Review

Potential of nanoparticles in sample preparation

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A B S T R A C T

The paper presents a general overview of the use of nanoparticles to perform sample preparation. In this way the main uses of nanoparticles to carry out solid phase extraction, solid phase microextraction, liquid–liquid extraction and filtration techniques are described for a wide range of nanoparticles including carbon nanoparticles, metallic, silica and molecular imprinted polymer nanoparticles.

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Contents

1. Contextualization

Nanoscience is the first step of Nanotechnology in the classical sequence Research-Development-Innovation. Owing to the impressive growth and increasing impact of Nanotechnology in industry and modern life, the intermediate step – development – of this sequence is frequently minimized. On the other hand, the Gartner Hype Cycle model [1] that describes the evolution of a traditional technology does not fit in Nanotechnology because the predictable depression of visibility after maximum expectations is very low in this case and the plateau of productivity has been reached very rapidly in the last years. This fact has positive but also

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negative connotations; a discussion of them is out of the scope of this paper.

There are many definitions of Nanoscience and Nanotechnology (N&N), the majority of which emphasize the nanometric size of the material (typically between 1 and 100 nm), but the most relevant aspect of nanostructured material is the impressive changes in physico-chemical properties as regards macromaterial and their dependency on size. Chemical, optical, electrical, thermal, magnetic, etc. characteristics are unique on the nanoscale, and that can also be exploited in the field of miniaturization. An ideal goal of N&N is to combine both the size and the extraordinary properties of nanostructured material, which is now a difficult task due to the associated technical problems.

1.1. Analytical nanoscience & nanotechnology

Analytical Science cannot be left out of N&N [2] and, in fact, it is present in many definitions of N&N because reliable information about the nanoworld is crucial to make well founded scientific and technical decisions in this area. In this case, the nanomaterials are the targets (analytes) as can be seen in Fig. 1 A. The role of Analytical Chemistry in this context is undeniable. The extraction of chemical information from the structured nanomaterial (composition, chirality, reactivity-also related with the biological activity, etc.) is an indispensable complement to the physical characterization, which is more well-known (dimensions, topography, typical physical properties). Both types of information are mutually related (e.g., physico-chemical characteristics, structure of nanoparticles) and physiscists, chemists and engineers should collaborate closely. A well recognized future in this context is the integration of instruments providing both types of information almost simultaneously such as in the case of the combination of the atomic force microscope (AFM) with Raman spectrometry [3]. Typical exclusions among areas are really bottle-necks for the full advancement of N&N. A recent scientometric study in the ISI web of knowledge shows that less than 35% of scientific papers on Analytical N&N are devoted to the analysis of nanomaterials, which is not consistent with the importance of the role that Analytical Science can play in N&N. No doubt, this proportion will increase in the forthcoming years.

On the other hand, nanomaterials can be used as analytical tools (see Fig. 1B) to develop new analytical processes or to improve existing ones. In this case, Analytical Chemistry takes advantage of N&N developments as do other areas such as energy, sports, material science, textiles, electronics. The present review can be ascribed to this facet. As can be seen in Fig. 1B, one can distinguish three situations according to which facet of the nanomaterial is exploited, namely: (1) The nanosize; (2) The exceptional physico-chemical properties of the nanomatter; and (3) Both facets. These situations give rise to three different alternatives, which are briefly commented on below.

(a) *Nanometric analytical systems* based exclusively on the nanosize of the devices involved. They represent a step towards miniaturization but they do not exploit the exceptional properties of the nanomatter. Such is the case of a nanopipette [4] and levitated nanodrops as analytical containers [5].

(b) In *Nanotechnological analytical systems* the exploitation of the exceptional nanotechnological properties allows one to develop improved analytical processes in terms of top, basic and complementary analytical properties and also they allow analysis of new matrices and analytes. The topic of this article is ascribed to this alternative.

(c) The ideal situation in Analytical N&N occurs when both the nanosize and the exceptional properties of the nanomatter are exploited. These systems are called *Analytical nanosystems.*

There are few of them because their development has technical restrictions. But they undoubtedly represent the future of Analytical N&N. Two representative examples are the so called lab-on-a-particle [6] and a nano-gas chromatography [7].

1.2. Types of nanoparticles

There are many ways to systematically describe existing nanoparticles using several classifications based on several complementary criteria such as origin (ex. natural, artificial), chemical nature (e.g., inorganic, organic, mixed), homogeneity (e.g., single or hybrid composition), etc. In the framework of nanotechnological analytical systems, a classification associated with the exploited properties is very relevant. Fig. 2 shows the most relevant nanoparticles used in Analytical Chemistry as well as the exceptional properties mainly exploited in each case. As can be seen, metallic and carbon nanoparticles are the most versatile, whereas silica nanoparticles only exploit chemical properties.

The panoramics of Fig. 2 can be amplified if hybrid nanoparticles (a topic of growing interest) are taken into account. There are two types of hybrid nanoparticles according the combined properties, namely: (1) Properties of the isolated nanoparticles are different but complementary; such as the case of the combination of carbon nanotubes (CNTs) and ferrite nanoparticles [8] and (2) Properties of the isolated nanoparticles are of the same nature but their combination produces important synergistic effects; such as the case of the combination of quantum dots [9].

1.3. Role of nanoparticles in analytical processes

As a rule, an analytical process can be divided into several steps, as is represented in Fig. 3, namely: sample preparation (including sampling), chromatographic (LC, GC) and capillary electrophoretic techniques, detection and data handling and treatment to offer the results as required.

Fig. 3 represents these steps and the proportion of described analytical procedures in which nanoparticles are involved. The majority of them are devoted to developing nanoparticle (e.g., gold, carbon nanotubes) based electrodes. There are many papers devoted to the exploitation of nanoparticles for sample treatment (sample clean-up, concentration of analytes or both), which is the topic of this review. The use of nanoparticles as stationary phases in gas chromatography (GC) and liquid chromatography (LC) and as pseudostationary phases in capillary electrophoresis is a topic of growing interest [10].

2. Main aims of the use of nanoparticles in sample preparation processes

The incorporation of nanoparticles in the sample treatment step, in general, helps to simplify this step. Nanoparticles, according to their participation and role in the sample treatment step, can be classified in the following groups:

i- Nanoparticles acting as sorbent agents. In this case there is a direct interaction between the analyte and the nanoparticle.

ii- Nanoparticles acting as an inert support. For example, a silica nanoparticle functionalized with a complexation agent.

iii- Nanoparticles having special magnetic properties. In this case the use of a magnetic field can help to simplify the analytical procedure. These nanoparticles can either absorb the analyte directly or must be functionalized with organic groups.

iv- Nanoparticles acting as ionization agent for the direct analysis of samples by ion secondary mass spectrometry.
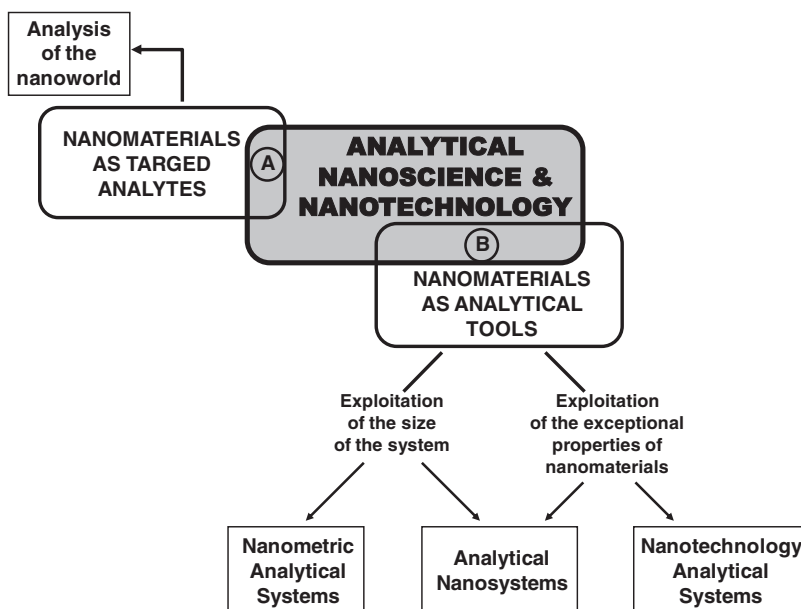
Fig. 1. The two connotations of Analytical Nanoscience and Nanotechnology based on the consideration of nanoparticles as analytes (A) and tools (B). For details, see text.

Fig. 2. The most relevant nanoparticles involved in analytical process and the corresponding exceptional properties of the nanomatter exploited. Figure adapted from reference [2].

Fig. 3. Overview of the relative proportion of nanoparticles in different steps of analytical processes.

In general, the chemical properties of the nanoparticles such as, sorption capabilities must be exploited but their physical properties such as magnetism can also be exploited. In both cases, nanoparticles or chemically modified nanoparticles are used to perform sample clean-up and the preconcentration of the analyte. It must be mentioned that, compared with traditional systems, the use of nanoparticles allows the simplification of the methods as well as the poss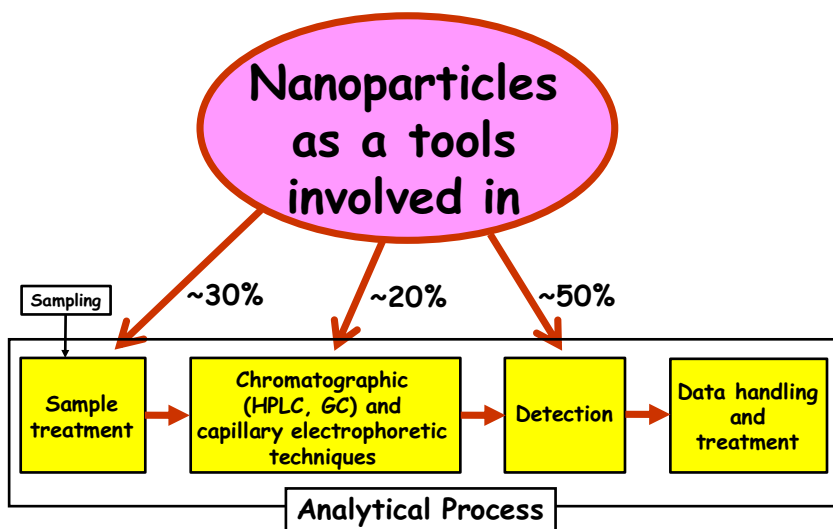ibility of treating small amounts of samples. In fact, two aspects must be considered: the possibility of analysing new sample matrices where the amount of sample is a key aspect or the analysis of samples but using a very small amount of sample.

3. Nanoparticles as sorbent materials in SPE

3.1. Carbon nanoparticles

Carbon exists in a number of allotropic forms. Since the first discovery of the spheric allotropic structure, C_{60} fullerene in 1985 [11], several others have been either accidentally found or synthesized. Among them, carbon nanotubes are by far the most exploited for analytical purposes thanks to their outstanding electrical, mechanical, thermal and sorbent properties [12]. In the field of solid-phase extraction, fullerenes, carbon nanotubes and recently carbon nanocones and nanodiamonds have been used to develop new analytical procedures with added value over existing alternatives.

Fullerenes are polyhedral nanostructures in which the carbons are bonded in arrangements of five to six membered rings. Fullerene C_{60} is an electron deficient structure which favours its interaction with compounds having electron donors groups. Fullerenes are extremely insoluble in aqueous and organic media. This characteristic, shared with other carbon nanoparticles, has limited their analytical applicability. However, they present lower aggregation tendency which facilitates their use as sorbents in miniaturized SPE procedures based on continuous flow devices. This alternative has been extensively used for the determination of metals and their organometallic derivatives by the on-line coupling of the continuous flow system to a flame atomic absorption spectrometer. Gallego et al. were the first to propose this alternative for the determination of total lead in waters [13]. The flow configuration is quite simple and permits the preconcentration of large volumes of water by placing the C_{60} sorbent column in the loop of an injection valve. Retention of the metal on the fullerene surface requires the previous formation of a neutral chelate, typically a carbamate derivative. This reaction takes place in the reaction coil located prior to the sorbent column. By using a second injection valve, an appropriate volume of eluent (typically methyl isobutyl ketone) is passed through the fullerene column for analyte elution. This organic plug is inserted in a water stream and directly introduced in the flame atomic absorption spectrometer. By using this approach, several metallic species have been determined in a variety of matrices such as cobalt in wheat flour [14] and cadmium in fish liver [15]. The information obtained from these approaches refers to the total concentration of the target metal, as the instrument does not discriminate between free and conjugated forms of the analyte. Thus, further efforts were aimed at the analysis of the organic fraction eluted from the system by gas chromatography. It also offered the possibility of studying the capability of fullerene to interact with organic aromatic species. Preliminary studies pointed out that although fullerenes present high affinity for organometallic species, their potential for organic compounds is rather limited [16]. The speciation of metals by gas chromatography requires previous derivatization of the species of interest in order to increase their volatility and facilitate their interaction with the chromatographic column. Several reagents have been pro-

posed for this aim. Thus, inorganic lead and alkyl lead compounds were derivatized using the Grignard reagent [17]. The method was applied to the determination of different lead species in rainwaters collected from different locations (urban park, vicinity of a petrol station and industrial area). All the samples (50 mL) were previously analysed by flame atomic absorption spectrometry (FAAS), which provides the global lead concentration. The chromatographic separation permits the individual quantification of the lead species if required. The flow configuration is similar in both cases as the derivatization reaction is carried out in an off-line manner. Taking into account the higher sensitivity of the GC/MS method, only 25 mL of sample was preconcentrated. As a result, inorganic lead, diethyl lead, triethyl lead and dimethyl lead were found to be present in the three waters analysed while trimethyl lead was undetected as it is easily degraded to dimethyl lead and Pb^{2+}. Organic metallic compounds can also been determined in environmental samples by using a similar approach [18].

As far as organic compounds are concerned, fullerene C_{60} has been compared with C_{18} and Tenax for the preconcentration of benzene, toluene, ethylbenzene and xylenes (BTEX) from waters and further determination by GC-MS [19]. The nanostructured material surpassed the conventional sorbents in terms of sensitivity, precision and sorbent capacity, this property being unaltered under acidic pH values which indirectly increased the method selectivity. Moreover, the authors developed and optimized a continuous flow configuration which includes a packed C_{60} minicolumn which allows sorbent reusability by including a clean-up step between samples. The proposed method was applied to the determination of BTEX in a variety of waters, the recoveries being acceptable for the proposed application. Recently, the discrimination between aromatic and non-aromatic nitrosamines has been accomplished [20]. The authors have designed an automated configuration including fullerene and LiChrolut tandem sorbent columns. The sample is first passed through the fullerene for aromatic amine retention. The effluent is then driven to the LiChrolut column where the non-aromatic fraction is isolated. In this way, the system permits the selective determination of the most toxic amines (non-aromatic) by virtue of the favoured interaction between the aromatic amines and the nanostructured material. In absence of the fullerene column, all the amines are preconcentrated on the conventional material. The method sensitivity is low enough to determine the pollutants at concentrations lower than the maximum admissible concentration established for drinking waters.

Carbon nanotubes can be considered as excellent materials for SPE thanks to their large adsorption surface and high affinity for organic compounds. Multi-walled carbon nanotubes are preferred over single-walled as the presence of concentric sheets resulted in an enhanced interaction with the analytes. The first application of carbon nanotubes in this context was proposed by Cai et al, who used a commercial polypropylene cartridge packed with 500 mg of carbon nanotubes for the enrichment of endocrine disruptors [21]. The method permits the preconcentration of up to 1 L of water without reaching the breakthrough volume. This fact, together with the low eluent volume used (2.5 mL of methanol) allows the target compounds to be detected at concentrations as low as 0.018 ng/mL. If the performance of carbon nanotubes is compared with that provided by conventional sorbents (viz. C_{18} or XAD-2) it turns out to be better for the more polar endocrine disruptors. Since then, several references have been reported in the literature dealing with the applicability of carbon nanotubes packed in cartridges. From them, it can be seen that the amount of sorbent was reduced up to 30 mg and the cartridge can be reused up to 200 times without performance losses regardless of the complexity of the matrix. The sorbent capacity of the carbon nanotubes is maintained even in organic media as the preconcentration of different pesticides from virgin olive oils has been reported [22]. The main problem

associated with the use of carbon nanotubes in SPE is the formation of aggregates which diminishes the real surface/area ratio [23]. Thus, reducing the dimensions of the extraction units can minimize this negative effect and favour the interactions at the nanoscale level, viz. on the nanotubes surface, while maintaining the retention capacity. The use of automated devices based on continuous configurations is quite relevant in this context. Therefore, as little as 6 mg of MWNT's can be packed in a large diameter column (ca. 9 mm i.d.) and then placed in the loop of an injection valve. The proposed configuration reduces the pressure in the whole system as well as the sorbent compactness, as the retention and elution steps can be accomplished in opposite directions. Based on this approach, the determination of tetracycline residues in waters [24] and sulfonamides in egg and pork [25] were described. Further reduction of the amount of carbon nanotubes used for preconcentration was accomplished by immobilizing the nanostructured material on the surface of inert controlled pore glass [26]. For this purpose, single-walled carbon nanotubes were selected on account of their easier functionalization. The presence of the carboxylic groups is necessary to anchor the nanotubes on the inert glass. As a result, the interaction of the analytes with the individual nanotubes is made possible while the compactness of the hybrid solid is dramatically reduced. Once synthesized, an accurately weighed amount of 15 mg of the resulting material was packed in a minicolumn further inserted in a continuous flow configuration. It was evaluated for nonsteroidal anti-inflammatory drugs in urine samples, being better than the conventional package of the same amount of single and multi-walled carbon nanotubes.

These automated configurations have also been used to determine metals in waters, although in these cases, larger amounts of sorbent (average 50 mg) are packed. The systems were online coupled to flame atomic absorption or inductively coupled plasma atomic emission spectrometers for the determination of cadmium, manganese, nickel, copper and lead [27–29]. The retention of the inorganic species requires the introduction of carbonyl, carboxylic and hydroxyl groups on the carbon nanotube surface. In this sense, the pH of the sample turned out to be crucial as the nanotubes should be negatively charged to interact with the cations.

Further attempts to miniaturize conventional SPE include the packing of the sorbent in pipette tips or syringe needles. These alternatives maintain high enrichment factors by using high performance sorbents which make it possible to reduce the eluent volume required for analyte elution. The potential of carbon nanotubes has been evaluated in these miniaturized techniques. Basheer et al. reported the use of multi-walled carbon nanotubes supported on a porous polypropylene membrane [30]. 6 mg of MWNT's were packed inside the membrane, whose edges were heat-sealed to avoid material losses. The micro device was evaluated for the extraction of organophosphorous pesticides from sewage sludge. The unit was tumbled in the sample, which facilitates extraction, while the membrane prevents the retention of potential interferents, further clean up of the extract not being required. The isolated pesticides were eluted with hexane and further analyzed by GC/MS reaching detection limits as low as 1 pg/g. The π–π interactions established between the analytes and the carbon nanotubes and the large surface area of the nanostructured material are behind this excellent performance. The authors estimate the device lifetime in ca. 30 uses. The proposal seems to be faster, more accurate and cost-effective than the hollow fibre protected solid phase microextraction or headspace solid phase microextraction methods. Recently, See and coworkers proposed a modification of this microextraction modality by retaining the multi-walled carbon nanotubes (3 mg) in a tiny cone shaped membrane located at the end of a 1 mL pipette tip [31]. The approach was evaluated for the extraction of selected triazine herbicides from river

waters. The extraction was carried out in a semiautomatic dynamic mode by means of a digital micropipette and 5 extraction cycles were implemented to increase the overall extraction efficiency. Once completed, the cone-shaped membrane was removed, rinsed with ultrapure water and immersed in 100 μL of acetonitrile. Elution was assisted by ultrasounds (15 min) and 0.5 μL of the organic phase was injected into the micro-LC for herbicide separation and quantification. The microextraction device is capable of preconcentrating the target compounds using a sample volume of up to 15 mL, which permits analyte detection at concentrations as low as 0.2 μg/L. The absolute extraction efficiency ranged from 5.5% (atrazine) to 71% (propazine) while relative recoveries were in all cases higher than 95%.

The use of carbon nanotubes as sorbents in micro-solid phase extraction in the needle of a syringe has also been explored. Conventional sorbents, such as C_{18} are ineffective in this miniaturized technique due to the low amount of sorbent that can be held in the needle (ca. 300 μg). Sae-Khow and Mitra evaluated the performance of pure and functionalized (–OH, –COOH) carbon nanotubes for this purpose [32]. The extraction device consists of a syringe fitted with a 100 mm long capillary packed with 0.3 g of the carbon nanotubes and plugged with glass wool at both ends. The nanomaterial requires activation with acetonitrile and distilled water prior to μSPE. 2-nitrophenol, 2,6-dichloroaniline and naphthalene were selected as model compounds. Packed SWNTs and MWNTs were found to be more efficient than the self-assembled configuration. This latter approach formed a layer of few microns on the inner surface of the capillary, resulting in a larger void volume, which reduces the contact between the sample and the sorbent. The packed configuration thus yielded the highest enrichment factors (2.8–6.8) and extraction efficiencies (11.1–27.1) with breakthrough volumes of 17.5 mL of water sample. Furthermore, the authors compared the performance of pure CNTs with that of functionalized ones. It was found that 2-nitrophenol and 2,6-dichloroaniline were more strongly adsorbed on functionalized carbon nanotubes while the underivatized sorbent was more appropriate for naphthalene isolation. OH-SWNTs or OH-MWNTs were the best sorbents for 2-nitrophenol while 2,6-dichloroaniline was more effectively retained on functionalized MWNTs.

Carbon nanotubes have also been self-assembled on the inside wall of a steel capillary to fabricate a microtrap for the adsorption/desorption of trace organics from a gaseous stream [33]. The microtrap acts as a nanoconcentrator and as injector for gas chromatography. The higher density of the carbon nanotubes layer involves a higher sorbent capacity. Moreover, the configuration allows a fast quantitative desorption. Toluene and hexane were selected as model compounds. As result, the adsorption of toluene was much stronger than that of hexane thanks to the π–π interactions between the carbon nanotubes surface and the aromatic ring of toluene.

Carbon nanotubes have also been successfully used to enhance the binding capacity of a molecularly imprinted polypyrrole modified stainless steel frit (0.5 μm pore size) for micro solid-phase extraction [34]. The approach was evaluated for the determination of ochratoxin A (OTA) in red wines. Taking into account the complexity of the sample matrix, multiple pulse elution was selected to eliminate the interferences. It was done automatically as the microextraction unit was located in the sample loop of the liquid chromatograph injection valve. The sample (0.1–3.0 mL) was passed through the frit by means of a syringe and eluted with 100 μL of 1% triethylamine in methanol. The mobile phase transferred the organic eluate to the chromatographic column. The limit of detection for OTA was 0.08 ng/mL using 3 mL of sample, with a total analysis time of ca. 30 min. The use of a molecularly imprinted polymer enhances the selectivity of the method towards endogenous compounds of the sample matrix.

Recently, a new carbon nanostructure, the carbon nanocone, has been proposed for its use in SPE [35]. The commercial product contains 20%wt carbon nanocones, 70%wt carbon discs and 10%wt amorphous carbon. The presence of the amorphous solid gives rise to irreversible interactions with the analytes and lower recovery values, as a result. This negative effect can be reduced by maintaining the commercial solid at 450 °C for 20 min. This treatment dramatically reduced the amorphous carbon content with negligible influence on the nanostructured material. In the model application developed for the determination of chlorophenols in waters, 20 mg of the thermally treated sorbent was packed in a 3-mL commercial SPE cartridge. Detection limits as low as 0.3 ng/mL were achieved by preconcentrating 2 mL of water sample and eluting the retained compounds with 200 µL of hexane. As compared with carbon nanotubes, the conical nanostructures proved to be more efficient in the preconcentration process as similar analytical features were obtained with lower sorbent amounts. This fact can be explained by taking into account that the carbon nanocones show a lower aggregation tendency than the carbon nanotubes and, therefore, the effective surface available for analyte interaction is higher with the former.

Diamonds have been described as an exceptional platform for protein adsorption and immobilization. They are optically transparent, chemically inert and biologically compatible [36]. The surface of this nanomaterial can be functionalized by strong oxidative acid treatment. The modified nanodiamonds are easily suspended in aqueous media which indicates that the surface is hydrophilic in nature. The surface modified nanodiamonds can be used as solid-phase extraction material for systematic proteome analysis of humeral fluids and potential disease biomarker discovery [37]. The platform allows the purification and concentration of intact proteins and their enzymatic digests for further sodium dodecyl sulphate-polyacrylamide gel electrophoresis or matrix assisted laser desorption/ionization mass spectrometry. The proteome analysis of human urine can be completed in 8 h as the whole process can be directly performed on the particles.

3.2. Metallic nanoparticles

Metallic nanoparticles is a term which involves a wide range of different inorganic nanoparticles. In this section, several selected examples will be presented in order to point out the analytical potential of this group of nanoparticles to carry out the preconcentration or clean-up of the sample. Currently, the most widely used method for the removal and separation of toxic metal ions as well as organic compounds is the solid phase extraction technique. Recently, there have been reports in the literature on the enrichment and separation of organometallic trace elements and organic compounds in the sample solutions by means of inorganic nanoparticles such as TiO_2, Al_2O_3, ZrO_2, MnO and CeO_2 [38–40]. Nanoparticles have unique properties such as large specific surface area, high adsorption capacity and low temperature modification, so they are promising solid-phase extractants and have contaminant scavenging mechanisms [41,42].

Waychunas et al. have discussed the structures and reactivity of FeOx nanoparticles, concretely, goethite, akaganeite, hematite, ferrihydrite and schwertmannite nanoparticles [43]. These nanoparticles are important constituents of soil with a high capacity to adsorb analytes. The adsorption properties of many oxides strongly depend on the characteristics of solids such as morphology, crystal structure, defects, specific surface area, hydroxyl coverage, surface impurities and modifiers. Most of these factors can be controlled by using appropriate chemical modification. The basic disadvantage of solid sorbents is the lack of intrinsic selectivity, which causes interference with target metal ions. Goethite nanoparticles are used for the adsorption of As(V), Cu(II), Hg(II) and

Zn(II) [43,44]. Other example is maghemite nanoparticles which have been used for the selective removal of Cr(VI), Cu(II) and Ni(II) from electroplating wastewater [45,46]. The group of Demarco have used hydrated Fe oxide nanoparticles for the selective removal of As(III) and As(V) [47]. TiO_2 nanoparticles have been widely used as sobent. In fact, the adsorption behaviour of toxic metal ions like Cu(II), Cr(III), Mn(II), Ni(II), Zn(II), Cd(II), Mo(VI) and rare earth elements on TiO_2 nanoparticles has been reported in environmental samples [48–50]. Al_2O_3 nanoparticles have been also used to analyze metal ion in environmental waters [51]. Some examples are given in Table 1. As can be seen, low limits of detection can be reached using these nanoparticles.

As it was commented before, the lack of selectivity is one of the shortcomings of the use of these nanoparticles. To overcome this problem, physical or chemical modification of the sorbent surface with organic compounds, especially chelating ones, is required. Immobilization using (a) dithizone, (b) diethyldithiocarbamate (DDTC), (c) 1-(2-pyridylazo)-2-naphthol or (d) 8-hydroxyquinoline on TiO_2 nanoparticles has been reported and these compounds have been used to preconcentrate toxic metal ions [52–54]. These chelating compounds have been also used to modify amunina nanoparticles. For example, the modification of alumina nanoparticles with dithizone has been reported for the preconcentration of Pb(II) from drinking and natural water [55]. These nanoparticles have been also modified with gallic acid. In this case, the gallic acid introduce selectivity for the preconcentration of Fe(II) and Fe(III) [56,57].

Organic compounds have been also purified with metallic nanoparticles. One example is the direct use of Ag nanoparticles. The reduction of Ag nitrate with sodium borohydrate in an aqueous medium in the presence of cetyltrimethylammonium bromide gives a stable solution of Ag nanoparticles, which can absorb nonpolar organic compounds, e.g., polycyclic aromatic hydrocarbons can be preconcentrated on the surface of metal nanoparticles. In addition, the presence of Ag nanoparticles allows the enhancement of analyte luminescence. This strategy has been demonstrated to be useful for the preconcentration and direct analysis of trace amounts of polycyclic aromatic hydrocarbons (PAHs) in aqueous samples [58].

In addition to small organic molecules, oxide nanoparticles have been also used to preconcentrate phosphoproteins. In this way, mesoporous TiO_2 nanocrystals have been described to preconcentrate phosphoproteins. In order to improve selectivity, it has been proposed the use of mesoporous TiO_2 clusters. For that, nanocrystals are self-assembled and stabilized by coating with a thin layer of silica. Afterwards, the calcination of this material at high temperature results in the interconnection of the nanocrystals resulting in a system with a high mechanical stability free of surfactant. The selectivity of this material to preconcentrate phosphoproteins has been pointed out by effectively enriching phosphopeptides from digests of phosphoprotein (α- or β-casein), protein mixtures of β-casein and bovine serum albumin, milk, and human serum samples [59]. Although the clusters have a high affinity towards phosphoproteins, nanosized titanium dioxide particles thanks to their higher superficial surface area also present a higher trapping capacity toward phosphopeptides. For example, TiO_2-coated magnetic (Fe_3O_4/TiO_2 core/shell) nanoparticles have been used to preconcentrate phosphopeptides from protein digest products. In this case, a magnetic field is used to remove the nanoparticles with the phosphoprotein from the matrix [60].

3.3. Silica nanoparticles

Silica nanoparticles are characterized to present high surface areas and exhibit intrinsic surface reactivity which allows the possibility of introducing chemical modifications. Chemical modification

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Table 1
Preconcentration of metal ions by nanoparticles.

Samples	Nanoparticles	Detection	Analyte	LOD (μg/L)	Ref
Environmental water samples	TiO$_2$	ICP-AES	Cu(II)	0.34	[49]
			Cr(III)	1.14	
			Mn(II)	0.52	
			Ni(II)	1.78	
Environmental water samples	Al$_2$O$_3$	ICP-MS	Mn(II)	0.0067	[51]
			Ni(II)	0.038	
			Zn(II)	0.078	
			Pb(II)	0.027	
			Co(II)	0.0082	
			Cd(II)	0.079	
Environmental water samples	ZrO$_2$	ICP-OES	Mn(II)	0.012	[40]
			Ni(II)	0.007	
Sediments	TiO$_2$	GFAAS	Se(IV)	0.16	[52]
			Se(VI)	0.14	
Sediments	TiO$_2$	ICP-AES	Au(III)	0.016	[50]
			Pd(II)	0.012	
			Ag(I)	0.006	

by a silanization procedure using different silylating agents such as 3-aminopropyltriethoxysilane, 3-chloropropyltriethoxysilane and aminopropyltriethoxysilane provides immobility, mechanical stability and water insolubility [61]. Mercaptopropyltrimethoxysilane modified nanometer sized alumina and N-[3-(trimethoxysilyl)-propyl]ethylenediamine modified silica nanoparticles have been used for the preconcentration of some toxic heavy metal ions such as Hg(II), Cu(II) and Zn(II) [62–64]. Thiol modified silica nanoparticles have been used for the preconcentration of drugs and also pesticides [65]. Silylation of silica nanoparticles has been carried out by 4-(2-pyridylazo)-resorcinol through a single-stage Mannich reaction and these modified SiO$_2$ nanoparticles have been used for the selective determination of Hg(II) [66]. SiO$_2$ has also been modified with acetylsalicylic acid, p-dimethylaminobenzaldehyde and 5-sulfonylsalicylic acid [67]. General strategies are depicted in Fig. 4.

Fig. 5 shows characteristic photos of nanoparticles used in sample treatment, in the image the high homogeneity of silica

Fig. 4. Main strategies of functionalization/modification of silica nanoparticles.

nanoparticles can be observed. For example, 1-(2-pyridylazo)-2-naphthol modified SiO$_2$ nanoparticles (SiO$_2$-PAN) as solid-phase extractants have been developed for the preconcentration of trace amounts of Cd(II) in different water samples [68]. The adsorption capacity of nanometer SiO$_2$-PAN was found to be 60.57 μmol/g. The adsorption equilibrium of Cd(II) on nanometer SiO$_2$-PAN was achieved in just 15 minutes. Adsorbed Cd(II) was easily eluted with 6 mL of 6 M hydrochloric acid [69]. SiO$_2$-PAN nanoparticles have been also used for the preconcentration of Zn(II) and Mn(II) in water and food samples [70]. The adsorption capacity of nanometer SiO$_2$-PAN was found to be 71.50 and 24.22 μmol/g. The extractant showed rapid sorption kinetics the adsorption equilibrium being achieved within just 15 min [71]. The preconcentration of Ni(II) on SiO$_2$-PAN nanoparticles has been also described. In this case the adsorption equilibrium is achieved in 10 min [72].

Other applications are related to the use of silica nanoparticle derivatives. Silica-coated magnetic nanoparticles (SCMNPs) modified with γ-mercaptopropyltrimethoxysilane (γ-MPTMS) have been used for solid phase extraction of trace amounts of Cd, Cu, Hg, and Pb from biological and environmental samples [73]. These nanoparticles present the advantage of silica nanoparticles with regard to surface reactivity as well as the advantage of magnetic nanoparticles. Magnetic nanoparticles carrying the target metals could be easily separated from the aqueous solution simply by applying an external magnetic field; no filtration or centrifugation was necessary. Using this new magnetic material, the authors have developed an efficient and cost-effective two-step method for detecting trace amts. of Cd, Cu, Hg, and Pb in environmental and biological samples [74]. The 1st step of the method is a separation and preconcentration step, in which metals are adsorbed onto γ-MPTMS-SCMNPs. In the 2nd step, inductively coupled plasma mass spectrometry is used to study the adsorbed metals. Relative standard deviations of the analysis of biological samples reach below 9%. Another related example is the solid-phase extraction of analytes based on mixed hemimicelles of cetyltrimethyl ammonium bromide (CTAB) on silica-coated magnetic nanoparticles (MNPs) developed for the extraction and preconcentration of compounds from biological samples [75]. With this strategy, rhein and emodin in urine and serum samples have been analysed. The authors described the absence of interferences caused by proteins or endogenous compounds in urine and serum samples. With the use of the combination of extraction hemimicelles/nanoparticles the detection limits reached for rhein and emodin were 0.2 and 0.5 ng/mL in urine samples and 7 and 10 ng/mL in serum samples, respectively, the recoveries being satisfactory. Gold nanoparticle
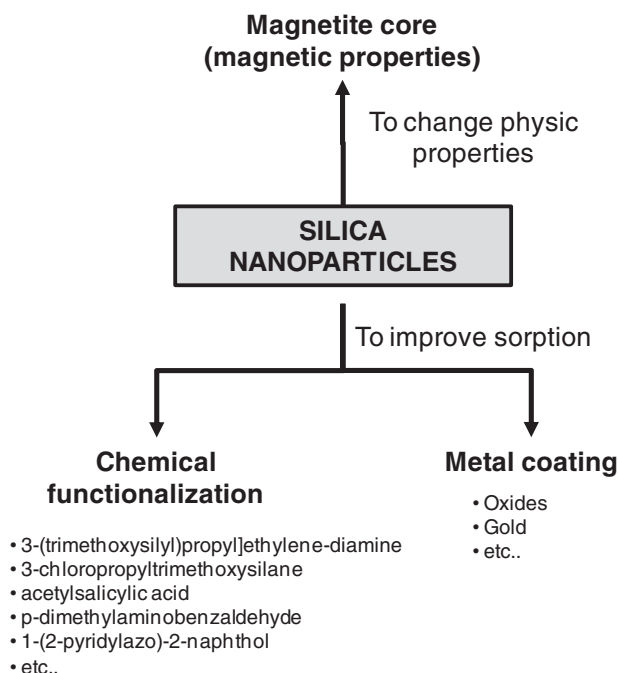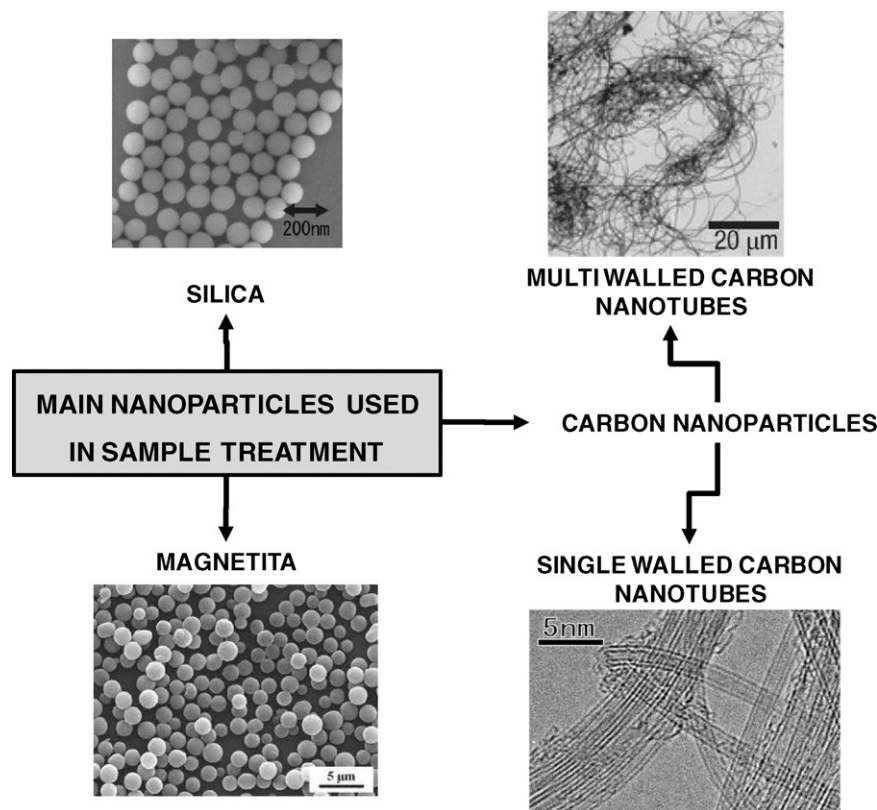
Fig. 5. Characteristic photos of the main nanoparticles used in sample treatment.

(Au NP)-coated silica nanoparticles have also been used for the pre-concentration of neutral steroids (testosterone, progesterone, and testosterone propionate) in urine samples. The preconcentration of the analytes was more efficient in this new sorbent than in a commercial C(18)-bonded silica gel [76].

Recently, gold-coated silica nanoparticles packed in a minicolumn has been described for the analysis of mercury in natural waters. The adsorbent was prepared by chemical reduction of a Au(III) solution with hydroxylamine in the presence of suspended silica particles [77]. The resulting Au nanoparticles on the silica surface were highly efficient for adsorbing different mercury species from acidified waters without additional reagents. The method offers significant advantages because no reagents are needed for species conversion, preconcentration, sample storage, or desorption and therefore the risk of contamination is minimized and blank values are lowered. This gives rise to a low detection limit of 180 pg/L using a sample volume of only 7 mL and good reproducibility, with relative standard deviations of <3.2%.

3.4. Imprinted nanomaterials

Molecularly imprinted polymers (MIPs) are a specific class of selective sorbents that are built-in functionalized in order to achieve the complementary recognition of a given chemical compound. They present several advantages over their counterpart highly selective materials such as immunosorbents or enzymatic/catalytic reactors, such as long-term stability and excellent performance under extreme pH and temperature conditions as well as the use of organic solvents. The field of imprinting materials has also attracted the interest of nanoscience and nanotechnology as their combination has a synergic effect on the final products obtained. In addition to their reduced size, the main advantages of imprinted nanomaterials are focused on their enhanced efficiency,

which is supported by: fast equilibration, increased number of binding sites and easier uptake and release of the template [78,79]. Moreover, they retain the well known outstanding properties (optical, electrical, and mechanical) of nanomaterials.

Molecular imprinting consists of the polymerization of a template molecule in the presence of a cross-linking monomer. As a result, specific nano-sized cavities or surface recognition sites are created. The main characteristics of such cavities are that they are steric and electronically complementary to the target compounds. This confers to the polymeric material a high degree of specificity, based on a combination of shape, size and functionality criteria. The template used can be either the target compound or a mimic. The former alternative is especially suitable for affinity separations while the latter has been reported to simulate enzymatic, antibody or catalytic functions [80].

The interaction between the template and the functional monomer can be covalent or non-covalent. Wulff and Sarhan were the first to propose the covalent synthesis of MIPs [81] while Arshady and Mosbach developed the non-covalent approach [82]. Non-covalent imprinting techniques prevail thanks to their versatility, expeditiousness and monomer availability. As a detailed description on this topic is out of the scope of the review, readers interested in general aspects are referred to [83–88]. However, some considerations will be commented on in this section in order to justify the relevance of the size-reduction in this context.

MIPs are predominantly prepared by free radical bulk polymerization, followed by crushing, sieving and drying steps, which gives rise to particles with diameters of between 10 and 25 μm. Two factors are considered of crucial importance when synthesizing MIP's for analytical purposes: the morphology and the accessibility of the recognition sites, as both variables determine the efficiency of the MIP. There are several articles dealing with this topic [89–91]. From these references, it can be concluded that a careful selection

of polymerization conditions is required in order to obtain comparable results with the irregular shaped particles obtained at the end of the process. Thus, the availability of synthetic procedures directly yielding micro or nano-sized MIP's is desirable in order to minimize these negative effects on the final performance of the imprinted material. In this sense, polymerization by precipitation [92,93] provides a simple way of obtaining spherical MIP particles with diameters of between 3 and 5 μm. Although the microsphere yields scarcely exceed 60%, this synthetic route still surpasses bulk polymerization because a large amount, out of the 90% of final particulate matter obtained, is not usable after the grounding and sieving [94]. MIP size can also be controlled by using composite beads. In this case, a polymer material (silica or latex with diameters of between 30 nm and 1 μm) is used as a core-shell, which is further coated with a thin, homogeneous imprinted layer on its surface. These imprinted nanoparticles are quite versatile as the core particle can present magnetic or fluorescent properties, with a synergic effect on molecular recognition. The main reported applications of these nanoMIP's fall in the field of chromatographic (affinity) and electrophoretic (as phseudophases) separations as well as drug delivery and sensing [95].

In order to extend the applicability of nano-sized imprinted material to the sample preparation step, research has also been focused on the application of this technology to other types of nanostructures such as nanowires, nanofilaments (nanobrushes) and nanofibres. The articles dealing with the usefulness of such approaches in the field of solid-phase extraction will be commented on.

Yoshimatsu et al. have recently proposed the use of nanofibre affinity membranes for the selective extraction of residues of drugs (propranolol) in water samples [96]. For this purpose, propranolol imprinted nanoparticles were encapsulated into (polyethylene terephthalate, PET) nanofibres by electrospinning and the process was verified by scanning microscopy. The micrographs obtained demonstrated that the nanoparticles were homogeneously distributed along the fibrous structure. The resulting composite is highly stable in organic media (pure acetonitrile or mixtures with water). Moreover, the encapsulating process does not affect the recognition capability of the MIP beads as the authors demonstrated by using aqueous standards of the labelled (s)-propranolol. 5 mg amounts of the synthesized nanofibre were used to extract the target analyte from 1 mL of water. The propranolol retained by means of hydrophobic, non-specific adsorption was removed by washing the nanofibre with acetonitrile:ammonium acetate buffer. The elution of the bonded analyte was accomplished by means of 1 mL of acetonitrile:water:acetic acid (40:30:30). The selectivity of the imprinted nanofibre was 64% versus the 16.3% provided by the non-imprinted one. Detection limits as low as 21 ng of propranolol were achieved by using 100 mL of water and 5 mg of sorbent.

Surface molecularly imprinted polymer nanowires have been proposed as a selective material for the isolation of large molecules, such as proteins and other biomacromolecules. They present a very low mobility and poor rebinding efficiency in conventional imprinted materials. Li et al. proposed imprinting at the polymer surface as the best alternative for the determination of proteins such as albumin, hemoglobin and cytochrome c [97]. They used a nanoporous alumina as support, the nanopores being filled by the functional and cross-linking monomers. Then, the alumina membrane is chemically dissolved leaving polymeric nanowires in which the binding sites are located on the surface. The authors stated that the specificity of the support is provided by the hydrogen bonding and shape of the interaction sites. The efficiency of the solid can be attributed to two main factors: good accessibility of the binding sites and large surface area of the polymer. Owing to the water solubility of the imprinted nanowire, it is fully compatible with biochemical measurements.

Xie et al. have also proposed imprinted polymer nanowire/nanotube arrays in porous alumina membrane for the determination of trinitrotoluene (TNT) [98]. The authors stated that the TNT template can spontaneously assemble onto 3-aminopropyltriethoxysilane-modified alumina pore walls by a charge-transfer interaction. The authors evaluated the recognition properties of the imprinted nanowires/nanotubes and confirmed that they show much higher binding capacities than the non-imprinted ones. This fact was attributed to the high ratio of surface-imprinted sites, the large surface-to-volume ratios and the complete removal of TNT templates. Finally, the rebinding capacity of the nanotube was larger than that of the nanowires as a likely result of their tubular structure, which allows the generation of imprinted sites on the inside surface of the nanotubes.

Sensors and on-chip devices based on molecularly imprinted polymer microstructures have also been proposed on silicon wafers using micromoulding in capillaries [99]. The procedure employs a polydimethylsiloxane (PDMS) stamp which is placed onto the silicon wafer to form a network of empty capillaries. These microchannels are further filled with the imprinting solution followed by polymerization. As a result, MIP microstructures are generated on the wafer surface using 2,4-dichlorophenoxy acetic acid (2,4-D) as the template molecule. The shape and size of the MIP micromonoliths can be modified by changing the feature sizes on the PDMS stamps. The yield was ca. 5 mg of MIP micromonoliths per 6.5 cm × 1.5 cm stamps. The MIP's were uniform in size and shape and the authors anticipate the possibility of using this approach for the fabrication of submicron-size imprinted materials.

4. Nanoparticles as sorbent materiales in SPME

Solid-phase microextraction (SPME) was first proposed in 1990 by Arthur and Pawliszyn [100]. It can be considered as a miniaturized sample pretreatment technique whose advantages over other well-established methodologies have been clearly identified. Among them, its easy on-line coupling which chromatographic and electrophoretic techniques should be mentioned. Operationally, this technique is based on the partition of the analyte between the sample (or its headspace) and the stationary phase coated on a solid support.

The type of coating used in SPME plays a crucial role in the efficiency of the extraction as it is the main factor affecting the distribution constant between the target compounds and the immobilized phase. Commercially available SPME fibres are made by PDMS, polyacrilate (PA), divinylbenzene (DVB), Carbowax (CW) and Carboxen (CAR). They are implemented into fully automated devices, compatible with the autosamplers of gas chromatographs. However, they present some shortcomings related to their instability with high temperatures, carry over and incompatibility with organic solvents. In recent years, research has been focused on the development of new coatings which can either overcome these limitations or extend the applicability of the technique.

Nanostructured particles have also emerged as useful tools for solid-phase microextraction taking into account their sorbent capacity pointed out in previous sections of this article. Carbon nanostructures, silica and titanium dioxide nanoparticles are the most reported in the literature for the development of new coatings for solid-phase microextraction.

Fullerenes were the first carbon nanostructure discovered and evaluated for analytical purposes. Their sorbent properties have already been discussed and they can also been exploited for SPME. The main problem found is that their poor solubility hinders the coating on a fibre, regardless of its nature. Therefore, for the use of fullerenes in SPME, they have to be attached to a polymeric matrix. Xiao et al. proposed the use of a polymeric fullerene for

the determination of semivolatile compounds using SPME under the headspace modality [101]. The synthesis of the coating involves the reaction between a polyazidosilicone backbone and the C_{60}. The resulting polymeric fullerene was coated on a treated silica capillary by using a high temperature epoxy resin. The fibre was 1 cm in length and 33 μm in thickness. The presence of fullerene favours interaction with aromatic compounds via π–π bounding. The detection limits for BTEX and PAHs varied between 0.8–2.2 ng/mL and 0.04–0.4 ng/mL with precision better than 5% and 6.8%, respectively. As for fibre stability, it can be reused more than 150 times when working at a maximum temperature of 280 °C.

Hydroxyfullerene has also been used as coating in SPME using the sol–gel technology [102]. In this case, a hydroxy-terminated silicon oil and methyltrimethoxysilane were used to construct the polymeric skeleton. The sol–gel coating requires 30 min to be formed and the process was repeated several times until the desired thickness (30 μm) was achieved. Ageing was completed in the injection port of a gas chromatograph (150–300 °C, 2–8 h, N_2). The SPME fibre was evaluated for polychlorinated biphenyls (PCBs), PAHs and aromatic amines under the headspace modality. The authors discuss the sol–gel process in depth with emphasis on the major reactions involved in the coating. 20 mg of fullerol was added to a total volume of 700 μL of reaction mixture; higher amounts leading to precipitation. The microscopic examination of the surface of the coating reveals that it presents a porous structure which is responsible for the increased surface area of the fibre, improving the kinetics of the extraction process and the extraction efficiency as a result. The high thermal stability of the fullerene permits the fibre to be used up to 360 °C at least 200 times. The presence of fullerol increased the selectivity of the extraction (compared with the absence of nanostructured material) owing to the similar partial planar structure of both the analytes and the fullerene.

Carbon nanotubes were first reported as SPME coating for the isolation of polybrominated diphenyl ethers in water and milk samples [103]. Multi-walled carbon nanotubes were immobilized onto a 2 cm fused silica fibre. For this aim, the MWNTs were dispersed in dimethylformamide and aliquots of the suspension were deposited on the fibre, previously cleaned with acetone. After a drying step, the procedure was repeated until the desired film thickness (40 μm) was achieved. It was assembled in the needle of a 5 μL syringe protected by a section of quartz capillary. The extraction of the analytes was carried out by direct immersion of the MWNT fibre in 10 mL of sample for 30 min. Then, the isolated compounds were thermally desorbed from the fibre at 295 °C (2 min) in the injection port of the gas chromatograph. Between samples, the fibre was heated to ensure no carry over. The detection limits ranged between 3.6 and 8.6 ng/L with relative standard deviations lower than 8.8%. The efficiency of the coated MWNTs was compared with that provided by activated carbon and poly (95% dimethylsiloxane–5% dibenzene) (PDMS-DB) with the same thickness, new fibre turning out to be ca. 5 times better in terms of enhancement factor.

The selectivity of the carbon nanotubes can be modified by introducing functional groups on their surface. Thus, oxidized multi-walled carbon nanotubes can be used as SPME coating for the determination of more polar compounds such as phenols [104]. The authors used a fused silica tubing as solid support for the carboxylated carbon nanotubes. The fibre stability was increased by using an epoxy resin glue as adhesive. The fibre was aged at 200 °C in an inert atmosphere and the final coating was ca. 50 μm in thickness. The phenols were extracted from 4 mL of water samples using the direct immersion modality and further eluted with 70 μL (3 min, room temperature) of acetonitrile:water 70:30 followed by liquid chromatographic separation. In this case, the fibre was maintained in the eluent until the baseline was achieved to eliminate carry

over between samples. All the variables affecting the extraction (temperature, pH, ionic strength) were studied by the authors. The c-MWNT SPME fibre was compared with both laboratory made and commercial fibres, the nanostructured coating providing the best results. As far as the lifetime of the coating is concerned, the authors found that the fibre maintains its performance up to 15 uses. However, in spite of the improved LOD's achieved, they were not low enough for the determination of the target pollutants at the legislated levels in waters.

Further efforts have been described in the literature aimed at increasing the thermal stability of the coating. Thus, Li et al. proposed the use of electrophoretic deposition of oxidized single-walled carbon nanotubes on Pt wires [105]. The thickness of the coating can be controlled by repeating the process for various cycles. The absence of both adhesives and solvents seems to be an advantage for the analytical application of the fibre as it did not swell in organic media or strip off from substances and possesses higher stability. The fibre was evaluated by extracting six phenols from waters by direct immersion. The coating process was studied in depth. The c-SWNTs (individual, in bundles or aggregate) moved to the anode once the voltage was applied to the Pt wires. A deposit was stuck to the Pt anode at the end of the process. In order to increase the interaction between the nanotubes, their vaporization with dimethylformamide was required. The stability of the fibre against organic solvents and its mechanical robustness was also evaluated. The fibre was recovered without detachment after being immersed in methanol, acetonitrile, acetone and dichloromethane. The carbon nanotubes were firmly stuck to the Pt wire as no particles were released after scratching with a piece of paper or maintaining it under ultrasounds for more than 10 min. The performance of the fibre was compared with that obtained with a PA fibre, the most commonly used for the analytical problem selected. The higher specific surface area and the polarity introduced by the carboxylic groups to the CNTs make the proposed fibre more efficient for the extraction of phenols from waters, with detection limits between 0.9 and 3.8 μg/L and average recoveries of 94.5% for seawater and 97.4% for tap water.

The advantages of the sol–gel methodology for SPME coating have been reported in the literature [106]. Fused silica substrate has commonly been used on account of the silanol groups that can be created in its surface. However, its high fragility has caused efforts to be focused on metals such as titanium wires [107], oxidized steel, [108] and stainless steel [109], all demonstrating that the metal wire can successfully replace the fused silica support. The sol–gel procedure has also been proposed for the application of carbon nanotube coating on a metal support under mild conditions [110]. The sol solution of the oxidized nanotubes was prepared in methyltrimethoxisilane, polymethylhydrosiloxane and trifluoroacetic acid. Then, it was transferred to a glass tube fitted with a par-film membrane at the bottom. The stainless steel wire (pretreated with NaOH) was pierced through the membrane and fixed on a thread that connects to a motor. This device permits the wire to draw at a constant rate. This movement allows the sol–gel coating layer to be formed on its surface. The procedure was repeated until the desired thickness was obtained. Prior to the first use, the fibres were conditioned for 6 h under a temperature gradient (50–260 °C). The analytical procedure involves analyte (BTEX, PAHs and phenols) preconcentration by headspace/direct immersion of the fibre in the sample. The batch reproducibility between fibres was better than 6.5%. This excellent result was justified by the fact that the proposed procedure permits a longer fibre to be coated and shorter pieces can be obtained by cutting it. Moreover, the fibre was solvent and thermally stable thanks to the chemical bonds between the sol–gel CNT coating and the stainless steel wire. Its performance was better than a commercial or pure sol–gel PDMS with negligible carry over between samples.

Two carbon nanotube composites have also been described in the literature as coatings in solid phase microextraction. Du et al. proposed a carbon nanotube-polyaniline (MWNTs-PANI) composite film coated on a Pt wire for the determination of phenols in waters [111]. The method is based on the capability of aniline to dissolve carbon nanotubes via a donor–acceptor complex [112]. The coating was formed by electrodeposition (ca. 40 μm thickness), with a potential scan between −0.1 and 0.9 V, 50 mV/s, 50 times. The fibre was characterized by infrared spectroscopy and SEM, which pointed out that the MWNT-PANI was more uniform and with smaller and denser pores, with a larger effective surface area than the PANI film. It makes the composite more favourable for the adsorption/extraction of the analytes. Once prepared, the fibre was fitted to a laboratory made SPME device and conditioned at 300 °C in an inert atmosphere until no background noise was observed in the chromatogram. The analytes were extracted from the samples under the headspace modality and thermally desorbed in the injection port of the gas chromatograph for 3 min. From the experiments carried out, the authors conclude that the composite is stable up to 320 °C, maintaining its extraction capacity towards the analytes over 216 uses. As far as the analytical problem selected is concerned, the phenols can be detected at the low nanogram per liter level, with a better than 12.2% fibre-to-fibre reproducibility. The analyte recoveries from the analyzed waters were in the 88–115% range.

The second alternative combines multi-walled carbon nanotubes with Nafion to obtain a composite suitable for the extraction of polar aromatic compounds from waters [113]. Although both have been individually used as coating in SPME, in this article, the authors employed Nafion as a binder to immobilize the carbon nanostructured material onto a stainless steel wire. In addition, the sorbent capacity of the polymer plays a synergic role for analyte extraction. The coating fibre was estimated by SEM and turned out to be ca. 12.5 μm, which corresponds to a double layer of MWNT/Nafion. It was selected as a compromise between extraction efficiency and procedure laboriousness, as the authors stated that the higher the number of layers, the better the fibre performance. The coating was stable under organic, alkaline and acidic conditions, the fibre to fibre reproducibility being in the range of 10% (as relative standard deviation). As in the previously described approaches, the performance of the fibre was better than that provided by pure Nafion or PA-based commercial devices. The detection limits were in the range of 30–50 ng/L for 5 mL of water.

Carbon nanotubes have also been used to perform in-tube solid-phase microextraction [114]. In the developed application, oxidized multi-walled carbon nanotubes were coated on the outer surface of a fused silica tubing, which was further inserted in a polyether ether ketone (PEEK) one and directly inserted in the loop of an injection valve. It was presented by the authors as a better alternative to the fibre SPME on account of the higher amount of sorbent that can be coated to the extraction device. One of the main advantages of the method is that the extraction step can be on-line coupled to the analytical instrument (liquid chromatograph) thus allowing the complete automation of the procedure. The sample (up to 40 mL) was passed through the capillary at a constant flow rate, controlled by the high pressure pump which positively affects the method precision. Substitute aniline compounds were selected as model analytes, the operational conditions being studied in depth by the authors. They found that up to 30 min were needed for preconcentration of the water samples at a flow rate of 1.4 mL/min. The elution was carried out by passing the mobile phase through the tube for 2 min. The detection limits were in the low nanogram per millilitre level. In the conclusions, the possibility of including different functional groups in the carbon nanotubes in order to increase the selectivity of the extraction for more complex samples was foreseen.

The sorbent capacity of carbon nanocones/disks has also been exploited for solid-phase microextraction [115]. The main advantage of their use as an active element of the coating arises from their lower aggregation tendency which permits a better dispersion/solubilization in the organic media with a subsequent simplification of paste preparation. In addition, it also permits the immobilization of higher amounts of nanostructured material. The fibre preparation is similar to that proposed by Lü et al. for SWNT's [116]. As it was previously optimized, the carbon nanocones were thermally treated to eliminate the amorphous carbon and thus minimize the irreversible interactions that would occur. The nanoparticles were fixed to a stainless steel needle using an organic binder, the final coating being 3 cm in length and ca. 50 μm in thickness. The efficiency of the fibre was evaluated for the determination of toluene, ethylbenzene and xylene isomers in waters. Taking into account the volatility of the analytes, the headspace modality was used for sampling and the isolated analytes were thermally desorbed in a vial (110 °C, 15 min) to preserve fibre integrity and extend its reusability. Despite the dilution involved in this step, the method is sensitive enough to tackle the determination of the pollutants in waters, with detection limits of 0.15 ng/mL (toluene excepted, 0.6 ng/mL). Analyte recoveries from tap and environmental waters were acceptable in all cases. However, the immobilization procedure should be improved in order to extend the method applicability to less volatile compounds.

Nanostructured lead dioxide has also been proposed as a coating for solid-phase extraction [117]. The PbO_2-SPME fibre was prepared by electrochemical deposition of the nanoparticles on a Pt wire. The SPME procedure was applied to the determination of BTEX in waters working under the headspace modality and gas chromatographic separation. The fibre preparation was studied in depth because PbO_2 can exist under two different phases, namely: α and β. This fact is very important as the α-PbO_2 is a compact structure while β-PbO_2 is porous. This species is generated when the PbO_2 deposition is carried out under acidic conditions. In addition, fluoride, methanol and nafion were added as additives to improve the mechanical stability and structural porosity of the PbO_2 coating. Under these experimental conditions, the nanoparticle size was in the 34–136 nm range. Before the first use, the fibre was conditioned at 250 °C for 30 min. Then, it can be used ca. 50 times with a negligible effect on fibre thickness and extraction performance. Although the linear range obtained with this fibre is narrower than those reported in the literature for commercial PDMS fibres, the detection limits were significantly improved (lower than 54 ng/l) with fibre-to-fibre reproducibility between 9.1 and 12.5% (as RSD). Among the advantages of the PbO_2 coating, the authors cited the chemical resistance, low cost and high porous structure.

Finally, silica nanoparticles have been used for in-tube solid-phase microextraction coupled with liquid chromatography [118]. The nanoparticles were immobilized on the inner surface of the capillary via liquid phase deposition. The procedure should be repeated three times on order to favour particle aggregation and therefore, a dense film was formed by the nanosize particles (ca. 100 nm) and their clusters. They were further modified with octadecyl groups. The resulting material presents hydrophobic properties and therefore, its performance was evaluated with families of compounds with different polarities. The hydrodynamic variables were optimized in each case using the corresponding mobile phase as eluent. The efficiency of the capillary was compared with that of octadecyl-grafted silica and octadecyl grafted sol–gel silica coated capillaries. The capillary with silica nanoparticles turned out to be better on account of the higher ratio of surface area exposed to the sample to the sample volume. This effect is less marked for compounds showing weak hydrophobic interaction towards the immobilized octadecyl groups. The capillary synthesis was quite reproducible and the resulting unit was highly stable in

terms of extraction efficiency, which permits its use in routine analysis. Moreover, it is very versatile as a variety of functional groups can be introduced in the silica nanoparticles.

5. Nanoparticles as pseudo-stationary phases in (micro)extraction procedures

5.1. Nanoparticles in liquid–liquid extraction

5.1.1. Surfactant coated nanotubes in liquid–liquid extraction

As previously commented, CNTs present excellent sorption properties which make them an excellent tool in solid phase extraction procedures. However, the main limitation for the use of CNTs in microextraction techniques arises from their aggregation tendency. In fact, CNTs tend to assemble in bundles and ropes by van der Waals interactions, reducing the active surface of the material and therefore restricting their applicability [119]. Moreover, the aggregation of the material produces over-pressures when conventional SPE cartridges are employed limiting also the volume of sample that can be loaded. This limitation has been overcome by different approaches such as their immobilization on to porous inert glass or their use in modified filters.

CNTs are also characterized by a low solubility in water and organic solvents. The aqueous solubility can be increased by chemical derivatization with oxidants which introduces oxygen-ionogenic groups (mainly, –OH, –COOH) on the CNT surface. This chemical modification may cause defects on the CNT walls and modify the π-electron conjugation altering their inherent properties. On the other hand, the use of surfactants as disperser materials has attracted much attention since they do not disturb the electron cloud of the graphene sheets. In this case, the surfactants are adsorbed by their hydrophobic tail to the CNT surface while their polar heads are oriented to the aqueous solution facilitating the stabilization of the CNTs. Surfactant coated CNTs have been used in Analytical Sciences with different purposes such as pseudostationary phase in capillary electrophoresis.

Surfactant dispersion enhances the sorption capabilities of CNTs since it reduces the aggregation process and increases the contact surface between the CNTs and the analytes. Moreover, this extraction presents certain selectivity and aromatic compounds are preferably extracted to aliphatic ones [120]. The aqueous nature of these pseudophases makes them an excellent tool for the extraction of oily samples. In fact, surfactant coated CNTs have been successfully applied to the determination of BTEXs [121] and phthalates [122] from olive oil samples in a selective and sensitive way. In these procedures a specific volume of sample and pseudophase are mixed and conveniently stirred in order to favour a good transference of the analytes between both phases. Finally, the pseudophase is analyzed by headspace/gas chromatrography/mass spectrometry.

The use of surfactant coated CNTs in these procedures signifies an evident improvement of selectivity since the matrix effect is conveniently reduced which is quite important when oily samples and sophisticated instruments are employed. Moreover, an evident improvement of sensitivity is obtained even when the distribution coefficient for the target analytes between the sample and the pseudophase is lower than one, which obviously involves a dilution in the liquid–liquid extraction. This fact can be explained by two different factors. On the one hand, the liquid–gas distribution coefficient depends directly on the nature of the donor liquid phase, the release to the gas being favoured if an aqueous phase (the pseudophase) is employed instead of an oily one (the sample). On the other hand, at high temperatures like those employed in the headspace generation, the pseudophase becomes unstable easily releasing the analytes to the headspace. This procedure provides a sensitivity enhancement factor compared to the direct headspace analysis of the oily sample in the range of 20–45 for BTEXs. Moreover, it allows the determination of different migrants in olive oil which are undetectable with the conventional headspace approach.

5.1.2. Nanoparticles in liquid phase microextraction

The use of nanoparticles as components of the extracting phase in liquid microextraction procedures has gained importance in recent years. Sudhir et al. first proposed the use of gold nanoparticles in the extraction of peptides from water and urine following a single drop microextraction technique [123]. The new technique is based on the surface charge of the gold nanoparticles and the iep (isoelectric point) of the target peptides. In fact, colloidal gold solutions in toluene are used as extracting media in these procedures. In order to achieve these solutions a phase transfer reagent such as a quaternary ammonium bromide salt is employed. This substance forms ion pairs with the gold nanoparticles with the bromide ion attached to the gold surface. As a result of this, gold nanoparticles exhibit a partial positive charge on their surface which allows their interaction with anions. In fact, peptides are extracted at pH's below their iep where they present a negative charge. Finally the extracted proteins are determined by matrix assisted laser desorption ionization-mass spectrometry (MALDI-MS). The main advantage of the proposed methodology is that the extracting phase can be directly analyzed not requiring further pretreatment.

Gold nanoparticles can be efficiently derivatized on the surface in order to promote diverse interactions with the target analytes. In this respect, Shastri et al. modified the NPs with (4-mercapthophenyliminomethyl)-2 methoxyphenol to serve as multifunctional nanoprobes for the extraction of peptides and proteins from milk samples in the fmol range [124].

In the same way silver nanoparticles have also been employed for the extraction of peptides and proteins in biological samples by means of a liquid–liquid extraction procedure [125]. For this purpose the silver nanoparticles were derivatized with hydrophobic ligands such as dodecanethiol or octadecanethiol. The proposed methodology involves a many-fold improvement in the determination of those compounds by MALDI-MS.

5.2. Nanoparticles as substrates for hemimicelles and admicelles

The adsorption of ionic surfactants on the surface of mineral oxides, such as alumina, silica, titanium dioxide and ferric oxyhydroxides, has been extensively employed for the development of new solid phase extraction materials. In this case, the mineral oxides act as substrates while the adsorbed ionic surfactants are the responsible for the extraction of the target analytes from the sample matrix. Essentially, the adsorption of the ionic surfactants on the surface of the mineral oxides can be divided into three specific regions (see Fig. 6) which clearly depend on the surfactant concentration: hemimicelles, mixed hemimicelles and admicelles. Hemimicelles, formed at low concentrations, consist of a monolayer of the surfactant with their ionic groups facing to the outer surface of the mineral oxide and interacting with it by electrostatic forces. Therefore, the hydrophobic groups of the surfactants are oriented to the aqueous solution making the extraction of apolar compounds possible. On the other hand, admicelles are formed by the interaction of a second layer of surfactants with the previously formed hemimicelles. In this case, the second layer is attached to the first one by hydrophobic interactions and the polar (mainly ionic) groups of the surfactants are oriented to the aqueous solutions allowing the extraction of polar analytes. Finally, mixed hemimicelles are an intermediate state between the two previously described and they allow double interaction (polar and
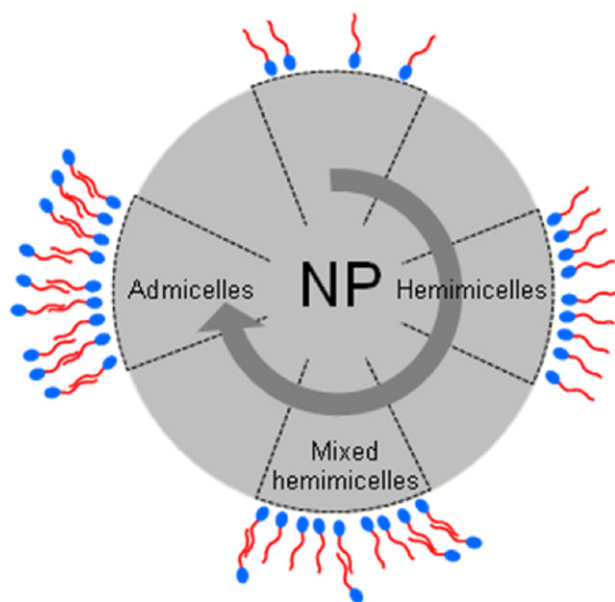
Fig. 6. Adsorption of ionic surfactants on the surface of the mineral oxides. The arrow indicates an increase in the surfactant concentration.

hydrophobic) with the target analytes. The great variety of surfactants commercially available allows an appropriate selection (regarding the polar and hydrophobic groups) for the extraction of a specific analyte.

Hemimicelles, admicelles and their combination have been proven to be excellent tools for the extraction of analytes from aqueous samples. When micro-sized particles are employed as substrates, the procedure lacks extraction capability and expeditiousness, especially when large sample volumes are required in order to achieve an appropriate sensitivity. The use of nanoparticles in this context proves to be an excellent alternative taking into consideration the great surface area of these materials.

Recently, the potential of carbon nanotubes to form hemimicelles and admicelles has been studied in depth [126]. In their raw form, CNTs are not able to form surfactant aggregates since they do not present a surface residual electrostatic charge and therefore a chemical derivatization of their surface is required. Carboxylated CNTs, obtained after treatment with oxidants, present a negative charge on the surface which allows their interaction with cationic surfactants such as cetyltrimethylammonium chloride (CTAC). This combination has been employed for the extraction of arsenic from environmental water samples.

In the same way, titanate nanotubes (TNTs) coated with cetyltrimethylammonium bromide have been proposed for the extraction of phthalate esters from natural waters [127]. In the light of the results, titanate nanotubes present superior properties compared with nano-sized titania due to their enhanced surface and hydroxyl group concentration.

In both c-CNT and TNT approaches, conventional SPE-cartridges are employed for the extraction of the target analytes. The SPE procedure is similar to the conventional one but it requires an extra step. In this respect, when the nano-sized material (c-CNTs or TNTs) is suitably packed and conditioned, an aqueous solution containing the surfactant at an appropriate concentration is passed through the cartridge allowing the formation of hemimicelles and admicelles. Once formed, the sample is loaded into the cartridge allowing the interaction between the active SPE-material and the target analytes.

The use of nano-sized sorbents packed in conventional cartridges usually provides high back-pressures making the loading

of the samples very difficult. This fact not only limits the potential enrichment factors that can be achieved (since high sample volumes cannot be processed) but also reduces the sample throughput. The introduction of magnetic nanoparticles overcomes this limitation allowing the development of new extraction strategies. Magnetite (Fe_3O_4) nanoparticles present a high surface area which may present a residual charge allowing the formation of hemimicelles and admicelles with ionic surfactants. The sign of the residual charge can be controlled by selecting the pH of the aqueous solution which clearly increases the range of application of magnetite nanoparticles since they can interact with cationic or anionic surfactant. In fact, magnetite nanoparticles present an isoelectric point (iep) of 6.5 and therefore the surface is negatively charged when the pH is above the iep and positively charged when it is below this value. Moreover, the main advantage of these NPs is their superparamagnetic properties which allow their simple isolation from the sample using a magnet.

In this case, the solid phase extraction procedure which is schematically depicted in Fig. 7 consists of various defined steps. First of all the magnetite nanoparticles are added to the sample and dispersed. Next, a specific amount of the ionic surfactant is added in order to form the appropriate aggregates, the sample being stirred (mechanically or assisted by sonication). Once the analytes have been extracted, the surfactant coated magnetic nanoparticles are isolated by means of a magnet which is located on the outer surface of the extraction vial. Finally, the analytes are chemically eluted for their subsequent analysis. This solid phase extraction procedure makes it possible to process high volumes of sample (in the range of 500–1000 mL) in a short period of time.

Li et al. successfully demonstrated that the surfactant coating does not affect the superparamagnetic properties of the magnetic nanoparticles [128]. The surfactant-nanoparticles also present a large saturation magnetization which indicates that they are susceptible to magnetic fields. In this case, the authors proposed the use of CTAB coated nano-magnets for the extraction of selected chlorophenols form water samples which were determined by liquid chromatography and UV detection. In the same way, magnetite nanoparticles coated with sodium dodecyl sulphate (SDS) have been employed for the extraction of Hg (II) as its complex with Michler's thioketone ($[Hg_2 (TMK)_4]^{2+}$) from water samples and its subsequent determination by inductively coupled plasma-optical emission spectrometry [129].

Pure magnetite nanoparticles tend to aggregate and can be oxidized losing their magnetic properties under acidic conditions. The development of core-shell nanoparticles which consist of a magnetic core coated by an appropriate material, mainly silica or alumina, overcome this limitation allowing the reusability of the nanoparticles in different extraction cycles. Zhao et al. proposed the use of silica coated magnetite nanoparticles in combination with cationic surfactants for the extraction of some phenolic compounds from water samples [130]. The authors demonstrated that the silica shell slightly affects the strength of the magnetism of the nanoparticles. In fact, the saturation magnetization of the magnetite nanoparticles was reduced from 63.2 to 39.9 emu/g by the silica coating, although this fact does not limit the isolation of the material with a conventional magnet. The iep of the coated nanoparticles was 3.0, which indicates an excellent coating since this value corresponds to the silica iep. Zhu et al. characterized these nanoparticles by infrared spectroscopy observing the characteristic Si–O band at $1066 \, cm^{-1}$ [75]. These authors used silica coated magnetite nanoparticles in combination with CTAB for the extraction of herbal bioactive compounds from biological samples.

The coating of magnetite nanoparticles with alumina has also been proposed for the extraction of trimethoprim, a folic acid metabolism blocker, from waters [131]. As previously commented,
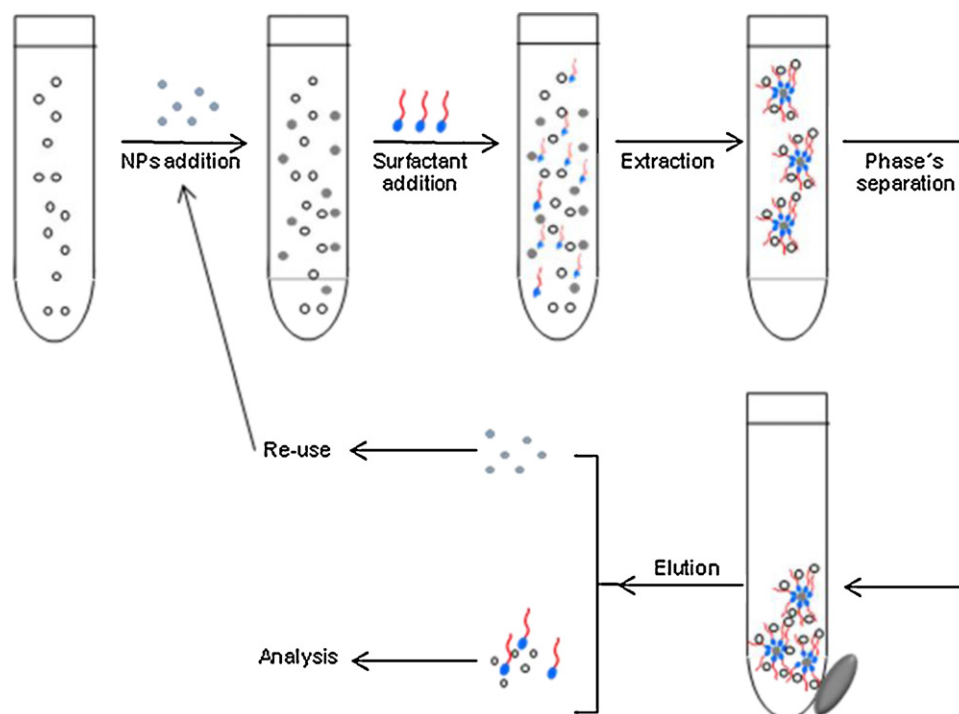
Fig. 7. Extraction procedure using magnetic nanoparticles to form hemimicelles and admicelles with ionic surfactants.

the coating affects the saturation magnetization achieving a value of 8.15 emu/g which is enough for the isolation of the nanoparticles. While silica coated nanoparticles are exclusively employed in combination with cationic surfactants, alumina coated nanoparticles can be employed with anionic ones according to their chemical composition and iep.

The main disadvantages of extraction procedures based on the use of hemimicelles/admicelles arose from the disruption of the surfactant/nanoparticles interaction in the elution process due to the weak attachment (by physisorption) of the first monolayer of surfactant to the nanoparticle surface. Therefore, the final elute fraction contains a great amount of surfactant which may not be compatible with different instrumental (mass spectrometry) or separation techniques (gas chromatography). The use of special surfactants, such as alkyl carboxylates, chemisorbed to the magnetite surface has been proposed recently in order to overcome this limitation [132]. Alkyl carboxylate provides a stable monolayer (hemimicelles) around the magnetite core thanks to the formation of bidentated complexes between the carboxylic groups and the iron atoms. This material has been successfully employed for the extraction of carcinogenic polycyclic aromatic hydrocarbons from water samples providing detection limits of up to 0.1 ng/L.

6. Nanoparticles in sample filtration

New advances in nanotechnology allow the possibility of having membranes with nanopores which open up new possibilities to Analytical Sciences [133]. For example it is possible to selectively separate microorganisms [134], or even biomolecules [135] from complex samples by a simple filtration. The most promising nanopores are achieved with carbon nanotubes. In fact, molecular simulations studying fluid characteristics through carbon nanotubes were the starting point for the development of membranes with nanopores thanks to the incorporation of these nanostructures both vertically aligned or in bundles [136]. Membranes with carbon nanotubes allow the formation of controlled nanopores, the

possibility of functionalising the CNT tip in order to achieve selectivity making the selective filtration of small molecules possible, in contrast with conventional nanopore membranes which contain a large array of pores with polydisperse structural parameters and whose nanopores exhibit a wide distribution in either shape, size, or surface chemistry.

Mass transport in nanoporous media is of interest for many technologically important reasons. To date, membranes have been used for delivery of therapeutic molecules such as drugs and genes through cellular matrixes [137], in the transdermal treatment of nicotine addiction and opioid withdrawal symptoms [138], or for the introduction of volatile analytes to a mass spectrometer by direct coupling of the membrane in substitution of the capillary tubes [139].

Two main types of membranes have been identified: membranes with vertically aligned carbon nanotubes and membranes with bundles of carbon nanotubes.

Perhaps the most interesting applications are with membranes with vertically aligned carbon nanotubes. The star in this field is water transport through the inner pores of the nanotubes [140] due to the importance of related applications such as efficient water desalination using reverse osmosis. A study which comprised two hexagonally packed CNT membranes demonstrated osmotic water transport with a flow that appears frictionless and limited primarily by the barriers at the entry and exit of the nanotube pore [141]. The membranes described above have been the subject of several and varied applications, namely nanofiltration of gold nanoparticles and N_2 adsorption [142]. Since no filler was used, permeation is also possible through the interstitial spaces between CNTs. Cylindrical membranes demonstrated their utility for the elimination of multiple components of heavy hydrocarbons from petroleum and the filtration of bacterial contaminants such as Escherichia coli or the nanometre-sized poliovirus from water [143]. The electrophoretic transport of single-stranded RNA molecules through 1.5-nm-wide pores of carbon nanotube membranes has also been studied [144]. RNA entry into the nanotube pores is controlled by conformational
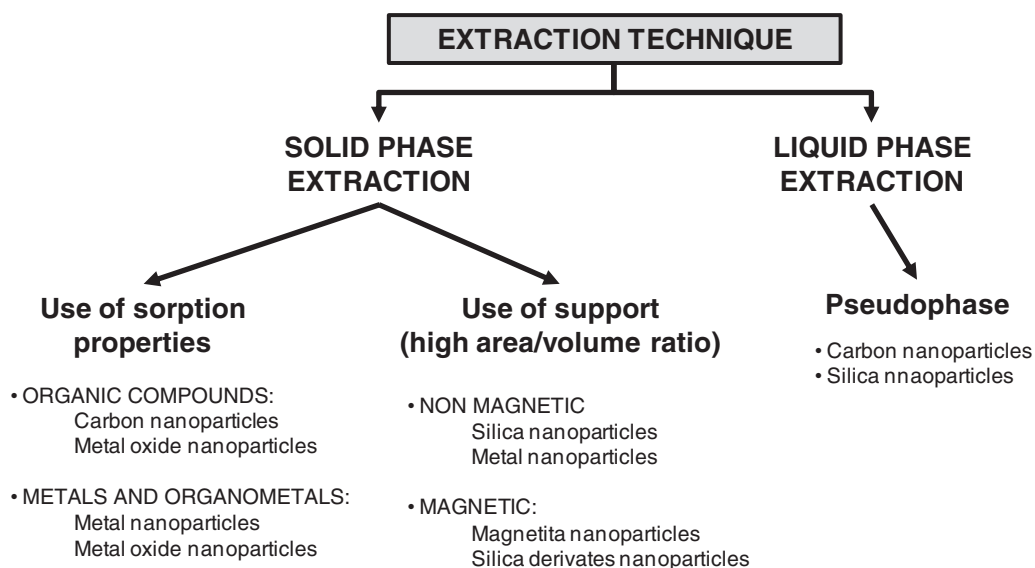
EXTRACTION TECHNIQUE

SOLID PHASE EXTRACTION

LIQUID PHASE EXTRACTION

Use of sorption properties

- ORGANIC COMPOUNDS:
  Carbon nanoparticles
  Metal oxide nanoparticles

- METALS AND ORGANOMETALS:
  Metal nanoparticles
  Metal oxide nanoparticles

Use of support (high area/volume ratio)

- NON MAGNETIC
  Silica nanoparticles
  Metal nanoparticles

- MAGNETIC:
  Magnetita nanoparticles
  Silica derivates nanoparticles

Pseudophase

- Carbon nanoparticles
- Silica nnaoparticles

Fig. 8. General overview of the potential of use of nanoparticles to improve solid or liquid phase extraction procedures.

dynamics, and exit by hydrophobic attachment of RNA bases on the pores. Moreover, binary permeance of CH_4/H_2 mixtures through defect-free (10,10) SWNTs acting as a membrane at room temperature has been predicted [145]. Carbon nanotubes are strongly selective for CH_4 over H_2 when a mixture of these gases permeates through a membrane. Finally, molecular dynamics are used to study the possibility of separating different species of atom using carbon nanotubes in torsion [146].

Membranes with bundles of carbon nanotubes are prepared by filtration of a dispersed solution of the CNTs through a membrane. CNTs are dispersed by surfactants such as SDS, Triton X-100, by dimethylsulphoxide or a suspension of functionalized MWNTs with polydiallyldimethylammonium chloride was directly filtered [147]. The membranes employed are diverse, such as cellulose ester membrane, PVDF, nylon-encased filter or qualitative filter paper [147,148]. In the case of CNT dispersion aided by surfactants o dimethylsulfoxide, they must be removed by passing, for instance, methanol or ethanol through the membrane. By using membranes with bundles of carbon nanotubes it has been possible to (i) selectively isolate and preconcentrate acidic proteins such as bovine serum albumin [149], (ii) preconcentrate and determinate carboxylic single-walled carbon nanotubes from environmental water samples [150], (iii) retain bacteria which were effectively inactivated upon contact with a SWNT filter and remove viruses which are captured by nanotube bundles inside the SWNT layer [147], and (iv) enrich phthalate esters, bisphenol A, 4-n-nonylphenol, 4-tert-octylphenol and chlorophenols from various volumes of solution [151].

7. Nanoparticles in other sample treatments

Time-of-flight secondary ion mass spectrometry (TOF-SIMS) is a powerful tool for the chemical analysis of surfaces [152]. It offers high-resolution imaging and mass spectral information about the molecular composition of biological and synthetic samples. In SIMS, secondary ions are generated under the impact of high-energy primary ions (Ga^+, Au_n^+, Bi_n^+, C_{60}^+, etc.) in a process known as sputtering [153]. The sputter yield is the number of sputtered molecules, atoms, or ions per primary ion impact. In order to solve biological questions at the cellular length scale using SIMS imaging, there is a tendency toward higher spatial resolution. Although matrix-

assisted laser desorption and ionization (MALDI) MS can be used for mass spectral imaging analysis, SIMS is the favoured technique in certain cases, especially when studying lipids and small molecules (<2000 Da) at the cellular length scale (<20 μm). Besides vacuum compatibility, SIMS does not require any sample treatment before analysis and therefore has no related spatial resolution constraints, e.g., the crystal size for matrix coating in case of MALDI. Buckminsterfullerene (C_{60}) as a primary ion for secondary ion mass spectrometry (SIMS) has shown many benefits over classical SIMS sources in the analysis of large organic molecules including many of biological significance [154–157].

A major reason why cluster ions show increased sputter yield lies in their surface fragmentation. Due to this fragmentation, the total energy of the primary particle is divided over the fragments and deposited at a shallower depth compared to atomic ions of the same velocity. The greater energy density in the surface region gives rise to increased sputtering, particularly for larger molecular species due to cooperative uplifting effects. For example, the secondary ion yield is increased by up to 3 orders of magnitude for C_{60}^+ compared to Ga^+ primary ions, especially for the mass range m/z 200–2000 [158]. This increase in secondary ion yield means that the detection limit is improved accordingly. In addition to sputtering events the impact of the primary ion initiates chemical damage, e.g., bond breaking, in the vicinity of the impact zone [159].

The efficiency gain from cluster projectiles is particularly important when performing high spatial resolution imaging, because of the low amount of material that is probed when imaging small regions. Together with the increased mass range afforded by cluster projectiles, this offers new possibilities for high resolution SIMS imaging of complex molecular systems including biological tissue samples [160]. The extremely low residual subsurface chemical damage under polyatomic sputtering means that the generation of diagnostic secondary ions is sustained under prolonged bombardment. Specifically, chemical analysis is possible beyond the traditional "static limit" (1% of the surface impacted), the point at which increased fluence of atomic or small-cluster projectiles produces the mass spectra characteristic of the chemical damage.

Where the analytes are present as minor components or have low secondary ion yield, the application of especially high-efficiency polyatomic ions, e.g., C_{60}, becomes particularly attractive.

This situation is likely to be the case in increasing numbers of applications, for example, the localization of drugs and metabolites at (sub)cellular dimensions in tissue and cell cultures. Therefore, the remainder of this manuscript is concerned with the development of methodologies for C_{60} SIMS imaging, leading to improved performance against a number of criteria including data quality and acquisition speed.

The major challenge in using a C_{60} source for SIMS imaging is the limited source brightness [161]. The electron impact method of creating the primary ions inherently gives rise to a space-charge limited primary ion beam with a large diameter and relatively low ion flux density compared to liquid metal ion sources. To obtain small-diameter beam spots, apertures can be used to collimate the beam. A focal diameter, and hence pixel size, of less than 200 nm is possible with this method using a beam energy of 40 keV but at the expense of the ion current, which is typically less than 0.05 pA. This low current, which is over 4 orders of magnitude lower than the 2 nA surface current that can be obtained using no apertures, illustrates the major disadvantage of beam collimation: the tremendous loss of beam current. This dramatic decrease in ion current inevitably leads to an increase in measurement time. High spatial resolution SIMS using a collimated C_{60}^{+} beam and conventional pulsed TOF acquisition is therefore very time-consuming and impractical for large areas (square millimeters). This is particularly true if the low-damage properties of C_{60} bombardment are to be exploited using a primary ion fluence beyond the static limit ($>10^{13}$ ions cm^{-2}) [162].

One approach, which is currently being pioneered to obtain high spatial resolution SIMS imaging at reasonable measurement time scales, is to decouple the bombardment process from the TOF measurement, allowing a nearly continuous ion beam to be used for TOF-SIMS measurements. Another approach is to circumvent the limitations that are connected with the limited focusing capabilities of C_{60} primary ion sources. To get around these limitations, the imaging resolution needs to be independent of the C_{60} probe size. This independence can be achieved by using stigmatic ion microscopy. In this technique, the localization of the ions generated at the sample surface is retained through the spectrometer and detected using a position-sensitive detector [163]. Until very recently, this technique was limited to two modes of operation: either a full image of one (or a few) selected ions was recorded, in which the other ions that are generated at the surface are blanked by electrostatic deflectors, or alternatively, the full mass spectrum was recorded in combination with a total ion current (TIC) image. Although this has proven to be a powerful tool in unraveling small spatial features, full spectral and spatial detail could never be recorded simultaneously.

The introduction of a delay line detector for SIMS has circumvented this issue. A delay line detector, which was first developed for photoemission electron microscopy, can detect both temporal and spatial information at the same time. Consequently, a full hyperspectral data cube, that contains both TOF and spatial information for each ion, can be measured simultaneously. High-resolution C_{60}^{+} SIMS imaging is possible at much faster rates by combining the microscope approach with a delay line detector [164].

8. Perspectives

Undoubtedly, the use of nanoparticles in sample preparation is a topic of growing interest in analytical sciences. They can be considered as very versatile tools taking into account the great variety of available nanoparticles, including carbon, metallic and silica ones among others. Their peculiar characteristics have been extensively exploited in different extraction/isolation techniques which

are considered in depth in this review (see Fig. 8). The involvement of nanoparticles in the sample treatment context will increase as the commercial firms introduce them in the market for such a purpose with the assurance of purity and physical (e.g., size) and chemical homogeneity. In this sense, the physico-chemical characterization of nanoparticles is essential in this context, being the second facet of Analytical Nanoscience and Nanotechnology.

The major trends in this context will be oriented to improve some of the characteristics of nanoparticles in such a way that crucial analytical properties (e.g., selectivity) will be increased because free nanoparticles themselves do not offer enough level of this property. Some most relevant avenues to improve the role of nanoparticles in analytical processes can be summarized as follows: (A) to use new nanoparticles, never assayed before, as the basis of sample preparation steps; (B) to derivatize nanoparticles by using chemical or biochemical agents in order to achieve higher levels of analytical properties including practical aspects such as easy of handling and manipulation; (C) to employ hybrid nanoparticles in order to take advantage of the combination of complementary properties (e. g. silica nanoparticles with a magnetic core or carbon nanotubes combined with magnetite, etc.); and (D) the automatic manipulation of nanoparticles to avoid human participation and to improve precision. The number of papers in this field will increase exponentially in the forthcoming years.

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