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## Review

# Nanoparticles and capillary electrophoresis: A marriage with environmental impact

The impact of nanomaterials in the environment and human health is a cause of big concern and even though intensive studies are currently being carried out, there is still a lot to elucidate. The development of validated methods for the characterization and quantification of nanomaterials and their impact on the environment should be encouraged to achieve a proper, safe, and sustainable use of nanoparticles (NPs). Recently, CE emerged as a well-adapted technique for the analysis of environmental samples. This review presents the application of NPs together with CE systems for environmental pollutants analysis, as well as the application of CE techniques for the analysis of various types of NPs.

### Keywords:

Capillary electrophoresis / Environment / Nanoparticles

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## 1 Introduction

Nowadays, nanotechnologies are well established and the uses of a great variety of nanomaterials present exponential growth. Indeed, the use of nanoscaled compounds in various fields of science, including health, energy, catalysis, agriculture, and environment, has increased significantly over the last decade [1]. The possibility to synthesize highly uniform nanoobjects with different size, shapes, and charge is an advantageous characteristic of nanotechnology. In particular, given their high superficial area/volume ratio and quantum effects ruling their behavior, manufactured nanoparticles (NPs) have unique properties differing from those of the originating bulk materials. The different properties that ma-

terials have when they are used at nanoscale levels open a wide range of possibilities for their beneficial use.

On the other hand, the use of these nanomaterials in household and industry leads to a new type of waste, the nanowaste [2], exposing human beings and the environment to new risks, triggered by unknown mechanisms. Thus, the normal defense mechanisms, for example, those associated with immune and inflammatory systems, may not be adequate to respond to the presence of NPs. At the environmental level, the impact of nanotechnology products is related to the spread and persistence of NPs in the environment. Consequently, the future impact on human health and the ecosystem are still unpredictable and unknown. Indeed, nanomaterials are increasingly being incorporated into consumer products, although research related to their potential effects on the environment and human health is still in progress and far from being complete.

In particular, nanomaterials containing metals are finding increased use in consumer, industrial, and medical products, and they are subsequently being released into the environment. For example, gold NPs (AuNPs) are promising nanomedicine candidates with great potential as gene transfer vectors, in tissue engineering, image processing and biosensors construction, among others. *In vitro* and *in vivo* toxicity studies showed a potential impact of nanowaste materials in human health. As an example, AuNPs have proved to be toxic to human neutrophils. *In vitro* studies demonstrated that 20 and 70 nm AuNPs induce polymorphonuclear

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**Abbreviations:** AgNP, silver NP; AuNP, gold NP; CNT, carbon nanotube; DLS, dynamic light scattering; MWCNT, multiwalled CNT; NP, nanoparticle; OP, organophosphorus pesticide; PSP, pseudostationary phase; QD, quantum dots; SWCNT, single-walled CNT; TEM, transmission electron microscopy

cell apoptosis by a caspase-dependent mechanism after 24 h [3]. Similarly, silver NPs (AgNPs), which due to their antimicrobial properties have been largely used in food, cosmetic, and medicinal products, have shown to be toxic after peroral exposure resulting in silver accumulation in the liver, kidneys, spleen, stomach, and small intestine after a single and multiple (over 30 days) administration of a 10 nm AgNPs dose to Sprague-Dawley male rats. The highest silver content was detected in the liver and kidney, being  $0.87 \pm 0.37$  and  $0.24 \pm 0.02$   $\mu\text{g/g}$ , respectively [4]. After 14 days of oral administration to male and female mice of 20 and 50  $\mu\text{g/mL}$  of AgNPs, liver enzymes, alanine, and aspartate transaminase were significantly increased [5]. Intranasal single and multiple (7 days) exposure of male C57BL/6 mice to 10  $\mu\text{L}$  (50–62.5 mg/mL) of 25 nm AgNPs showed a decrease in NK- and T-cell populations and in the reduced (GSH) and oxidized (GSSG) glutathione ratio [6].

Other widely employed nanomaterials are titanium dioxide, zinc oxide, and iron oxide NPs. The production of titanium dioxide NPs, widely employed in sunscreens and cosmetics, is the highest [7]. Zinc oxide NPs are also widely used in cosmetics (sunscreens, unguents, and feet care products), as well as in pigments, electronics, and catalyzers. Recently, it was reported that  $\text{TiO}_2$  NPs could be more toxic than ZnO NPs, as confirmed by mutagenic index assays [8]. In both cases, even though the main route of exposure of the final products is the skin, the inhalation route should be taken into consideration as well, mainly for those working with NPs powders. At the same time, there is an increased use of iron oxide NPs for energy, environmental and medical applications, water treatment (ionic pollutants remover agent), pharmaceutical industry, and soil treatment for lowering bioavailability of heavy metals. There are studies that show their toxicity at high concentrations, but little is known about the toxicity at low concentrations. Taze *et al.* showed that the exposure to 10 and 50 mg/L iron oxide NPs induced toxicity after 7 days in mussels, showing oxidative stress with a significant increase in the production of reactive oxygen species, protein carboxylation, lipid peroxidation, ubiquitin conjugates, and DNA damage [9].

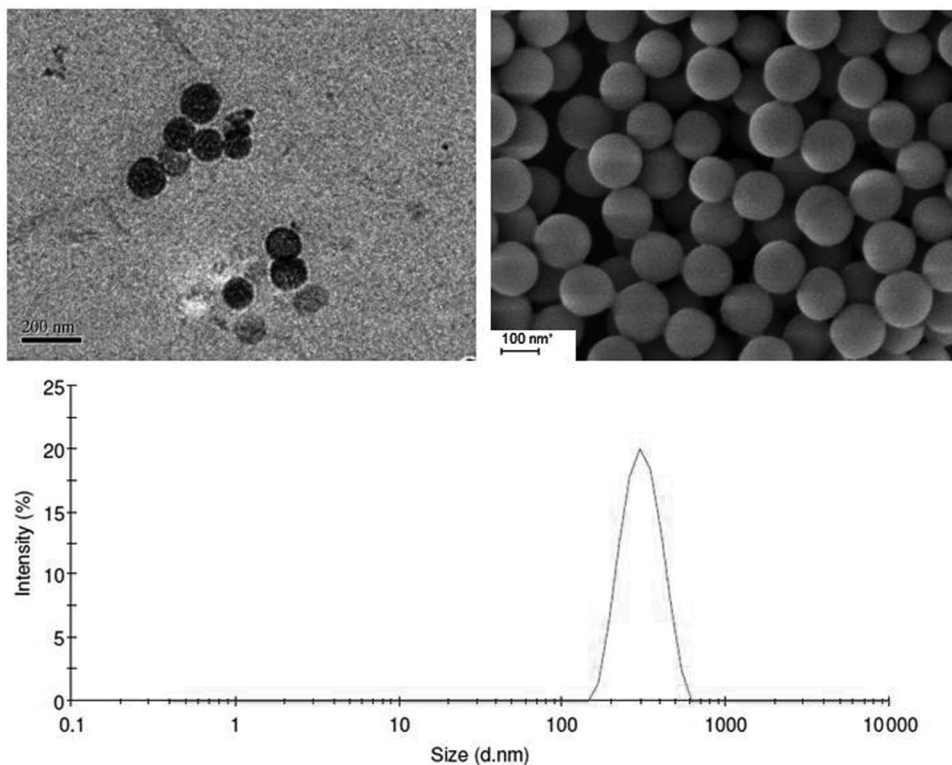
More recently, it was reported that NPs have a deleterious effect over insects [10]. In this sense, Stadler and co-workers have reported the use of nanostructured alumina for controlling two species of stored food pest; *Sitophilus oryzae* and *Rhyzoperthadominica* [11]. In addition, the synthesis of AgNPs combined with extracts of plants and fungi have been used as mosquito larvicide [12–15]. Moreover, studies on different genera of mosquitoes such as *Aedes*, *Anopheles*, and *Culex*, which are vectors of yellow fever, dengue, chikungunya, and malaria, with silicon NPs demonstrated their effectiveness as a potential insecticide for controlling these insects [16]. Several authors have demonstrated that nanosilica also has the potential to act as drug delivery vehicle in medical treatments and as a veterinary and agricultural pesticide [17, 18]. A comparative advantage of silicon NPs in contrast with other types of NPs (alumina, silver, and lipid) is their versatility. Since this kind of NP can act

by itself according to their charge, size and concentration, it is also possible to use them as delivery carriers. In this case, silica NPs can transport compounds adsorbed on their surface and/or inside of them with adequate stability and environmental safety [19]. The insecticide capacity is attained through physical adsorption and dehydration of the insect cuticle [20].

Moreover, Cr (III) oxide NPs ( $\text{Cr}_2\text{O}_3$  NPs) are employed in the manufacture of pigments for the textile industry, in leather tanning, and in the pigmentation of ceramics.  $\text{Cr}_2\text{O}_3$  NPs are toxic toward the microcrustacean *Daphnia magna* ( $\text{EC}_{50} = 6.79$  mg/L) and toward the luminescent marine bacteria *Aliivibrio fischeri* ( $\text{EC}_{50} = 16.10$  mg/L). Moreover, chronic effects on parameters such as longevity, reproduction, and growth were verified when *D. magna* was exposed to sublethal concentrations [21].

So far, different nanoparticulate systems have been discussed and there are many more, all of which could reach the environment, inducing changes that may ultimately impact on human health. Thus, in this context, it is highly desirable to develop methods of analysis to evaluate their presence on both the ecosystem and human health, especially considering the potential deleterious effects of these new nanomaterials to the environment and living organisms. Currently, there are well-established methodologies for their size and shape characterization, identification, and quantitative detection of NPs (i.e., scanning electron microscopy [SEM], transmission electron microscopy [TEM], dynamic light scattering [DLS]; Fig. 1). In addition, it becomes a real challenge to adapt existing analytical techniques or develop new ones to carry out the analysis of NPs in complex samples where they are found not only in small quantities but have also changed throughout their lifecycle. In the case of electron imaging, the technique works by bombarding the sample with a stream of electrons and monitoring the resulting transmitted (TEM) or scattered (SEM) electrons. This information is used to generate particle data, such as size, size distributions, shape, and morphology. SEM and TEM both offer unique benefits for NP characterization. In this sense, CE is also a good tool to determine NPs size and it has the advantage that parameters such as charge distribution,  $\zeta$ -potential, and surface functionality can be determined at the same time [22]. DLS is also a tool for determining particle size and distribution with a moderately peak-resolved distribution. It works by measuring the random changes in the intensity of light scattered. Its main advantages are short measuring time and relatively low cost of the apparatus. It has got some drawbacks as the influence of dust particles or small amounts of large aggregates [23]. While SEM is fully capable of resolving different particle sizes, DLS is unable to resolve bimodal distributions [24]. The interested reader can find some comparative works, in particular the ones written by Laborda *et al.* and Part *et al.*, with an interesting overview on the analytical techniques and sample preparation methods suitable for the analysis of inorganic engineered nanomaterials and nanowaste [25, 26].

Therefore, CE is one novel separation and analytical technique that is adapting its systems to respond to a major



**Figure 1.** TEM, SEM, and DLS analysis of silica nanoparticles.

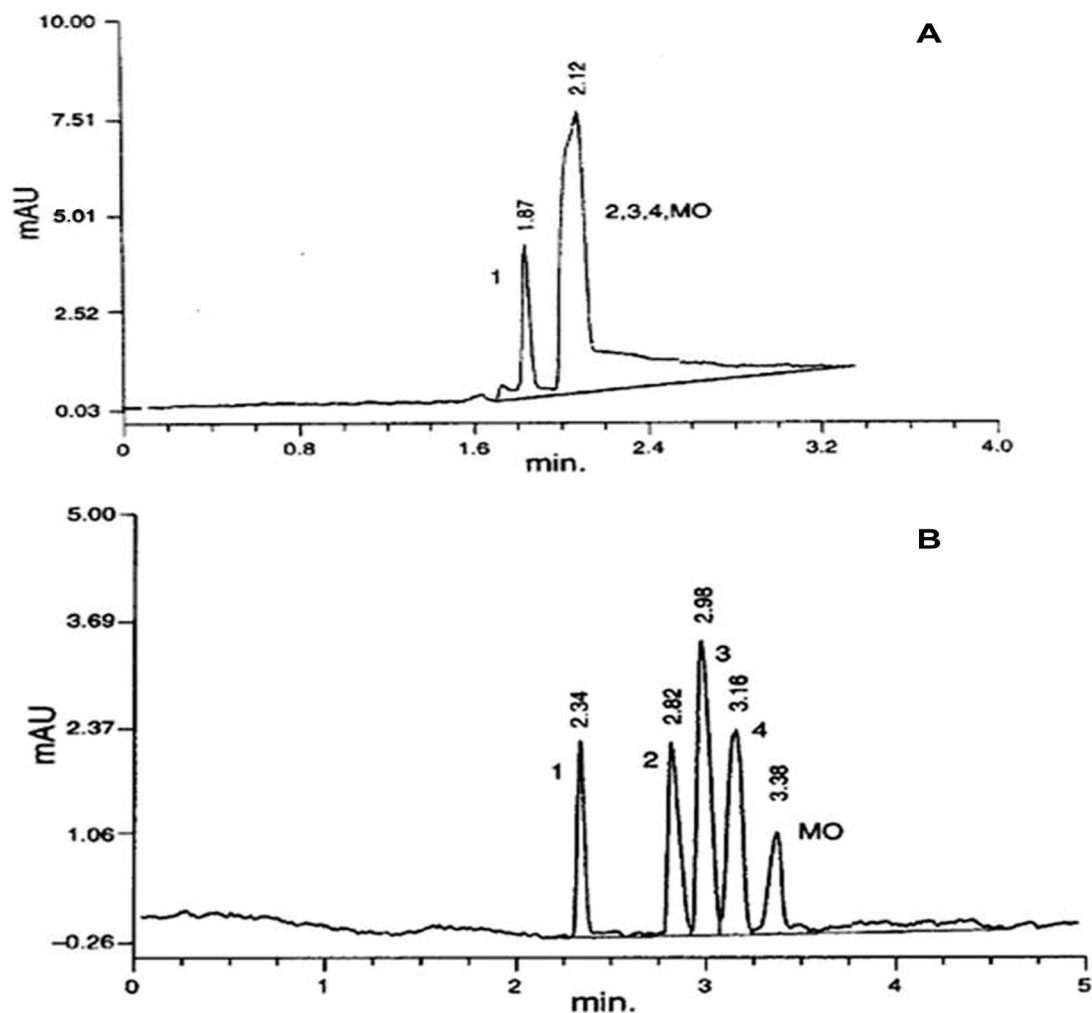
demand: the environmental analysis. In this regard, the use of NPs together with CE systems provides a promising tool for environmental analysis. In addition, CE has also the advantage to be considered a “green” method; the major reason is due to the low amount of organic solvent that is used and the limited residue that is produced in comparison with other analytical techniques. CE is a powerful technique used for the separation of both charged and uncharged compounds based on the differential electrophoretic mobility in the presence of a background electrolyte when a voltage is applied. Moreover, the presence of nanomaterials can modify the conductivity, viscosity, and pH of buffers used in the separations [27]. In this regard, the state of aggregation and rate of sedimentation of three different metal oxide NPs ( $\text{TiO}_2$ ,  $\text{ZnO}$ , and  $\text{CeO}_2$ ) was studied taking samples from different environments like seawater, river, or groundwater. The presence of organic matter and the ionic strength of the samples were the more influent parameters affecting the stability of the particles. It was found that the organic matter adsorbed onto the particles significantly reduced their aggregation while a high ionic strength in seawater increased the rate of sedimentation. Particularly, the pH of the samples was not determinant for NPs stability [28]. One way to achieve high selectivity and high efficiency while using CE as a separation technique is the use of a pseudostationary phase (PSP). PSPs are interaction phases that are moving with (or against) the mobile phase. No column packing or frits are needed in these types of systems. By using a PSP, the phase is continuously replaced and an entirely fresh column is used for every new

analysis. Such a system benefits from the absence of stationary phase carry-over effects, which simplifies sample analysis in complex matrices [29]. Since 1989, when Wallingford and Ewing [30] incorporated NPs as a PSP in CEC to separate five catecholamines, the number of applications of NPs in CE has continuously increased [29, 31, 32]. An interesting work, by Ban *et al.*, reviews the analysis and applications of NPs in CE [33].

Herein, we summarize representative articles in the matter with an environmental focus. In the first part of this review, the application of various NPs together with CE for the analysis of environmental pollutants is presented. While, in the second part we present an overview of the application of CE for the analysis of different NPs that would reach the environment and affect human health.

## 2 NPs in environmental analysis

NPs have received much attention due to their novel chemical, physical, and electrical properties. In this sense, nanomaterials must be considered new materials because their properties are far from those possessed by larger materials. The applications of NPs are increasing in separation science. They provide unique opportunities for the development of higher performance separation techniques that use NPs that possess a large surface to volume ratio [34–38]. In this section of the review, we will focus on the use of NPs as PSPs to analyze environmentally important contaminants.



**Figure 2.** Electropherograms of (1) p-phenyldiamine, (2) p-aminophenol, (3) p-anisidine, and (4) p-toluidine (A) without gold nanoparticles in the running buffer and (B) with 75 nM 3-mercaptopropionate gold nanoparticles in the running buffer. The detector was on the cathodic side of the capillary. Reprinted with permission from [39].

## 2.1 NPs as PSPs

### 2.1.1 Gold NPs

When considering AuNPs as PSPs, the first article describing the application of this novel PSP was reported by Lev and co-workers in 2001. They separated four modified phenols within 4 min [39]. The AuNPs were citrate stabilized or thiol stabilized. They observed that changes in the motilities due to the presence of the NPs in the running buffer were reflected in changes in the selectivity and in other additional benefits like improved precision of data and improved efficiency, as could be seen from the increase in the number of plates: from around 8 600 obtained without AuNPs in the running buffer to around 18 600 plates obtained with a running buffer containing 75 nM of AuNPs (Fig. 2).

### 2.1.2 Quantum dots

Quantum dots (QD) are particles that possess high luminescence, good photochemical stability, and tunable excitation/fluorescence wavelength at different particle sizes, therefore providing a suitable photochemically stable fluorescence agent for LIF detection. In 2012, Chen *et al.* determined nicotine residues on vegetables where cadmium telluride QD were used as fluorescent background. This was achieved by adding the fluorescent QD into the background electrolyte solution. When nonfluorescent analytes pass through the separation channel, the fluorescent substance located in the analyte zones is displaced, resulting in lower background fluorescence and producing negative peaks for the analytes in the sample. The indirect LIS method does not require derivatization of nonfluorescent

analytes. The group managed to match excitation and emission wavelengths to the LIS detector by engineering QD size. Pesticides analyzed were thiamethoxam, acetamiprid, and imidacloprid. Detection limits were 0.05, 0.01, and 0.009  $\mu\text{g}/\text{mL}$ , respectively [40].

### 2.1.3 Carbon-based NPs

The main drawback associated with the use of carbon nanostructured based pseudostationary phases is their insolubility in water as well as their great tendency to aggregate. For this reason, covalent and noncovalent functionalizations have been proposed to obtain effective dispersions of the carbon nanostructures. Noncovalent methods preserve the intrinsic properties of carbon nanostructures, so these procedures are preferred. In 2007, Suárez *et al.* managed to separate aromatic compounds by using surfactant-coated single-walled carbon nanotubes (SWCNTs). Their results showed that by using this novel pseudostationary phases they could achieve high resolution and selectivity of nine chlorophenol compounds in a single 20-min run, even when the sensitivity was compromised by the PSP employed [41]. Another approach using carbon structures was reported by Treubig and Brown, who employed fullerene 60 ( $\text{C}_{60}$ ). They managed to separate eight PAHs using CE with UV detection. They demonstrated an enhancement in the performance of the system when compared to MEKC using SDS alone as pseudostationary phases. One of the differences observed between the two conditions (with and without  $\text{C}_{60}$ ) is the higher retention for the group of PAHs in the  $\text{C}_{60}$ -SDS buffer. This was expected since the  $\text{C}_{60}$  fullerenes, which are encapsulated within the region of the micelles, enhance the hydrophobic retention of the PAHs through  $\pi$ - $\pi$  interactions. The capacity factors of the PAHs increased by 35% using the  $\text{C}_{60}$ -SDS buffer, and the resolution increased by a factor of 39 and 62% for the first and second pair of solutes, respectively [42]. In parallel, the determination of four antibiotics for veterinary use (ciprofloxacin, enrofloxacin, florfenicol, and chloramphenicol) of two different families (fluoroquinolones and amphenicols) in bovine milk was carried out using MEKC with a common sodium borate-SDS buffer solution containing SWCNTs. In this way, a great improvement in the electrophoretic resolution and the separation efficiency was achieved compared to MEKC. The limit of detection for the four compounds was between 6.8 and 13.8  $\mu\text{g}/\text{L}$  [43]. Similarly, a CE method to determine four sulfonylureas (widely used pesticides) in grain samples was developed using 10 mM of 1-butyl-3-methyl imidazoliumtetrafluoroborate as the electrophoretic buffer solution and 2 mg/L of surfactant-coated SWCNTs were added to the buffer solution to improve the resolution. The separation was achieved in 16 min. Detection limits (LODs) for each analyte were between 16.8 and 26.6  $\mu\text{g}/\text{kg}$  [44]. A similar strategy was also employed for the analysis of four sulfonylureas in natural waters. The analysis took only 3 min versus 6 min with the uncoated capillary. The peaks were symmetrical and high efficiencies of about 150 000 theoretical plates were ob-

tained [45]. Phenolic compounds were analyzed using aqueous BGE containing CNTs. The benefits of using these BGE containing CNTs were reflected in higher sensitivity in the electrochemical signal and additional improved resolution in the electrophoretic separation of catechin and sinapic acid. When the CNTs dispersed in SDS were added to the BGE, sharper peaks and longer migration times were observed as well as higher peak heights. This effect was reflected in an increase in both efficiency (3300 and 10 800 theoretical plates for ( $\pm$ )-catechin and sinapic acid, respectively) and resolution ( $R$  value of 4.5). The authors also pointed out that the detection method used allows working with CNTs concentrations much higher than those compatible with UV-visible detection [46].

### 2.1.4 Silica NPs

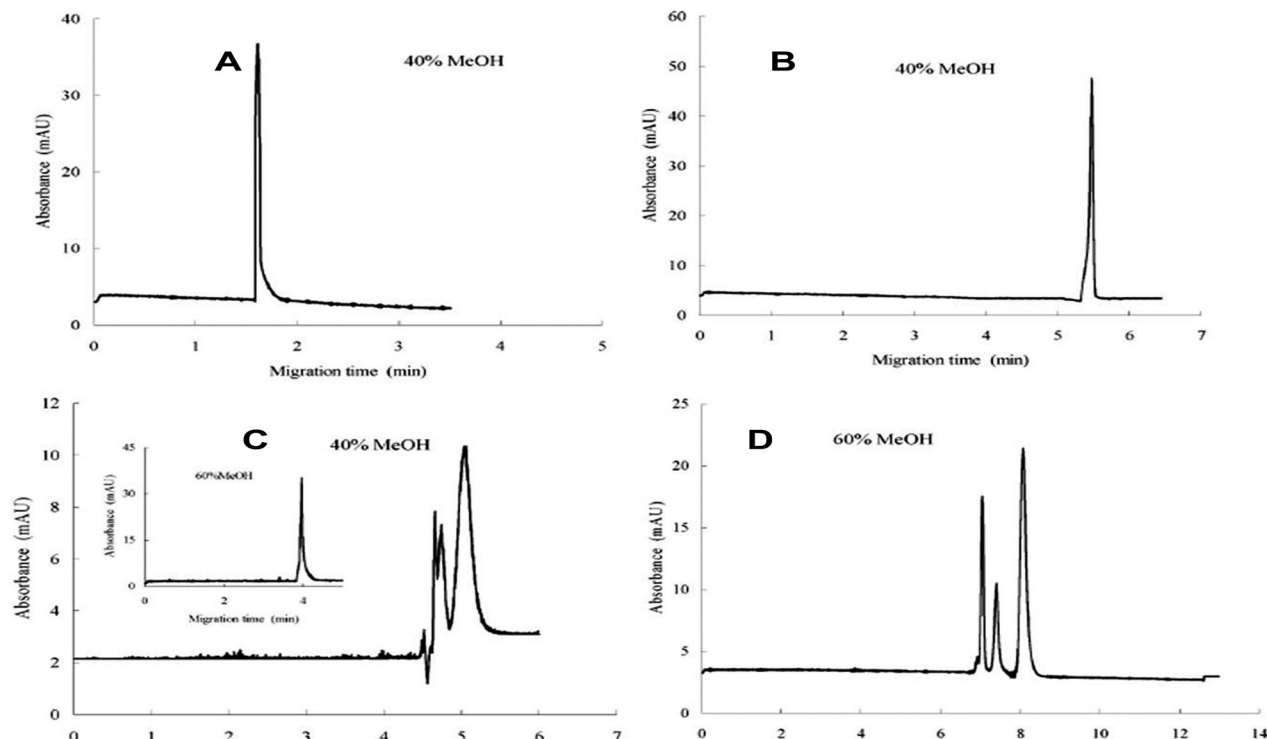
Göttlicher and Bächmann used a suspension of reversed phase (RP18) silica NPs as PSP for the separation of polycyclic aromatic hydrocarbons achieving plate numbers higher than 20 000 plates/m. The particle size was in the range of 500 nm. NPs were coated with ionic detergents (added to the BGE) to form stable suspensions and to introduce the charges responsible for their mobility to the electric field [47]. A few years earlier, they used the NP-based PSP in CEC for the separation of nine phenol derivatives [48].

In 2015, Liu *et al.* managed to create a PSP that could both perform an extraction and improve 60-fold the detection limit of food colorants within 8 min. Their results showed that this strategy provides an efficient sample preparation technique for the extraction of food colorants in complex matrices. Their strategy included diamino moiety functionalized silica NPs [49].

## 2.2 NPs attached to the capillary wall

### 2.2.1 Gold NPs

Open tubular capillary electrochromatography, unlike CEC, is a technique where the filler occupies the entire column and the stationary phase covers the inner wall of the capillary, ensuring efficiency, short conditioning times, and simple instrumental handling. For covalent immobilization, AuNPs were functionalized by adding SH groups, while the inner wall of the capillary was derivatized with an organosilane coupling agent. Such modified capillaries are easy to produce and easier to use than the packaged capillaries used in CEC. This modified capillary was successfully employed by O'Mahony *et al.* to separate a mixture of benzophenone, biphenyl, and pyrethroid pesticides. The pesticides fenpropathrin, fenvalerate, and fluralinate, were analyzed with an organic modifier that varied from 60 to 75% methanol. The separation of fenpropathrin and fenvalerate with 75% of methanol achieved 208 914 and 120 656 plates/m, respectively [50].



**Figure 3.** Electrochromatograms representing the separations of naphthalene and biphenyl with thiourea as EOF marker on various capillaries: (A) bare capillary 34 cm (25.5 cm)  $\times$  50  $\mu$ m, 40% MeOH; (B) etched bare capillary 42 cm (33.5 cm)  $\times$  50  $\mu$ m, 40% MeOH; (C) unetched gold nanoparticles capillary 40 cm (31.5 cm)  $\times$  50  $\mu$ m, 40% MeOH; the inserted picture, 60% MeOH; (d) etched gold nanoparticles capillary 40 cm (31.5 cm)  $\times$  50  $\mu$ m, 60% MeOH. Conditions: mobile phase MeOH-25 mM phosphate buffer pH 7.0; separation voltage, 25 kV. Analyte peaks in (c) and (d) (in order of elution): thiourea, naphthalene, and biphenyl. Reprinted with permission from [51].

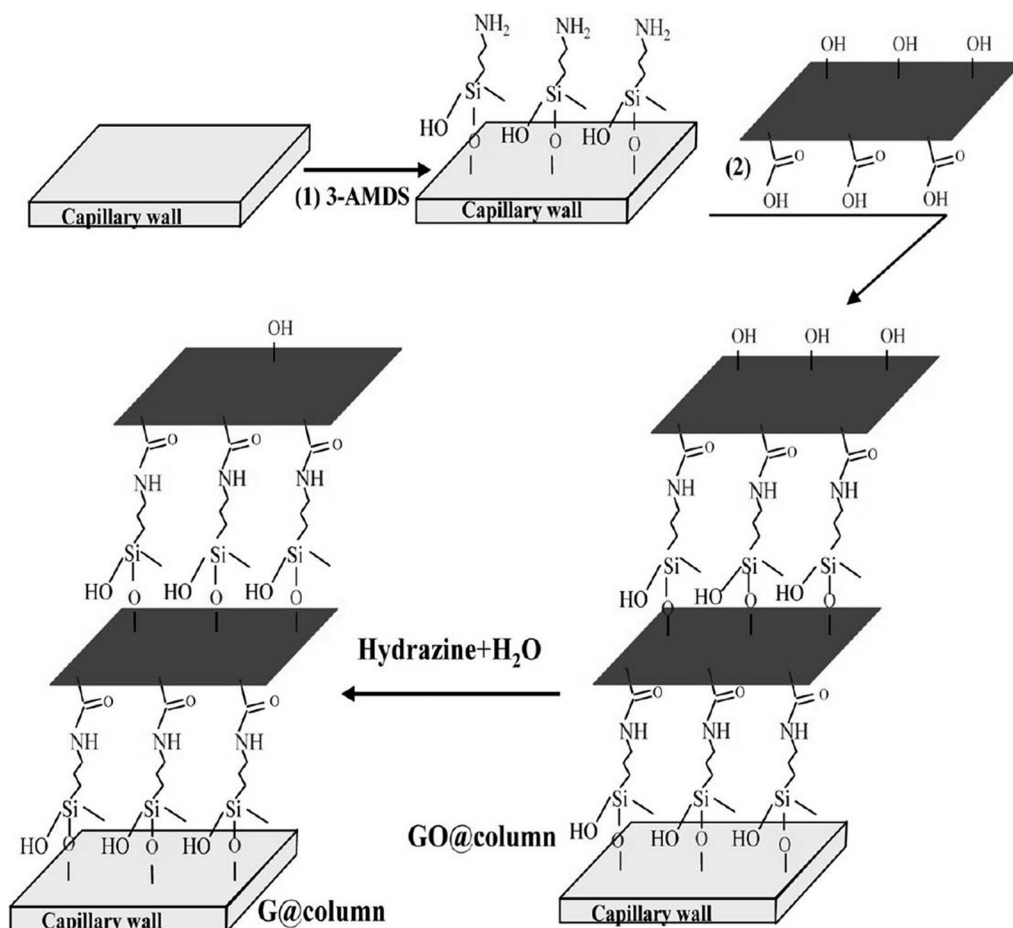
Several works were presented where the objective was to improve the stationary phase. Good results were obtained by etching the inner wall of the capillary with ammonium hydrogendifluoride prior to its silanization. In 2005, Yang *et al.* managed to separate polycyclic aromatic hydrocarbons on etched AuNPs capillaries. The reported results confirmed that dodecanethiol gold particles bonded to the etched inner wall of the fused silica capillary can provide sufficient solute-bonded phase interactions to obtain open-tubular capillary electrochromatography separations with reproducible retention, as well as characteristic behavior, even with the inner diameter of the capillary of 50  $\mu$ m (Fig. 3). Separation of selected PAHs with 60% MeOH and 10 mM phosphate buffer at pH 7.0 was obtained with 225 000 (thiourea), 153 000 (naphthalene), 125 000 (fluorene), and 38 000 (triphenylene) theoretical plates [51].

Another strategy is to apply the sol-gel technique to the process of silanization. A sol-gel layer was developed on the inner wall of the capillary using 3-mercaptopropyltrimethoxysilane, prior to the assembly of dodecanethiol AuNPs over the generated sol-gel layer through specific interaction between the AuNPs and surface terminating thiol groups. The results presented by the authors confirm that dodecanethiol AuNPs, bound to the sol-gel-based inner layer of fused-silica capillary, can provide sufficient solute-bonded phase interactions for open tubular capillary electrochromatography with reproducible retention as well as char-

acteristic reversed-phase behavior. These capillaries were successfully tested using a PAHs mixture [51].

### 2.2.2 Quantum dots

In 2010, Chen and Fung, based on the highly sensitive and selective fluorescence enhancement of water-soluble CdTe/CdS core-shell QD by organophosphorus pesticides (OP) such as mevinphos, phosalone, methidathion, and diazinon, developed a method using QD and LIS detection. They immobilized QD on the inner wall of the capillary and the results showed that the selectivity for the analytes was significantly enhanced. The main advantage pointed out by the authors is the fact that immobilization reduces the use of expensive laser dye during LIF operation. Besides, the good photochemical stability of QD when compared to organic dyes that can easily undergo photo bleaching leads to the choice of QD as the immobilized fluorescence agent for LIF detection in this study. In addition, the interaction of QD with OP is unique, leading to an enhancement rather than quenching of fluorescence. The developed method showed low detection limit from 50 to 180 ng/g, wide working ranges between 0.1 and 30  $\mu$ g/g, repeatability (%RSD,  $n = 3$ ) from 0.36 to 0.75% for migration time, and 2.9–5.7% for peak height from the four OPs investigated [52].



**Figure 4.** Schematic representation of the fabrication processes of graphene oxide and graphene-coated capillary columns. Reprinted with permission from [54].

### 2.2.3 Carbon nanomaterials

An open tubular capillary electrochromatography using multiwalled CNTs (MWCNTs) immobilized into a fused-silica capillary as a stationary phase was employed for the quantification of seven important drugs of abuse in racehorses. The interactions between the analytes and the MWCNTs resulted in an increased migration time and an improvement of the electrophoretic separation. Authors claim that under the optimum conditions determined in their work, seven abuse drugs could be separated in less than 25 min giving separation efficiencies of up to 46 972 average experimental electrophoretic plates ( $N$ ) [53]. Alternatively, a new CE method with higher separation efficiency was achieved using graphene oxide coated capillary as a stationary phase. (Fig. 4) [54].

### 2.3 Preconcentration strategies using NPs coupled with CE system

As it is well known, CE has huge advantages over other analytical techniques, namely, high separation efficiency, short

analysis times, low consumption of solvents and samples, low operating costs, and good selectivity. Nevertheless, the main drawback of the CE is the lower concentration sensitivity with on-column UV detection, which has somewhat limited its use as an effective method for trace analysis in environmental samples. This fact was a driving force for diverse groups to develop various strategies to enable the online and off-line preconcentration of analytes. An interesting work from Thabano *et al.* shows the capability of silica nano-templated polymer monoliths used for in-line SPE of weak bases by analyzing trace levels of caffeine in biological, food, and environmental samples. The preconcentration zone comprised the first 8 cm of the column (75  $\mu\text{m}$  ID). The volume injected was increased to 26 capillary volumes without any loss in resolution or efficiency. These columns exhibited a 33-fold increase in ion-exchange capacity when compared to untemplated monoliths prepared and treated under similar conditions [55]. The use of magnetic materials in automatic systems is gaining much attention as a promising technique in the frame of green chemistry. In particular, nanosized magnetic particles have received considerable attention due to their superparamagnetic nature as well as their unique physical and chemical properties such as high dispersibility,

relative large surface area, and the high ratio of surface-to-volume [56]. Suarez *et al.* used MWNTs to preconcentrate traces of tetracyclines from environmental water samples in a flow system at-line coupled to the CE-MS equipment [57]. The placing of MWNTs in an at-line preconcentration device with CE-MS allows the single elution of analytes in a low volume of eluent. The preconcentration of tetracyclines on MWNTs followed by CE-MS allows the detection of 0.30–0.69  $\mu\text{g/L}$  of tetracyclines for the analysis of 10 mL of surface water samples.

### 3 Separation and characterization of pollutant NPs by CE

The huge demand in techniques for speciation analysis of NPs and their ions in complex matrices are based on their different environmental and toxicity behavior. The potential toxicity of these nanomaterials depends on particle material, concentration, size, shape and surface modification, among others [58]. In this way, CE is a promising tool for nanowaste qualitative and quantitative analysis and a promising tool in this new challenge involving the separation and characterization of NPs. Separation in CE is based mainly in the difference in size and superficial charge. We summarize in a general overview some works classified by similar nature of the background electrolyte in order to discuss competency of CE as an implement for the environmental analysis of NPs. Some samples also require some kind of prior treatment that consists of removing the matrix, such as digestion, separation, or preconcentration by centrifugation, filtration, dialysis, and liquid/solid phase, cloud-point extraction, among others, to be suitable for their analysis by CE [25].

#### 3.1 Preconcentration strategies to analyze NPs

A reversed electrode polarity stacking mode has proved to be a potential tool for enhancing the detection of NPs. When a negative polarity ( $-20$  kV) was applied for 12–24 s, a significant online enhancement effect of the separation efficiency of AuNPs was achieved. It was observed that the increase in time decreased the intensity of the signal, presumably because some of the AuNPs were being pumped from the capillary column. The possibility to perform online monitoring of electropherograms through the use of a diode array detector enabled obtaining of optical spectra for different sizes of AuNPs after their separation, with detection limits for the Au NPs and Au/Ag NPs increased by ca. 30- and 140- fold, respectively. Thus, the presented method is rapid and shows high sensitivity for monitoring AuNPs, at the same time that is suitable to obtain the optical properties of each particle size [59]. It was concluded that the combination of reversed electrode polarity stacking mode for online concentration, followed by electrophoretic separation using electrolyte background containing SDS and 3-cyclohexylamino-1-propanesulfonic acid, for characterizing the size of AuNPs was fruitful. There was

a good correlation between electrophoretic mobility and size of the NPs and the electrophoretic separation took place in less than 4 min. Moreover, the validation of the accuracy of the CE size characterization for the NPs was performed and compared to the results obtained using a transmission electron microscope with excellent results [60].

#### 3.2 Detection

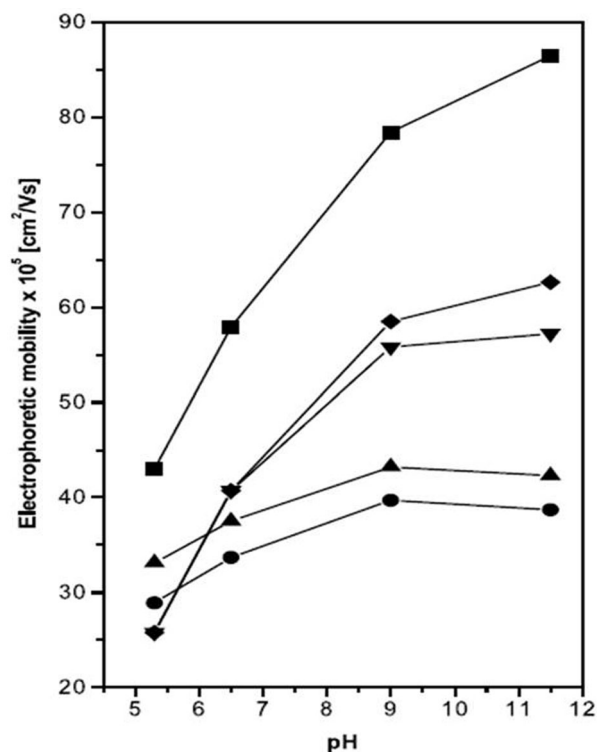
On-column and off-column detection techniques are successfully employed for the analysis of NPs. In the case of on-column detection, a remarkable advantage is that the on-line optical spectrum of NPs in most cases depends on their size and shape. Indeed, separation and characterization of AgNPs mixtures with different size and shape was possible combining CE with diode array detection [61]. Alternatively, NPs can be detected by UV but because of the inherent sensitivity of this technique, single particle inductively coupled plasma mass spectrometry detection is gaining particular attention. With this detection technique, detection limits in the range of 0.8–1.0 ng/mL for AuNPs were achieved in blood serum samples [62]. In aqueous suspensions, 5, 10, 20, and 40 nm size particles were injected and detected in a concentration of  $4 \times 10^{-11}$  M, the calculated limit of detection was  $2 \times 10^{-15}$  M [63].

#### 3.3 Background electrolyte and particle separation

##### 3.3.1 Buffer in the BGE

Size separation is possible by capillary zone electrophoresis. AuNPs that only differ by 3 nm in diameter (3.5, 6.5, and 10.5 nm) were successfully separated with 20 mM ammonium acetate, 20 mM Tris, 10 mM CAPS buffer, pH 8.5, and evaporative light scattering detection [64]. In addition, a good linear relationship among the reciprocal migration time and NP size ( $R^2 = 0.998$ ) was found between 10, 20, and 40 nm commercially available AgNPs (citrate-coated), with 10 mM Tris, 10 mM  $\text{H}_3\text{BO}_3$ , 10 mM  $\text{Na}_2\text{B}_4\text{O}_7$  buffer, and pH 9.0 (75  $\mu\text{m}$  ID  $\times$  60 cm fused capillary) with ICP-MS detection. This method is suitable for the characterization and screening of NPs in complex media such as consumer products and environmental samples [65]. Alternatively, in another work, silica sols, in the range of 5 nm to 500 nm, were separated by CZE with ammonia buffers pH 9.0, and turbidity detection measurements at 190 nm [66]. The mobility and separation of the NPs depends on the electrolyte concentration and pH, and the optimum condition depends on the sample composition. Silica sols with particle diameters between 50 and 442 nm were separated with 2.5 or 10.0 mM phosphate buffer, pH 5.3–11.5 (75  $\mu\text{m}$  ID  $\times$  28.5 cm to the detector length, fused silica capillary) with detection from 190 to 400 nm. For all  $\text{SiO}_2$  NPs sizes, in acidic conditions, the electrophoretic mobility decreased with the increase in the phosphate buffer concentration, while the opposite tendency was found in





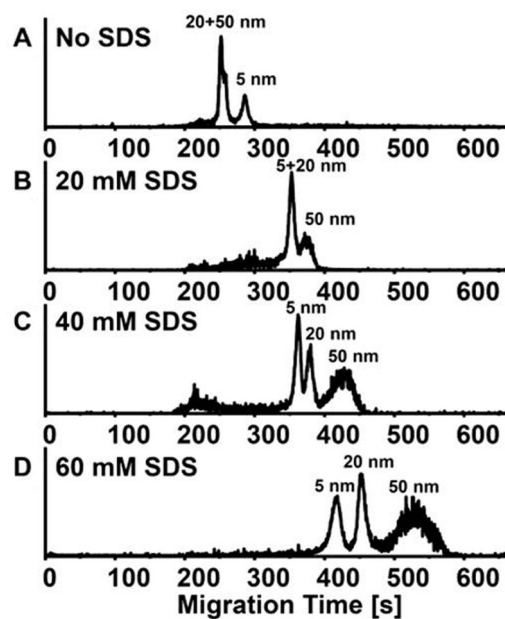
**Figure 5.** Dependence of absolute values of silica nanosphere electrophoretic mobility on pH. Carrier electrolyte: 2.5 mM phosphate buffer. Plot: (●) 50 nm; (▲) 100 nm; (▼) 355 nm; (◆) 442 nm; (■) EOF. Reprinted with permission from [67].

alkaline conditions. Concerning the pH conditions, an increase in the mobility was shown with the increase in the pH, as expected (Fig. 5) [67]. This is expected as the increase in the amount of deprotonated silanol groups on the inner surface of the capillary column leads to an increase in the electroosmotic flow. Moreover, the influence of the buffer concentration and pH in the analysis of AuNPs was tested by Lin *et al.*, An increase in the concentration of CAPS (10–50 mM) led to an increase in the migration time and peak width, while the detection sensitivity was weaker, thus the lowest concentration was chosen as optimal [59].

### 3.3.2 Surfactants in the BGE

An improvement in the separation has been reported in many cases by adding SDS to the BGE. It is proposed that the hydrophobic tail of the SDS molecule is adsorbed to the gold surface and therefore the charge of the NPs is related to the number of molecules of SDS on the surface. This causes a change in the charge-to-size ratio of the NPs related to the surface area of NP and the surfactant concentration of the running electrolyte [68, 69].

CE separation in aqueous medium of 30, 50, 80, and 200 nm AuNPs was conducted with 40 mM SDS and 10 mM CAPS, pH 7.3 (75  $\mu$ m ID  $\times$  80 cm fused capil-



**Figure 6.** Representative electropherograms for mixtures of ~5, ~20, and ~50-nm-sized AuNPs obtained with CE/MEKC-ICP-MS (monitoring  $m/z$  197) and increasing SDS concentrations in the buffer. (A) No SDS, (B) 20 mM SDS, (C) 40 mM SDS, and (D) 60 mM SDS. Reprinted with permission from [69].

lary) and SP-ICPMS detection as a semiquantitative technique for measuring particle elemental mass, finding good agreement between the calculated diameters and the nominal values up to at least 200 nm [70]. Liu *et al.* found that the optimized separation conditions for AuNPs in the range of 5.3–38 nm involved 70 mM SDS and 10 mM CAPS buffer, pH 10 [68]. Similar conditions were used for separation of 5, 20, and 48 nm AuNPs. In this study, the main role of the surfactant (SDS) in the separation was studied; it was found that higher SDS concentrations enhanced the electrophoretic mobility. While no separation between 20 nm and 50 nm was observed without SDS, the best separation was achieved with 60 mM SDS and 10 mM CAPS buffer, pH 10 (Fig. 6). It was suggested that the number of surfactant molecules limited the total charge of a NP, which are available for adsorption onto the particle surface. Also a reversed order was observed compared to SDS-free conditions [69]. The main role in the separation of the surfactant was also discussed in another work, showing low separation between AgNPs without SDS. Spherical 17 and 50 nm AgNPs were successfully separated by size as well as 6–55 nm nanorods and 80 nm spherical NPs by their shape by CE with 20 mM SDS and 10 mM Tris, pH 8.5 (75  $\mu$ m ID  $\times$  48.5 cm length fused capillary) and UV-visible detection (DAD) [41]. The value of adding SDS was also reported in the separation and analysis of two kinds of NPs, 17 nm Au and 60 nm Au/Ag core/shell (Au core) particles, in the range of 20–80 mM. This study consistently revealed the strong influence of the surfactant concentration with the separation of these NPs, finding an increase in the electrophoretic mobility with the increase in SDS, and a poor

separation at a relative poor concentration. Best separation conditions were found with 40 mM SDS and 10 mM CAPS buffer, pH 10 [59].

Likewise, as SWCNTs are too large to reside in the intracellular region, in this case SDS provides a negative surface charge through the hydrophobic interaction between SDS tails and the nanotube surface that favors the separation. Separation of tubes according to their length was successfully achieved with 50 mM 2-amino-2-(hydroxymethyl)-1,3-propanediol (trizma base) and 0.5% SDS buffer (75  $\mu\text{m}$  ID  $\times$  75 cm length fused capillary) and absorbance detection at 360 nm [71]. On the other hand, Kumar *et al.* found that there is no significant interaction between like-charged SiNPs and the SDS micelles leading to any structural changes. In this sense, the incorporation of this surfactant should not bring any benefit [72]. Later, Kato *et al.* also reported that the addition of SDS into the BGE had a small effect on the electrophoretic mobility of SiNPs but a significant effect on the electrophoretic mobility of polyethylene glycol NPs [33].

### 3.3.3 Different kind/modified NPs

Separation between different kinds of nanomaterials is also a main goal in nanowastes. Closely related particles were analyzed by CE. In this sense, a bimodal mixture containing two closely size-related nanolatexes were successfully separated by CE complemented with the absolute size-based determination provided by Taylor dispersion analysis [73]. Capped AuNPs core (radius about 2 nm) with different hydrophilic coatings was analyzed by CE with 30 mM disodium tetraborate decahydrate pH 9.2 buffer (75  $\mu\text{m}$  ID  $\times$  50.5 cm to the detector length, fused silica capillary) and absorbance detection. Moreover, zeta potential was successfully estimated in this study. Five different kinds of negatively charged capped AuNPs dodecanethiol over coated with the poly(isobutylene-alt-maleic anhydride)-graft-dodecyl or poly((2-(methacryloyloxy)ethyl)phosphonic acid)*x*-stat-poly(lauryl methacrylate) or exchanged with 11-mercaptopundecanoic acid, and two extra coatings were achieved treating the first ones with different ratios of polyethyleneglycol [74]. Later, the same authors showed that with this method the determination of size distribution was also possible by transforming the intensity-weighted electrophoretic mobility distribution into an intensity-weighted hydrodynamic radius distribution [75]. In another work, d'Orlyé *et al.* reported a correlation between the amino derivatization rates of silanol groups with the electrophoretic mobility. Different functionalization rates with 3-(aminopropyl)triethoxysilane and 2-[methoxy(polyethyleneoxy)-propyl]-trimethoxysilane at different molar ratios of maghemite/silica core/shell were determined by CE. To prevent particle adsorption, a semipermanent capillary coating was obtained with dodecyltrimethylammonium bromide. Various ionic strength (1–100 mM) and pH values (7.0–8.2) of phosphate (or 149.5 mM MOPS, 100 mM NaOH, and buffer at pH 7.4) were evaluated in this

work (50  $\mu\text{m}$  ID  $\times$  26.5 cm to the detector fused silica capillary) with detection wavelengths of 200 or 254 nm depending on the BGE nature. The best resolutions were obtained at pH 8.0 with high ionic strength (100 mM) [76].

## 4 Conclusion

There is an increasing demand of methods for detecting, quantifying, and characterizing nanomaterials in complex matrices, involving both chemical and physical information, as well as composition, concentration, size, and shape [25]. Techniques commonly used for NP characterization, such as light scattering techniques, electron microscopy, and atomic spectrometry, can provide useful information in most cases, but separation techniques, including field-flow fractionation, CE, and hydrodynamic chromatography, are growing as tools moving to the nanodomain providing qualitative and quantitative information [25].

The development of validated methods for the characterization and quantification of nanomaterials and their impact on the environment should be considered and encouraged to achieve a proper, safe, and sustainable use of NPs. NPs that are strongly incorporated in composites are not considered to have a big impact in human health, while labile or free NPs should draw the attention. However, it should be taken into account that particles may aggregate and their impact also depends in the solubility, possible degradation and possible chemical, and size modification in the time. For this purpose, adaptation of existing and/or development of analytical methods for analyzing low concentration of NPs in complex samples are required. In this sense, CE is a promising tool as routine method for determining size, shape, and superficial charge based on the NPs different electrophoretic mobility, in particular in aqueous samples, with the advantage of being a known green analytical method. The possibility of combining this technique with various detectors types brings in the advantage of an increase in the detection limit (i.e., ICP-MS) or employs physical properties of the particles (i.e., DAD). As well, CE proved to be a suitable technique as it is capable to distinguish different surface grafting. Hereby it is not surprising that CE is growing as a method for separation of inorganic NPs (Au, Ag, TiO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, among others) latex particles, polystyrene microspheres, and QD bioconjugates. While there are many works about the analysis and characterization of newly developed and synthesized nanomaterials, few papers were written concerning the analysis of NPs in complex samples, as are the environmental ones, to learn more about what happens to them once they have been released into the environment. When analyzing NPs, it is important to consider their stability and tendency to aggregate in solution as a consequence of their intrinsic characteristics such as size or surface chemistry in combination with the complex aqueous matrices found in realistic environmental conditions. This nanomaterial instability can result in unstable baselines and irreproducible separations. The measurement of the zeta potential of the sample in a running buffer might be of help to

predict the stability of the NPs. The incorporation of additives in the buffer such as surfactants may alter the surface chemistry of the particles and modified their rate of aggregation.

On the other hand, not everything about using NPs as PSPs is an advantage. Several drawbacks have been described, among them the light-scattering problem in ultraviolet detection and interference with the ionization process in mass spectrometric detection. In addition, preparing a stable suspension of NPs, which is required for application in CE, is not as easy as dissolving a water-soluble salt. The stability of NPs is readily affected by particle size, surface charge density, and ionic strength of the dispersion medium. An unstable suspension in CE will result in poor analytical precision and even a clogged capillary [77].

Since CE has proved to be an extremely powerful tool for the analysis and characterization of NPs in relatively simple samples, it is necessary to put much effort into the adaptation of the existing ones and/or the development of new methods for the analysis of nanomaterials in complex samples, taking into account the need of using off-line and/or online sample preconcentration and clean-up.

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