillier. *Discuss. Faraday Soc.*, **11**, 55 (1951)
208. S.C.Yang, Y.P.Wang, Q.F.Wang, R.L.Zhang, B.J.Ding. *Colloids Surf., A*, **301**, 174 (2007)
209. S.Remita, G.Picq, J.Khatouri, M.Mostafavi. *Radiat. Phys. Chem.*, **54**, 463 (1999)
210. C.-H.Su, P.-L.Wu, C.-S.Yeh. *J. Phys. Chem. B*, **107**, 14240 (2003)
211. H.Huang, Q.Yuan, X.Yang. *Colloids Surf., B*, **39**, 31 (2004)
212. H.Huang, X.Yang. *Carbohydr. Res.*, **339**, 2627 (2004)
213. D.Wei, W.Qian. *Colloids Surf., B*, **62**, 136 (2008)
214. L.Zhang, X.Sun, Y.Song, X.Jiang, S.Dong, E.Wang. *Langmuir*, **22**, 2838 (2006)
215. S.V.Agarwal, S.S.Reddy, M.Dhayal. *RSC Adv.*, **4**, 18250 (2014)
216. Y.Wang, L.Q.Chen, Y.F.Li, X.J.Zhao, L.Peng, C.Z.Huang. *Nanotechnology*, **21**, 305601 (2010)
217. C.E.Hoppe, M.Lazzari, I.Pardias-Blanco, M.A.Lôpez-Quintela. *Langmuir*, **22**, 7027 (2006)
218. T.Yonezawa, T.Kunitake. *Colloids Surf., A*, **149**, 193 (1999)
219. Z.S.Pillai, P.V.Kamat. *J. Phys. Chem. B*, **108**, 945 (2004)
220. A.Henglein, M.Giersig. *J. Phys. Chem. B*, **103**, 9533 (1999)
221. S.T.Gentry, S.F.Kendra, M.W.Bezpalko. *J. Phys. Chem. C*, **115**, 12736 (2011)
222. D.D.Evanoff, G.Chumanov. *ChemPhysChem*, **6**, 1221 (2005)
223. G.Chang, Y.Luo, W.Lu, F.Liao, X.Sun. *J. Nanopart. Res.*, **13**, 2689 (2011)
224. P.C.Lee, D.Meisel. *J. Phys. Chem.*, **86**, 3391 (1982)
225. N.Leopold, B.Lendl. *J. Phys. Chem. B*, **107**, 5723 (2003)
226. G.S.Métraux, C.A.Mirkin. *Adv. Mater.*, **17**, 412 (2005)
227. Z.Cao, H.Fu, L.Kang, L.Huang, T.Zhai, Y.Ma, J.Yao. *J. Mater. Chem.*, **18**, 2673 (2008)
228. B.Wiley, Y.Sun, B.Mayers, Y.Xia. *Chem.– Eur. J.*, **11**, 454 (2005)
229. A.Taguchi, S.Fujii, T.Ichimura, P.Verma, Y.Inouye, S.Kawata. *Chem. Phys. Lett.*, **462**, 92 (2008)
230. S.Peng, Y.Sun. *Chem. Mater.*, **22**, 6272 (2010)
231. H.Liang, H.Yang, W.Wang, J.Li, H.Xu. *J. Am. Chem. Soc.*, **131**, 6068 (2009)
232. J.Fang, S.Liu, Z.Li. *Biomaterials*, **32**, 4877 (2011)
233. G.Xu, X.Qiao, X.Qiu, J.Chen. *Rare Met. Mater. Eng.*, **39**, 1532 (2010)
234. D.D.Evanoff, G.Chumanov. *J. Phys. Chem. B*, **108**, 13948 (2004)
235. L.M.Lyu, W.C.Wang, M.H.Huang. *Chem.– Eur. J.*, **16**, 14167 (2010)
236. B.Pietrobon, V.Kitaev. *Chem. Mater.*, **20**, 5186 (2008)
237. B.Pietrobon, M.McEachran, V.Kitaev. *ACS Nano*, **3**, 21 (2009)
238. H.Liang, W.Wang, Y.Huang, S.Zhang, H.Wei, H.Xu. *J. Phys. Chem. C*, **114**, 7427 (2010)
239. A.Shkilnyy, M.Soucé, P.Dubois, F.Warmont, M.L.Saboungi, I.Chourpa. *Analyst*, **134**, 1868 (2009)
240. M.Popa, T.Pradell, D.Crespo, J.M.Calderón-Moreno. *Colloids Surf., A*, **303**, 184 (2007)
241. C.Luo, Y.Zhang, X.Zeng, Y.Zeng, Y.Wang. *J. Colloid Interface Sci.*, **288**, 444 (2005)
242. X.W.Lou, C.Yuan, L.A.Archer. *Chem. Mater.*, **18**, 3921 (2006)
243. L.Lu, A.Kobayashi, K.Tawa, Y.Ozaki. *Chem. Mater.*, **18**, 4894 (2006)
244. H.Liang, Z.Li, W.Wang, Y.Wu, H.Xu. *Adv. Mater.*, **21**, 4614 (2009)
245. B.K.Jena, B.K.Mishra, S.Bohidar. *J. Phys. Chem. C*, **113**, 14753 (2009)

246. Z.Cai, C.Tian, L.Wang, W.Zhou, B.Wang, H.Fu. *J. Raman Spectrosc.*, **42**, 5 (2011)
247. X.S.Shen, G.Z.Wang, X.Hong, W.Zhu. *Phys. Chem. Chem. Phys.*, **11**, 7450 (2009)
248. A.S.Sarycheva, N.A.Brazhe, A.A.Baizhumanov, E.I.Nikelshparg, A.A.Semenova, A.V.Garshev, A.E.Baranchikov, V.K.Ivanov, G.V.Maksimov, O.V.Sosnovtseva, E.A.Goodilin. *J. Mater. Chem. B*, **3**, 539 (2016)
249. G.C.Phan-Quang, H.K.Lee, I.Y.Phang, X.Y.Ling. *Angew. Chem., Int. Ed.*, **54**, 9691 (2015)
250. J.Neddersen, G.Chumanov, T.M.Cotton. *Appl. Spectrosc.*, **47**, 1959 (1993)
251. D.C.Tien, C.Y.Liao, J.C.Huang, K.H.Tseng, J.K.Lung, T.T.Tsung, W.S.Kao, T.H.Tsai, T.W.Cheng, B.S.Yu, H.M.Lin, L.Stobinski. *Rev. Adv. Mater. Sci.*, **18**, 750 (2008)
252. P.Gangopadhyay, S.K.Srivastava, P.Magudapathy, T.N.Sairam, K.G.M.Nair, B.K.Panigrahi. *Vacuum*, **84**, 1411 (2010)
253. A.L.Stepanov. *Rev. Adv. Mater. Sci.*, **26**, 1 (2010)
254. S.M.Wells, S.D.Retterer, J.M.Oran, M.J.Sepaniak. *ACS Nano*, **3**, 3845 (2009)
255. L.A.Osminkina, V.Y.Timoshenko. *Mesoporous Biomater.*, **3**, 39 (2016)
256. M.B.Gongalsky, L.A.Osminkina, A.Pereira, A.A.Manankov, A.A.Fedorenko, A.N.Vasiliev, V.V.Solovyev, A.A.Kudryavtsev, M.Sentis, A.V.Kabashin, V.Y.Timoshenko. *Sci. Rep.*, **6**, 1 (2016)
257. E.Tolstik, L.A.Osminkina, C.Matthäus, M.Burkhardt, K.E.Tsurikov, U.A.Natashina, V.Y.Timoshenko, R.Heintzmann, J.Popp, V.Sivakov. *Nanomedicine: Nanotechnol., Biol. Med.*, **12**, 1931 (2016)
258. K.Vijayaraghavan, S.P.K.Nalini. *Biotechnol. J.*, **5**, 1098 (2010)
259. N.Kannan, S.Subbalaxmi. *Rev. Adv. Mater. Sci.*, **27**, 99 (2011)
260. M.N.Nadagouda, R.S.Varma. *Green Chem.*, **10**, 859 (2008)
261. A.R.Vilchis-Nestor, V.Sánchez-Mendieta, M.A.Camacho-López, R.M.Gómez-Espinosa, M.A.Camacho-López, J.A.Arenas-Alatorre. *Mater. Lett.*, **62**, 3103 (2008)
262. M.C.Moulton, L.K.Braydich-Stolle, M.N.Nadagouda, S.Kunzelman, S.M.Hussain, R.S.Varma. *Nanoscale*, **2**, 763 (2010)
263. K.Govindaraju, S.K.Basha, V.G.Kumar, G.Singaravelu. *J. Mater. Sci.*, **43**, 5115 (2008)
264. S.P.Chandran, M.Chaudhary, R.Pasricha, A.Ahmad, M.Sastry. *Biotechnol. Prog.*, **22**, 577 (2006)
265. D.Philip, C.Unni, S.A.Aromal, V.K.Vidhu. *Spectrochim. Acta, Part A*, **78**, 899 (2011)
266. S.Ravindra, Y.M.Mohan, N.N.Reddy, K.M.Raju. *Colloids Surf., A*, **367**, 31 (2010)
267. N.Roy, S.Mondal, R.A.Laskar, S.Basu, D.Mandal, N.A.Begum. *Colloids Surf., B*, **76**, 317 (2010)
268. N.A.Begum, S.Mondal, S.Basu, R.A.Laskar, D.Mandal. *Colloids Surf., B*, **71**, 113 (2009)
269. J.Zhou, K.Ren, Y.Zhao, W.Dai, H.Wu. *Anal. Bioanal. Chem.*, **402**, 1601 (2012)
270. W.Hüttner, K.Christou, A.Göhmann, V.Beushausen, H.Wackerbarth. *Microfluid. Nanofluid.*, **12**, 521 (2012)
271. I.M.White, S.H.Yazdi, W.W.Yu. *Microfluid. Nanofluid.*, **13**, 205 (2012)
272. Y.S.Huh, A.J.Chung, B.Cordovez, D.Erickson. *Lab Chip*, **9**, 433 (2009)
273. L.Malfatti, P.Falcaro, B.Marmiroli, H.Amenitsch, M.Piccinini, A.Falqui, P.Innocenzi. *Nanoscale*, **3**, 3760 (2011)
274. S.Kaniyankandy, J.Nuwad, C.Thinaharan, G.K.Dey, C.G.S.Pillai. *Nanotechnology*, **18**, 125610 (2007)
275. M.V.Mandke, S.H.Han, H.M.Pathan. *CrystEngComm*, **14**, 86 (2012)
276. Q.Zhou, S.Wang, N.Jia, L.Liu, J.Yang, Z.Jiang. *Mater. Lett.*, **60**, 3789 (2006)
277. R.Brayner, R.Iglesias, S.Truong, Z.Beji, N.Felidj, F.Fiévet, J.Aubard. *Langmuir*, **26**, 17465 (2010)
278. Y.H.Kim, D.K.Lee, Y.S.Kang. *Colloids Surf., A*, **257 – 258**, 273 (2005)
279. Z.Chen, T.Gang, Y.Wang, X.Chen, C.Guan, J.Zhang, Z.Sun, K.Zhang, B.Zhao, B.Yang. *Colloids Surf., A.*, **277**, 37 (2006)
280. J.C.Flores, V.Torres, M.Popa, D.Crespo, J.M.Calderón-Moreno. *Colloids Surf., A*, **330**, 86 (2008)
281. M.L.Cheng, J.Yang. *J. Raman Spectrosc.*, **41**, 167 (2010)
282. M.Bardosova, M.E.Pemble, I.M.Povey, R.H.Tredgold. *Adv. Mater.*, **22**, 3104 (2010)
283. S.Abalde-Cela, S.Ho, B.Rodríguez-González, M.A.Correa-Duarte, R.A.Álvarez-Puebla, L.M.Liz-Marzán, N.A.Kotov. *Angew. Chem., Int. Ed.*, **48**, 5326 (2009)
284. A.Tao, F.Kim, C.Hess, J.Goldberger, R.He, Y.Sun, Y.Xia, P.Yang. *Nano Lett.*, **3**, 1229 (2003)
285. W.J.Cho, Y.Kim, J.K.Kim. *ACS Nano*, **6**, 249 (2012)
286. T.H.Kim, D.W.Kim, J.M.Lee, Y.G.Lee, S.G.Oh. *Mater. Res. Bull.*, **43**, 1126 (2008)
287. R.Lupitskyy, M.Motornov, S.Minko. *Langmuir*, **24**, 8976 (2008)
288. A.A.Semenova, E.A.Goodilin, N.A.Brazhe, V.K.Ivanov, A.E.Baranchikov, V.A.Lebedev, A.E.Goldt, O.V.Sosnovtseva, S.V.Savilov, A.V.Egorov, A.R.Brazhe, E.Y.Parshina, O.G.Luneva, G.V.Maksimov, Y.D.Tretyakov. *J. Mater. Chem.*, **22**, 24530 (2012)
289. A.A.Semenova, V.K.Ivanov, S.V.Savilov, E.A.Goodilin. *CrystEngComm*, **15**, 7863 (2013)
290. D.Suzuki, H.Kawaguchi. *Colloid Polym. Sci.*, **284**, 1471 (2006)
291. A.B.Pawar, I.Kretzschmar. *Langmuir*, **24**, 355 (2008)
292. G.Zhang, D.Wang, H.Mohwald. *Nano Lett.*, **5**, 143 (2005)
293. C.G.Khoury, T.Vo-Dinh. *J. Phys. Chem. C*, **116**, 7534 (2012)
294. Y.H.Ngo, D.Li, G.P.Simon, G.Garnier. *Adv. Colloid Interface Sci.*, **163**, 23 (2011)
295. M.L.Cheng, B.C.Tsai, J.Yang. *Anal. Chim. Acta*, **708**, 89 (2011)
296. C.J.Choi, Z.Xu, H.Y.Wu, G.L.Liu, B.T.Cunningham. *Nanotechnology*, **21**, 415301 (2010)
297. G.Giallongo, R.Pilot, C.Durante, G.A.Rizzi, R.Signorini, R.Bozio, A.Gennaro, G.Granozzi. *Plasmonics*, **6**, 725 (2011)
298. Y.Song, D.Luo, S.Ye, H.Hou, L.Wang. *Appl. Surf. Sci.*, **258**, 2584 (2012)
299. S.D.Hudson, G.Chumanov. *Anal. Bioanal. Chem.*, **394**, 679 (2009)
300. S.Pahlow, A.März, B.Seise, K.Hartmann, I.Freitag, E.Kämmer, R.Böhme, V.Deckert, K.Weber, D.Cialla, J.Popp. *Eng. Life Sci.*, **12**, 131 (2012)

301. W.Xie, L.Su, A.Shen, A.Materny, J.Hu. *J. Raman Spectrosc.*, **42**, 1248 (2011)
302. C.R.Yonzon, C.L.Haynes, X.Y.Zhang, J.T.Walsh, R.P.Van Duyne. *Anal. Chem.*, **76**, 78 (2004)
303. K.Ma, J.M.Yuen, N.C.Shah, J.T.Walsh, M.R.Glucksberg, R.P.Van Duyne. *Anal. Chem.*, **83**, 9146 (2011)
304. C.Ren, Y.Song, Z.Li, G.Zhu. *Anal. Bioanal. Chem.*, **381**, 1179 (2005)
305. T.Y.Liu, K.T.Tsai, H.H.Wang, Y.Chen, Y.H.Chen, Y.C.Chao, H.H.Chang, C.H.Lin, J.K.Wang, Y.L.Wang. *Nat. Commun.*, **2**, 538 (2011)
306. B.B.Xu, R.Zhang, X.Q.Liu, H.Wang, Y.L.Zhang, H.B.Jiang, L.Wang, Z.C.Ma, J.F.Ku, F.S.Xiao, H.B.Sun. *Chem. Commun.*, **48**, 1680 (2012)
307. J.F.Betz, Y.Cheng, G.W.Rubloff. *Analyst*, **137**, 826 (2012)
308. R.M.Connatser, S.M.Prokes, O.J.Glembocki, R.L.Schuler, C.W.Gardner, S.A.Lewis, L.A.Lewis. *J. Forens. Sci.*, **55**, 1462 (2010)
309. J.S.Taurozzi, V.V.Tarabara. *Environ. Eng. Sci.*, **24**, 122 (2007)
310. Z.Xu, J.Hao, W. Braida, D.Strickland, F.Li, X.Meng. *Langmuir*, **27**, 13773 (2011)
311. I.Izquierdo-Lorenzo, I.Alda, S.Sanchez-Cortes, J.V.Garcia-Ramos. *Langmuir*, **28**, 8891 (2012)
312. A.Jaworska, R.Wietecha-Posłuszny, M.Woźniakiewicz, P.Kościelniak, K.Malek. *Analyst*, **136**, 4704 (2011)
313. H.Sui, L.Chen, X.X.Han, X.Zhang, X.Wang, B.Zhao. *Anal. Sci.*, **33**, 53 (2017)
314. R.Stosch, A.Henrion, D.Schiel, B.Güttler. *Anal. Chem.*, **77**, 7386 (2005)
315. X.Du, H.Chu, Y.Huang, Y.Zhao. *Appl. Spectrosc.*, **64**, 781 (2010)
316. D.H.Murgida, P.Hildebrandt. *J. Phys. Chem. B*, **105**, 1578 (2001)
317. L.Quaroni, J.Reglinski, R.Wolf, W.E.Smith. *Biochim. Biophys. Acta*, **1296**, 5 (1996)
318. A.F.Chrimes, K.Khoshmanesh, S.Y.Tang, B.R.Wood, P.R.Stoddart, S.S.E.Collins, A.Mitchell, K.Kalantar-zadeh. *Biosens. Bioelectron.*, **49**, 536 (2013)
319. K.Kneipp, H.Kneipp, V.B.Kartha, R.Manoharan, G.Deinum, I.Itzkan, R.R.Dasari, M.S.Feld. *Phys. Rev. E*, **57**, R6281 (1998)
320. Y.Kang, M.Si, Y.Zhu, L.Miao, G.Xu. *Spectrochim. Acta, Part A*, **108**, 177 (2013)
321. S.Feng, R.Chen, J.Lin, J.Pan, G.Chen, Y.Li, M.Cheng, Z.Huang, J.Chen, H.Zeng. *Biosens. Bioelectron.*, **25**, 2414 (2010)
322. S.Lee, H.Chon, J.Lee, J.Ko, B.H.Chung, D.W.Lim, J.Choo. *Biosens. Bioelectron.*, **51**, 238 (2014)
323. Z.Wu, Y.Liu, Y.Liu, H.Xiao, A.Shen, X.Zhou, J.Hu. *Biosens. Bioelectron.*, **65**, 375 (2015)
324. H.Cho, B.Lee, G.L.Liu, A.Agarwal, L.P.Lee. *Lab Chip*, **9**, 3360 (2009)
325. J.M.Yuen, N.C.Shah, J.T.Walsh, M.R.Glucksberg, R.P.Van Duyne. *Anal. Chem.*, **82**, 8382 (2010)
326. K.E.Shafer-Peltier, C.L.Haynes, M.R.Glucksberg, R.P.Van Duyne. *J. Am. Chem. Soc.*, **125**, 588 (2003)
327. Z.Pan, S.H.Morgan, A.Ueda, R.Mu, Y.Cui, M.Guo, A.Burger, Y.Yeh. *J. Raman Spectrosc.*, **36**, 1082 (2005)
328. C.David, N.Guillot, H.Shen, T.Toury, M.L.Chapelle. *Nanotechnology*, **21**, 475501-1 (2010)
329. V.P.Drachev, M.D.Thoreson, V.Nashine, E.N.Khaliullin, D.Ben-Amotz, V.J.Davisson, V.M.Shalaev. *J. Raman Spectrosc.*, **36**, 648 (2005)
330. G.Das, F.Mecarini, F.Gentile, F.De Angelis, H.G.M.Kumar, P.Candeloro, C.Liberale, G.Cuda, E.Di Fabrizio. *Biosens. Bioelectron.*, **24**, 1693 (2009)
331. G.V.P.Kumar, S.Shruthi, B.Vibha, B.A.A.Reddy, T.K.Kundu, C.Narayana. *J. Phys. Chem. C*, **111**, 4388 (2007)
332. J.J.Feng, U.Gernert, M.Sezer, U.Kuhlmann, D.H.Murgida, C.David, M.Richter, A.Knorr, P.Hildebrandt, I.M.Weidinger. *Nano Lett.*, **9**, 298 (2009)
333. R.Bohme, M.Richter, D.Cialla, P.Rosch, V.Deckert, J.Popp. *J. Raman Spectrosc.*, **40**, 1452 (2009)
334. R.M.Jarvis, A.Brooker, R.Goodacre. *Faraday Discuss.*, **132**, 281 (2006)
335. W.R.Premasiri, D.T.Moir, M.S.Klempner, N.Krieger, G.Jones, L.D.Ziegler. *J. Phys. Chem. B*, **109**, 312 (2005)
336. K.Fujita, S.Ishitobi, K.Hamada, N.I.Smith, A.Taguchi, Y.Inouye, S.Kawata. *J. Biomed. Opt.*, **14**, 024038-1 (2009)
337. S.Shanmukh, L.Jones, J.Driskell, Y.Zhao, R.Dluhy, R.A.Tripp. *Nano Lett.*, **6**, 2630 (2006)
338. Ö.F.Karataş, E.Sezgin, Ö.Aydın, M.Culha. *Colloids Surf., B*, **71**, 315 (2009)
339. S.Feng, J.Lin, Z.Huang, G.Chen, W.Chen, Y.Wang, R.Chen, H.Zeng. *Appl. Phys. Lett.*, **102**, 043702-1 (2013)
340. J.H.An, W.A.El-Said, J.-W.Choi. *J. Nanosci. Nanotechnol.*, **11**, 1585 (2011)
341. H.Hwang, H.Chon, J.Choo, J.K.Park. *Anal. Chem.*, **82**, 7603 (2010)
342. T.Vo-Dinh, D.L.Stokes, in *Biomedical Photonics Handbook*. (Ed. T.Vo-Dinh). (Boca Raton, FL: CRC Press, 2003). P. 1872
343. J.Ni, R.J.Lipert, G.B.Dawson, M.D.Porter. *Anal. Chem.*, **71**, 4903 (1999)
344. M.H.Shin, W.Hong, Y.Sa, L.Chen, Y.-J.Jung, X.Wang, B.Zhao, Y.M.Jung. *Vib. Spectrosc.*, **72**, 44 (2014)
345. J.-M.Li, W.-F.Ma, C.Wei, J.Guo, J.Hu, C.-C.Wang. *J. Mater. Chem.*, **21**, 5992 (2011)
346. B.Guven, N.Basaran-Akgul, E.Temur, U.Tamer, İ.H.Boyaci. *Analyst*, **136**, 740 (2011)
347. J.-W.Chen, Y.Lei, X.-J.Liu, J.-H.Jiang, G.-L.Shen, R.-Q.Yu. *Anal. Bioanal. Chem.*, **392**, 187 (2008)
348. E.A.Sergeeva, O.E.Eremina, A.V.Sidorov, T.N.Shekhovtsova, E.A.Goodilin, I.A.Veselova. *Mater. Technol.*, **32**, 881 (2017)
349. X.Dou, T.Takama, Y.Yamaguchi, H.Yamamoto. *Anal. Chem.*, **69**, 1492 (1997)
350. J.Langer, S.M.Novikov, L.M.Liz-Marzán. *Nanotechnology*, **26**, 322001 (2015)
351. J.Kneipp, H.Kneipp, B.Wittig, K.Kneipp. *Nanomedicine*, **6**, 214 (2010)
352. D.Mandal, M.E.Bolander, D.Mukhopadhyay, G.Sarkar, P.Mukherjee. *Appl. Microbiol. Biotechnol.*, **69**, 485 (2006)
353. A.Shamsaie, M.Jonczyk, J.Sturgis, J.P.Robinson, J.Irudayaraj. *J. Biomed. Opt.*, **12**, 020502 (2007)
354. R.M.Jarvis, N.Law, I.T.Shadi, P.O'Brien, J.R.Lloyd, R.Goodacre. *Anal. Chem.*, **80**, 6741 (2008)
355. W.Mu, D.K.Hwang, R.P.H.Chang, M.Sukharev, D.B.Tice, J.B.Ketterson. *J. Chem. Phys.*, **134**, 124312 (2011)

356. Z.Huang, G.Meng, Q.Huang, Y.Yang, C.Zhu, C.Tang. *Adv. Mater.*, **22**, 4136 (2010)
357. X.Y.Zhang, A.Hu, T.Zhang, W.Lei, X.J.Xue, Y.Zhou, W.W.Duley. *ACS Nano*, **5**, 9082 (2011)
358. I.R.Nabiev, H.Morjani, M.Manfait. *Eur. Biophys. J.*, **19**, 311 (1991)
359. Z.Huang, Z.Li, R.Chen, G.Chen, D.Lin, G.X.Y.Chen, H.Lin, J.Lei. *J. Phys.: Conf. Ser.*, **277**, 012014-1 (2011)
360. S.C.Pînzaru, L.M.Andronie, I.Domsa, O.Cozar, S.Astilean. *J. Raman Spectrosc.*, **39**, 331 (2008)
361. X.Wang, X.Qian, J.J.Beitler, Z.G.Chen, F.R.Khuri, M.M.Lewis, H.J.C.Shin, S.Nie, D.M.Shin. *Cancer Res.*, **71**, 1526 (2011)
362. J.Kneipp, H.Kneipp, B.Wittig, K.Kneipp. *Nano Lett.*, **7**, 214 (2007)
363. Z.Wang, A.Bonoiu, M.Samoc, Y.Cui, P.N.Prasad. *Biosens. Bioelectron.*, **23**, 886 (2008)
364. P.I.T.Thomson, V.L.Camus, Y.Hu, C.J.Campbell. *Anal. Chem.*, **87**, 4719 (2015)
365. L.-L.Qu, D.-W.Li, L.-X.Qin, J.Mu, J.S.Fossey, Y.-T.Long. *Anal. Chem.*, **85**, 9549 (2013)
366. A.Sivanesan, E.Witkowska, W.Adamkiewicz, Ł.Dziewit, A.Kamińska, J.Waluk. *Analyst*, **139**, 1037 (2013)
367. B.Kang, L.A.Austin, M.A.El-Sayed. *ACS Nano*, **8**, 4883 (2014)
368. E.A.Vitol, Z.Orynbayeva, M.J.Bouchard, J.Azizkhan-Clifford, G.Friedman, Y.Gogotsi. *ACS Nano*, **3**, 3529 (2009)
369. E.A.Vitol, E.Brailoiu, Z.Orynbayeva, N.J.Dun, G.Friedman, Y.Gogotsi. *Anal. Chem.*, **82**, 6770 (2010)
370. Q.Zhang, X.Lu, P.Tang, D.Zhang, J.Tian, L.Zhong. *Plasmonics*, **11**, 1361 (2016)
371. H.Xu, E.J.Bjerneld, M.Käll, L.Börjesson. *Phys. Rev. Lett.*, **83**, 4357 (1999)
372. N.Shaklai, J.Yguerabide, H.M.Ranney. *Biochemistry*, **16**, 5585 (1977)
373. R.T.Tom, A.K.Samal, T.S.Sreeprasad, T.Pradeep. *Langmuir*, **23**, 1320 (2007)
374. In *Red Cell Membrane Transport in Health and Disease*. (Eds I.Bernhardt, C.Ellory). (Berlin: Springer-Verlag, 2003). P. 748
375. O.G.Luneva, N.A.Brazhe, N.V.Maksimova, O.V.Rodnenkov, E.Y.Parshina, N.Y.Bryzgalova, G.V.Maksimov, A.B.Rubin, S.N.Orlov, E.I.Chazov. *Pathophysiology*, **14**, 41 (2007)
376. M.S.Pankratova, A.A.Baizhumanov, A.I.Yusipovich, M.Faassen, T.Yu.Shiryaeva, V.A.Peterkova, S.S.Kovalenko, T.A.Kazakova, G.V.Maksimov. *Peer J.*, **3**, e1055 (2015)
377. N.A.Brazhe, A.A.Baizhumanov, E.Yu.Parshina, A.I.Yusipovich, M.Ya.Akhalaya, Yu.V.Yarlykova, O.I.Labetskaya, S.M.Ivanova, B.V.Morukov, G.V.Maksimov. *Human Physiol.*, **40**, 804 (2014)
378. S.M.Ivanova, B.V.Morukov, G.V.Maksimov, A.A.Churin, Yu.V.Yarlykova, O.I.Labetskaya. *Human Physiol.*, **38**, 786 (2012)
379. M.Mahato, P.Pal, B.Tah, M.Ghosh, G.B.Talapatra. *Colloids Surf., B*, **88**, 141 (2011)
380. N.A.Brazhe, M.Treiman, B.Faricelli, J.H.Vestergaard, O.Sosnovtseva. *PLoS One*, **8**, e70488 (2013)
381. N.A.Brazhe, M.Treiman, A.R.Brazhe, N.L.Find, G.V.Maksimov, O.V.Sosnovtseva. *PLoS One*, **7**, 41990 (2012)
382. A.Beljebbar, G.D.Sockalingum, J.F.Angiboust, M.Manfait. *Spectrochim. Acta, Part A*, **51**, 2083 (1995)
383. H.Morjani, J.F.Riou, I.Nabiev, F.Lavelle, M.Manfai. *Cancer Res.*, **53**, 4784 (1993)
384. L.Rivas, S.Sanchez-Cortes, J.Stanicova, J.V Garcia-Ramos, P.Miskovsky. *Vib. Spectrosc.*, **20**, 179 (1999)
385. E.Horvath, J.Mink, J.Kristof. *Mikrochim. Acta*, **14**, 745 (1997)
386. A.Ruperez, R.Montes, J.J.Laserna. *Vib. Spectrosc.*, **2**, 145 (1991)
387. K.Faulds, W.E.Smith, D.Graham, R.J.Lacey. *Analyst*, **127**, 282 (2002)
388. P.Sevilla, F.Garcia-Blanco, J.V.Garcia-Ramos, S.Sanchez-Cortes. *Phys. Chem. Chem. Phys.*, **11**, 8342 (2009)
389. K.Ock, W.I.Jeon, E.O.Ganbold, M.Kim, J.Park, J.H.Seo, K.Cho, S.W.Joo, S.Y.Lee. *Anal. Chem.*, **84**, 2172 (2012)
390. M.Kim, K.Ock, K.Cho, S.W.Joo, S.Y.Lee. *Chem. Commun.*, **48**, 4205 (2012)
391. K.S.Ock, E.O.Ganbold, J.Park, K.Cho, S.W.Joo, S.Y.Lee. *Analyst*, **137**, 2852 (2012)
392. L.Rivas, A.Murza, S.Sanchez-Cortes, J.V.Garcia-Ramos. *Vib. Spectrosc.*, **25**, 19 (2001)
393. G.Lajos, D.Jancura, P.Miskovsky, J.V.Garcia-Ramos, S.Sanchez-Cortes. *J. Phys. Chem. C*, **112**, 12974 (2008)
394. Y.Wang, Y.S.Li, J.Wu, Z.Zhang, D.An. *Spectrochim. Acta, Part A*, **56**, 2637 (2000)
395. I.Izquierdo-Lorenzo, S.Sanchez-Cortes, J.V.Garcia-Ramos. *Langmuir*, **26**, 14663 (2010)
396. R.W.Berg, T.Norbygaard, P.C.White, S.Abdali. *Appl. Spectrosc. Rev.*, **46**, 107 (2011)
397. M.C.Netti, M.E.Zoorob, M.D.B.Charlton, P.Ayliffe, S.Mahnkopf, P.Stopford, K.Todd, J.R.Lincoln, N.M.B.Perney, J.J.Baumberg. *Proc. SPIE*, **6093**, 1605 (2006)
398. S.Farquharson, C. Shende, A.Sengupta, H.Huang, F.Inscor. *Pharmaceutics*, **3**, 425 (2011)
399. S.T.Bálint., S.Rao, M.M.Sánchez, V.Huntosová, P.Miskovsk, D.Petrov. *J. Biomed. Opt.*, **15**, 027005 (2010)
400. A.P.Craig, A.S.Franca, J.Irudayaraj. *Annu. Rev. Food Sci. Technol.*, **4**, 369 (2013)
401. X.F.Zhang, M.Q.Zou, X.H.Qi, F.Liu, X.H.Zhu, B.H.Zhao. *J. Raman Spectrosc.*, **41**, 1655 (2010)
402. M.Lin, L.He, J.Awika, L.Yang, D.R.Ledoux, H.Li, .Mustapha. *J. Food Sci.*, **73**, 129 (2008)
403. M.Jahn, S.Patze, T.Bocklitz, K.Webera, D.Cialla-May, J.Popp. *Anal. Chim. Acta*, **860**, 43 (2015)
404. J.Gao, Y.Hu, S.Li, Y.Zhang, X.Chen. *Spectrochim. Acta, Part A*, **104**, 41 (2013)
405. C.Müller, L.David, V.Chiş, S.C.Pînzaru. *Food Chem.*, **145**, 814 (2014)
406. S.H.Choi, H.G.Park. *Appl. Surf. Sci.*, **243**, 76 (2005)
407. N.Peica. *J. Raman Spectrosc.*, **40**, 2144 (2009)
408. N.Peica, C.Lehene, N.Leopold, S.Schlucker, W.Kiefer. *Spectrochim. Acta, Part A*, **66**, 604 (2007)
409. J.Olavarria-Fullerrton, S.Wells, W.Ortiz-Rivera, M.J.Sepaniak, M.A.Jesus. *Appl. Spectrosc.*, **65**, 423 (2011)
410. E.Podstawka, M.Swiatłowska, E.Borowiec, L.M.Proniewicz. *J. Raman Spectrosc.*, **38**, 356 (2007)
411. Y.Li, Y.Sun, Y.Peng, S.Dhakal, K.Chao, Q.Liu. *Sens. Agric. Food Qual. Safet.*, **8369**, 1 (2012)

412. B.Liu, P.Zhou, X.Liu, X.Sun, H.Li, M.Lin. *Food Bioproc. Technol.*, **6**, 710 (2013)
413. L.Guerrini, S.Sanchez-Cortes, V.L.Cruz, S.Martinez, S.Ristori, A.Feis. *J. Raman Spectrosc.*, **42**, 980 (2011)
414. Y.Xie, X.Zhu, Y.Sun, H.Wang, H.Qian, W.Yao. *Eur. Food Res. Technol.*, **235**, 555 (2012)
415. R.Li, H.Zhang, Q.W.Chen, N.Yan, H.Wang. *Analyst*, **136**, 2527 (2011)
416. Y.Zhang, Y.Huang, F.Zhai, R.Du, Y.Liu, K.Lai. *Food Chem.*, **135**, 845 (2012)
417. K.Lai, Y.Zhang, R.Du, F.Zhai, B.A.Rasco, Y.Huang. *Sens. Instrum. Food Qual. Safet.*, **5**, 19 (2011)
418. S.He, W.Xie, W.Zhang, L.Zhang, Y.Wang, X.Liu, Y.Liu, C.Du. *Spectrochim. Acta, Part A*, **137**, 1092 (2015)
419. H.Hu, Z.Wang, S.Wang, F.Zhang, S.Zhao, S.Zhu. *J. Alloys Compd.*, **509**, 2016 (2011)
420. J.Stropp, G.Trachta, G.Brehm, S.Schneider. *J. Raman Spectrosc.*, **34**, 26 (2003)
421. N.Peica, I.Pavel, S.C.Pînzaru, V.K.Rastogi, W.Kiefer. *J. Raman Spectrosc.*, **36**, 657 (2005)
422. T.Y.Olson, A.M.Schwartzberg, J.Liu, J.Zhang. *Appl. Spectrosc.*, **65**, 159 (2011)
423. T.Wang, Y.J.Xiao, Y.Yang, H.A.Chase. *J. Environ. Sci. Health, Part A*, **34**, 749 (1999)
424. E.Vogel, R.Geßner, M.H.B.Hayes, W.Kiefer. *J. Mol. Struct.*, **195**, 482 (1999)
425. F.Cataldo. *J. Raman Spectrosc.*, **39**, 169 (2008)
426. E.J.Liang, Y.H.Yang, W.Kiefer. *J. Environ. Sci. Health, Part A*, **31**, 2477 (1996)
427. G.Xue, J.Ding, P.Lu, J.Dong. *J. Phys. Chem.*, **95**, 7380 (1991)
428. M.M.Carrabba, R.B.Edmonds, R.D.Rauh. *Anal. Chem.*, **59**, 2559 (1987)
429. N.Weißenbacher, B.Lendl, J.Frank, H.D.Wanzenbiick, B.Mizaikoff, R.Kellner. *J. Mol. Struct.*, **410**, 539 (1997)
430. J.Li, L.Chen, T.Lou, Y.Wang. *ACS Appl. Mater. Interfaces*, **3**, 3936 (2011)
431. W.R.Premasiri, R.H.Clarke, S.Londhe, M.E.Womble. *J. Raman Spectrosc.*, **32**, 919 (2001)
432. A.E.Kandjani, Y.M.Sabri, M.Mohammad-Taheri, V.Bansal, S.K.Bhargava. *Environ. Sci. Technol.*, **49**, 1578 (2015)
433. S.Gajaraj, C.Fan, M.Lin, Z.Hu. *Environ. Monit. Assess.*, **185**, 5673 (2013)
434. M.J.Jager, D.P.McClintic, D.C.Tilotta. *Appl. Spectrosc.*, **11**, 1617 (2000)
435. Y.Xie, X.Wang, X.Han, X.Xue, W.Ji, Z.Qi, J.Liu, B.Zhao, Y.Ozaki. *Analyst*, **135**, 1389 (2010)
436. B.D.Piorek, J.L.Seung, J.G.Santiago, M.Moscovits, S.Banerjee, C.D.Meinhart. *Proc. Natl. Acad. Sci. USA*, **104**, 18898 (2007)
437. J.M.Sylvia, J.A.Janni, J.D.Klein, K.M.Spencer. *Anal. Chem.*, **72**, 5834 (2000)
438. L.X.Quang, C.Lim, G.H.Seong, J.Choo, K.J.Do, S.K.Yoo. *Lab Chip*, **8**, 2214 (2008)
439. R.F.Aroca, R.A.Alvarez-Puebla, N.Pieczonka, S.Sánchez-Cortés, J.V.Garcia-Ramos. *Adv. Colloid Interface Sci.*, **58**, 267 (2005)
440. A.V.Sidorov, O.E.Vashkinskaya, A.V.Grigorieva, T.N.Shekhovtsova, I.A.Veselova, E.A.Goodilin. *Chem. Commun.*, **50**, 6468 (2014)
441. O.O.Alabi, A.N.F.Edilbi, C.Brolly, D.Muirhead, J.Parnell, R.Stacey, S.A.Bowden. *Chem. Commun.*, **51**, 7152 (2015)
442. N.R.Agarwal, A.Lucotti, M.Tommasini, F.Neri, S.Trusso, P.M.Ossi. *Sens. Actuators, B*, **237**, 545 (2016)
443. R.S.Golightly, W.E.Doering, M.J.Natan. *ACS Nano*, **3**, 2859 (2009)
444. K.Hering, D.Cialla, K.Ackermann, T.Dorfer, R.Moller, H.Schneidewind, R.Mattheis, W.Fritzsche, P.Rosch, J.Popp. *Anal. Bioanal. Chem.*, **390**, 113 (2008)
445. C.L.Haynes, A.D.McFarland, R.P.Van Duyne. *Anal. Chem.*, **77**, 338A (2005)
446. R.A.Halvorson, P.J.Vikesland. *Environ. Sci. Technol.*, **44**, 7749 (2010)
447. K.W.Fomba, P.Galvosas, U.Roland, J.R.Kärger, F.-D.Kopinke. *Environ. Sci. Technol.*, **43**, 8264 (2009)
448. P.S.Redwood, J.R.Lead, R.M.Harrison, I.P.Jones, S.Stoll. *Environ. Sci. Technol.*, **39**, 1962 (2005)
449. J.P.Lafleur, S.Senkbeil, T.G.Jensen, J.P.Kutter. *Lab Chip*, **12**, 4651 (2012)
450. N.Weißenbacher, J.Frank, H.D.Wanzenböck. *Analyst*, **123**, 1057 (1998)
451. K.I.Mullen, D.X.Wang, L.G.Crane, K.T.Carron. *Anal. Chem.*, **64**, 930 (1992)
452. T.Vo-Dinh. *TRAC: Trends Anal. Chem.*, **17**, 557 (1998)
453. S.Sánchez-Cortés, C.Domingo, J.V.García-Ramos, J.A.Aznárez. *Langmuir*, **17**, 1157 (2001)
454. P.A.Mosier-Boss, S.H.Lieberman. *Appl. Spectrosc.*, **57**, 1129 (2003)
455. S.Lee, J.Choi, L.Chen, B.Park, J.B.Kyong, G.H.Seong, J.Choo, Y.Lee, K.-H.Shin, E.K.Lee, S.-W.Joo, K.-H.Lee. *Anal. Chim. Acta*, **590**, 139 (2007)
456. W.F.Pearman, S.M.Angel, J.L.Ferry, S.Hall. *Appl. Spectrosc.*, **62**, 727 (2008)
457. X.Zhang, J.Zhao, A.V.Whitney, J.W.Elam, R.P.Van Duyne. *J. Am. Chem. Soc.*, **128**, 10304 (2006)
458. L.Bao, S.M.Mahurin, R.G.Haire, S.Dai. *Anal. Chem.*, **75**, 6614 (2003)
459. S.E.J.Bell, N.M.S.Sirimuthu. *Chem. Soc. Rev.*, **37**, 1012 (2008)
460. O.Francioso, S.Sánchez-Cortés, D.Casarini, J.V.Garcia-Ramos, C.Ciavatta, C.Gessa. *J. Mol. Struct.*, **609**, 137 (2002)
461. G.Corrado, S.Sánchez-Cortés, O.Francioso, J.V.Garcia-Ramos. *Anal. Chim. Acta*, **616**, 69 (2008)
462. R.Baigorri, J.M.García-Mina, R.F.Aroca, R.A.Alvarez-Puebla. *Chem. Mater.*, **20**, 1516 (2008)
463. A.M.Alak, T.Vo-Dinh. *Anal. Chem.*, **59**, 2149 (1987)
464. J.C.S.Costa, A.C.Sant'Ana, P.Corio, M.L.A.Temperini. *Talanta*, **70**, 1011 (2006)
465. P.Leyton, I.Córdova, P.A.Lizama-Vergara, J.S.Gómez-Jeria, A.E.Aliaga, M.M.Campos-Vallette, E.Clavijo, J.V.García-Ramos, S.Sánchez-Cortés. *Vebr. Spectrosc.*, **46**, 77 (2008)
466. O.Péron, E.Rinnert, M.Lehaitre, P.Crassous, C.Compère. *Talanta*, **79**, 199 (2009)
467. X.Wang, W.Hao, H.Zhang, Y.Pan, Y.Kang, X.Zhang, M.Zouc, P.Tong, Y.Du. *Spectrochim. Acta, Part A*, **139**, 214 (2015)
468. S.D.Stewart, P.M.Fredericks. *J. Raman Spectrosc.*, **26**, 629 (1995)
469. Y.Xie, X.Wang, X.Han, W.Song, W.Ruan, J.Liu, B.Zhao, Y.Ozaki. *J. Raman Spectrosc.*, **42**, 945 (2011)

470. P.Leyton, S.Sánchez-Cortés, J.V.Garcia-Ramos, C.Domingo, M.Campos-Vallette, C.Saitz, R.E.Clavijo. *J. Phys. Chem. B*, **108**, 17484 (2004)
471. C.L.Jones, K.C.Bantz, C.L.Haynes. *Anal. Bioanal. Chem.*, **394**, 303 (2009)
472. A.V.Sidorov, O.E.Eremina, I.A.Veselova, E.A.Goodilin. *Mendeleev. Commun.*, **25**, 460 (2015)
473. A.V.Sidorov, O.E.Eremina, I.A.Veselova, E.A.Goodilin, V.N.Surtaev. *Oil Industry J.*, (11), 68 (2015)
474. O.E.Eremina, A.V.Sidorov, I.A.Veselova, V.G.Lakeev, E.A.Goodilin, V.N.Surtaev, K.B.Rudyak. *Oil Industry J.*, (11), 68 (2016)
475. M.J.Ayora, L.Ballesteros, R.Perez, A.Ruperez, J.J.Laserna. *Anal. Chim. Acta*, **355**, 15 (1997)
476. P.A.Mosier-Boss, S.H.Lieberman. *Anal. Chim. Acta*, **488**, 15 (2003)
477. C.L.Wong, U.S.Dinish, M.S.Schmidt, M.Olivo. *Anal. Chim. Acta*, **844**, 54 (2014)
478. R.A.Alvarez-Puebla, D.S.Santos, R.F.Aroca. *Analyst*, **132**, 1210 (2007)
479. M.A.De Jesus, K.S.Giesfeldt, M.J.Sepaniak. *J. Raman Spectrosc.*, **35**, 895 (2004)
480. N.A.Hatab, G.Eres, P.B.Hatzinger, B.Gu. *J. Raman Spectrosc.*, **41**, 1131 (2010)
481. S.S.R.Dasary, A.K.Singh, D.Senapati, H.Yu, P.C.Ray. *J. Am. Chem. Soc.*, **131**, 13806 (2009)
482. B.Saute, R.Narayanan. *Analyst*, **136**, 527 (2011)
483. X.Jiang, Y.Lai, M.Yang, H.Yang, W.Jiang, J.Zhan. *Analyst*, **137**, 3995 (2012)
484. O.Péron, E.Rinnert, T.Toury, M.L.de la Chapelle, C.Compère. *Analyst*, **136**, 1018 (2011)
485. J.Du, C.Jing. *J. Phys. Chem. C*, **115**, 17829 (2011)
486. J.Du, C.Jing. *J. Colloid Interface Sci.*, **358**, 54 (2011)
487. C.Ruan, W.Luo, W.Wang, B.Gu. *Anal. Chim. Acta*, **605**, 80 (2007)
488. T.Senapati, D.Senapati, A.K.Singh, Z.Fan, R.Kanchanapally, P.C.Ray. *Chem. Commun.*, **47**, 10326 (2011)
489. D.Senapati, S.S.R.Dasary, A.K.Singh, T.Senapati, H.Yu, P.C.Ray. *Chem.–Eur. J.*, **17**, 8445 (2011)
490. K.C.Vernon, T.J.Davis, F.H.Scholes, D.E.Gómez, D.Lau. *J. Raman Spectrosc.*, **41**, 1106 (2010)
491. E.L.Holthoff, D.N.Stratis-Cullum, M.E.Hankus. *Sensors*, **11**, 2700 (2011)
492. D.K.Corrigan, M.Cauchi, S.Piletsky, S.Mccrossen. *PDA J. Pharm. Sci. Technol.*, **63**, 568 (2009)
493. M.Lin, L.He, J.Awika, L.Yang, D.R.Ledoux, H.Li, A.Mustapha. *J. Food Sci.*, **73**, T129 (2008)
494. K.Lai. *Sens. Instrum. Food Qual. Safet.*, **5**, 19 (2011)
495. X.Song, H.Li, H.M.Al-Qadiri, M.Lin. *J. Food Meas. Charact.*, **7**, 107 (2013)
496. Y.Zheng, T.Thai, P.Reineck, L.Qiu, Y.Guo, U.Bach. *Adv. Funct. Mater.*, **23**, 1519 (2013)
497. H.S.Gill, S.Thota, L.Li, H.Ren, R.Mosurkal, J.Kumar. *Sens. Actuators, B*, 220, 794 (2015)
498. E.C.Le Ru, M.Meyer, E.Blackie, P.G.Etchegoin. *J. Raman Spectrosc.*, **39**, 1127 (2008)
499. D.E.Charles, D.Aherne, M.Gara, D.M.Ledwith, Y.K.Gun'ko, J.M.Kelly, W.J.Blau, M.E.Brennan-Fournet. *ACS Nano*, **4**, 55 (2010)
500. A.V.Sidorov, A.V.Grigorieva, A.E.Goldt, O.E.Eremina, I.A.Veselova, S.V.Savilov, E.A.Goodilin. *Funct. Mater. Lett.*, **9**, 1650016-1 (2016)
501. A.Bree, R.Zwarich. *Spectrochim. Acta, Part A*, **27**, 599 (1971)
502. D.Cialla-May, X.-S.Zheng, K.Weber, J.Popp. *Chem. Soc. Rev.*, **46**, 3945 (2017)