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TRENDS

Recent advances in the development of capillary electrophoresis methodologies for optimizing, controlling, and characterizing the synthesis, functionalization, and physicochemical, properties of nanoparticles

Laura Trapiella-Alfonso [1,2,3,4] · Fanny d'Orlyé [1,2,3,4] · Anne Varenne [1,2,3,4]

Abstract This paper gives a critical overview of capillary electrophoresis (CE) methodologies recently developed for controlling and optimizing the synthesis of nanoparticles as well as characterizing their functionalization in terms of physicochemical properties. Thanks to their electrophoretic mobility, various parameters can be determined, such as NP size and charge distribution, ζ-potential, surface functionality, colloidal stability, grafting rates, and dissociation constants, allowing not only the complete characterization of new nanoprobes but also helping in their design and in the selection of chemical conditions for their storage and further manipulation. New strategies for the improvement of CE detection sensitivity are also described.

Introduction

The rapid development of nanotechnology has led to a wide variety of manufactured nanoparticles (NPs) for applications in industrial and personal care products. The properties of NP are directly dictated by their intrinsic characteristics such as their size and chemical composition, but can also be affected by their local environment. Thus, the characterization of these nanomaterials and their conjugates remains a challenging issue.

Till now, many different microscopic, spectroscopic, optical and chromatographic techniques have been employed for such purpose with their benefits and limitations [1]. Among them, capillary electrophoresis (CE) is already known as a powerful separation technique, allowing rapid analysis, low sample and reagent consumption, as well as high resolution. It has emerged in the last years as a simple and versatile technique for the physicochemical characterization of NPs in terms of electrophoretic mobility, size and charge distribution, ζ-potential, surface functionality, colloidal stability and grafting rates [2–4].

This review describes the main tendencies of the last 2 years (2013–2015) in this challenging topic, with non-exhaustive examples, proving the power of CE for optimizing the synthesis and characterization of NPs for further use in various fields. Thus, for a comprehensive lecture, the article is organized into three sections: (1) determination of fundamental physicochemical parameters governing the properties of NPs; (2) quality control of NP synthesis and surface engineering; and (3) strategies to improve the detection sensitivity

✉ Fanny d'Orlyé
fanny.dorlye@chimie-paristech.fr

✉ Anne Varenne
anne.varenne@chimie-paristech.fr

1   PSL Research University, Chimie ParisTech, Unité de Technologies Chimiques et Biologiques pour la Santé, 75005 Paris, France

2   INSERM, Unité de Technologies Chimiques et Biologiques pour la Santé (U 1022), 75006 Paris, France

3   CNRS, Unité de Technologies Chimiques et Biologiques pour la santé (UMR 8258), 75006 Paris, France

4   Sorbonne Paris Cité, Unité de Technologies Chimiques et Biologiques pour la Santé, Université Paris Descartes, 75006 Paris, France

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of electrokinetic methods (see Scheme 1). To conclude and open perspectives, the relevance of electrokinetic methodologies will be pointed out for the quantification of noncovalent interaction involving nanoparticles.

CE for the characterization of NP physicochemical parameters

In the literature, we can find CE methodologies for the characterization of NPs including noble-metal NPs, semiconductor quantum dots (QDs), polymeric NPs, and magnetic NPs. However, there is a need for general methodologies easily adaptable to any type of NP. Since the first works [5, 6] involving latex NPs as model particles for the development of size-based separation methodologies using CE, great efforts were made to refine models describing the electrophoretic behaviour of NPs as a function of their intrinsic properties, surface chemistries, and colloidal stability, as well as dispersion conditions [7–11].

Very recently, Pyell et al. [12] have proposed a new approximation that consists on a simplification of the Oshima's model [10], extending the applicability of the model to the use of any buffered electrolytes (containing one type of strong counter-ions and co-ions with a mobility very close to the NPs). The approach does not take into account the interparticle interactions, and is only valid for NPs with electric charges homogenously distributed and located within a very thin shell close to the surface of shear and for diluted NP dispersions. In addition, they performed Taylor dispersion analysis (TDA) for measuring the hydrodynamic radii of gold NPs with different coatings. This measurement, along with the electrophoretic mobility determined by CE, allowed calculating the ζ-potential of a given NP, revealing that for $\zeta > 25$ mV the relaxation effect must be taken into account. Moreover, they were able to determine the surface charge density and the effective charge number as well as to figure out the type of NP size-distribution (monomodal, bimodal, or multimodal).

The authors have also been working on the interpretation of electrophoretic mobility profiles to transform them into size distribution profiles [13]. Under specific conditions, the function $\mu = f(\kappa a)$ (where μ is the effective electrophoretic mobility; κ is the Debye-Hückel parameter; and a is the sphere radius) can be approximated by a straight line. The parameters of these calibration lines allowed transforming the intensity-weighted electrophoretic mobility distribution profile of a given NP population into intensity-weighted hydrodynamic radius distribution.

The addition of surfactants in the background electrolyte (BGE) can impact the separation performances, depending on

Scheme 1 A comprehensive scheme for the control and optimization of nanoparticle synthesis and properties based on analytical electrokinetic methodologies
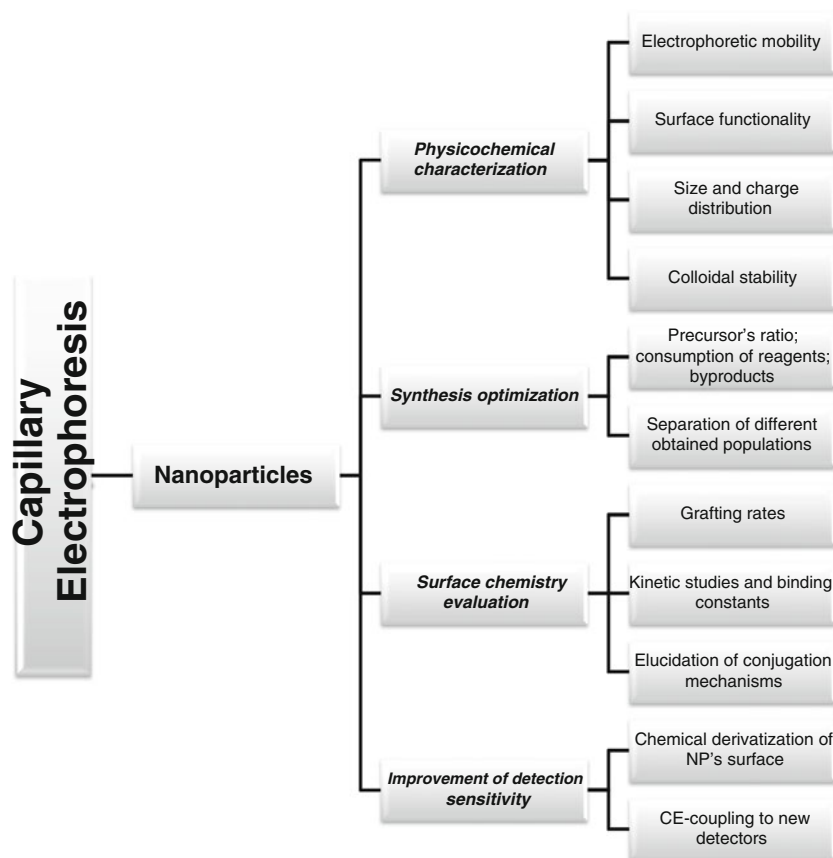
the surface chemistry of NPs. Kato et al. [14] performed a systematic comparison by micellar electrokinetic chromatography (MEKC) of the electrophoretic behavior of polyethylene glycol (PEG) and silica NPs of similar average diameter. They presented very different migration behaviors in the presence of SDS, probably because of the difference in the NP surface chemistries. The PEG chains probably enable SDS to be incorporated into the PEG shell giving rise to a great difference in the global NP charge that explains the different electrophoretic behavior observed between both NPs.

Once the parameters that influence the separation and characterization of NPs are defined CE instrument is ready to go deeper and emerges as an analytical tool for the control, evaluation and optimization of synthetic and functionalization processes of NPs. This aspect of CE methodologies is revised in the following section.

Development of CE methodologies for the optimization and characterization of the synthesis or surface modification of NPs

CE can play an important role for (1) helping in the design of new nano-probes, and (2) assessing their biocompatibility, toxicity, surface chemistry, and stability in physiological media. Indeed, the electrophoretic behavior of NPs is dependent on their surface chemistry (surface modification and possible grafting with a (bio)molecule). The following selected examples illustrate the features mentioned above.

CE methodologies for optimizing, controlling, and characterizing NP synthesis

Very recently, a new class of QDs named "carbon nanodots, C-dots, or carbon nanoparticles" was investigated. C-dots are NPs based on carbon with diameters less than 10 nm that present tunable photoluminescent emission, good photostability, and excellent biocompatibility. Nevertheless, a strong influence of the surface chemistry on their photoluminescent properties is observed. In addition, the synthetic process is still under study, producing very heterogeneous mixture of products. For that, a complete characterization of both synthetic process and final properties of C-dots are required. In this sense, two publications from the group of Choi demonstrate the usefulness of CE for such purpose [15, 16].

CE coupled with UV and LIF detection allowed to evaluate C-dots synthesis by microwave-assisted pyrolysis [15] and to optimize their surface functionalization with –NH2 and –COOH moieties present in the precursors. In this context, the influence of the reaction time and molar ratio of NH_2/COOH precursors on the final composition of synthesized mixtures of C-dots is shown in Fig. 1. Under optimized CE

conditions, a simultaneous separation of positive, neutral, and negative C-dots was obtained, allowing the control of grafting rate and synthesis yield considering the relative increase observed for the peak intensity of each particle population (see Fig. 1b).

Moreover, Liu et al. [16] focused their studies on the optimization of the bottom-up synthesis of hollow carbon nanoparticles (HC-NPs) by wet-chemical approach. This synthesis, which entailed the simple reaction of acetic acid, water, and P_2O_5 led to a mixture of different HC-NPs. Thanks to CE coupled on-line to UV and LIF detectors, the authors were able to separate four different fractions that were collected for further classic characterizations (transmission electron microscope (TEM), MS, absorption, and fluorescence spectroscopy). In such a way, electrokinetic separations enabled a better understanding of the chemical composition, structure, and optical properties of a new type of nanoparticles.

CE methodologies for the evaluation and characterization of different NP surface modifications

CE can contribute evaluating and displaying information about the interaction between the surface of NPs and some ligands. In this sense, López-Lorente et al. [17] evaluated the formation of self-assembled monolayers (SAMs) of thiol ligands onto Au- and Ag-NP surface by ligand exchange process. For such purpose, the synthesized citrate-NPs were injected into the capillary column, whereas the ligands (thioctic acid and thiomatic acid) were introduced as additives in the BGE. Thus, the on-line formation of SAMs led to significant shifts in NP electrophoretic mobility. Eventually, the authors observed that the relative concentration and differential affinity for the metal surface of the two ligands allowed separating citrated Au-NPs from Ag-NPs of similar size and shape in mixtures.

The number of noncovalent attached ligands on NP surface was also determined. In this way, the work of Vorácová et al. [18] estimated the effective surface charge density and the number of ligands attached to QDs, as well as their dissociation constants. The study was performed using three CdTe QDs of different sizes and two different thiol ligands. The information provided by this CE method was highly appreciated because the knowledge of potential reactive sites on QD surface for conjugation to biomolecules facilitates the design and the preparation of new nanoprobes. In addition, the knowledge of the stability constants helps selecting appropriate dispersion conditions for both conjugation and purification processes as well as for NP storage and further handling.

Electrokinetic methodologies are not only of interest for evaluating the synthesis and surface modification of NPs, but also for selecting dispersion conditions ensuring the colloidal stability and chemical integrity of synthesized objects. Thus, Ramirez-García et al. [19] illustrated the use of capillary
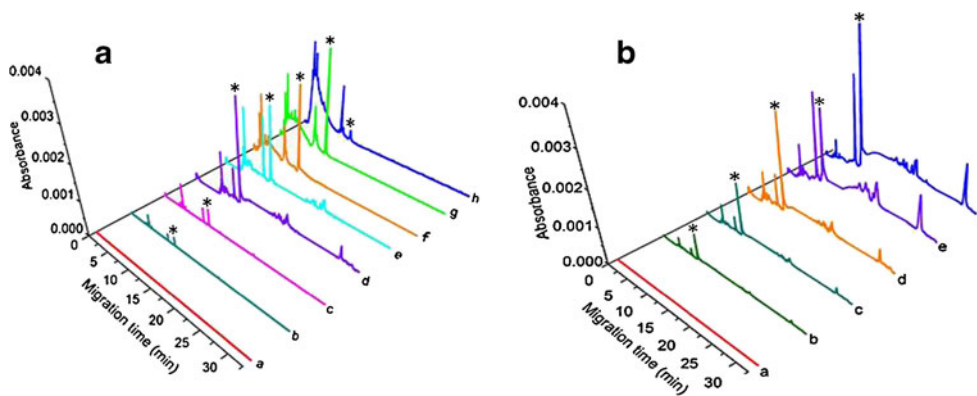
Fig. 1 (a) Electropherograms of C-dots synthesized in 4 min with different molar ratio of amine/carboxylic acid group in the precursors: (a) 0.00; (b) 0.25; (c) 0.50; (d) 0.67; (e) 0.80; (f) 1.00; (g) 1.33; and (h) 2.00. (b) Electropherograms of C-dots synthesized with a 0.67 molar ratio of amine/carboxylic acid group at different reaction times: (a) 1.0; (b) 2.0; (c) 3.0; (d) 4.0; (e) 5.0; and (f) 6.0 min. In both cases, the peaks labeled with asterisks are neutral C-dots. Peaks migrating before and after neutral C-dots are positively and negatively charged C-dots, respectively. Adapted from reference [15] with permission of Elsevier

zone electrophoresis (CZE) for controlling, optimizing and evaluating the synthesis, functionalization and colloidal stability of zinc gallate nanoparticles doped with chromium persistent luminescent NPs with different surface chemistries. The authors were able to assess the effective functionalization of NPs, optimize their synthesis conditions, as well as identify the best dispersion media for storage and handling of these NPs in biological fluids. Thus, they found that whereas for negative NPs phosphate buffers prove to be an adequate dispersion medium, zwitterion buffers are preferred for positive ones. In the case of neutral NPs, both types of buffer ensured their colloidal stability over time.

The conjugation of NP to molecular protein probes has already been studied by CE [20]. Here, we focus on some molecular affinity probes, such as aptamers and DNA that have been recently used. Aptamers are single-stranded DNA or RNA oligonucleotide sequences that are alternative recognition molecules to antibodies. They are widely used in the biomedical field and their conjugation to NPs is an active investigation field. In the work of Girardot et al. [21], a CE-based methodology was developed to prove the formation of NP-aptamer conjugates, evaluate their electrophoretic behavior, determine their physicochemical characteristics, colloidal stability, as well as biological activity. After a systematic optimization of CE conditions, the authors were able to determine the grafting rates showing no significant influence of the linker length on the grafting efficiency and no aggregation phenomena induced by the aptamer immobilization process. In addition, the authors observed that the conjugate is stable in the 5 to 9 pH range, whereas pH below 5 provokes aggregation attributable to the attenuation of interparticle electrostatic repulsions.

Also, CE methodologies for elucidating the mechanism of QD-DNA conjugation have been developed. For example, Stanisavljevic et al. [22] performed the characterization of 2 nm diameter glutathione-CdTe QDs synthetic process and

the full optimization of their complexation with DNA by CE-laser induced fluorescence (LIF). Thanks to its inherent resolution capability, CE-LIF allowed the monitoring of the conjugated-NP formation, enabling the optimization of the bioconjugation process in terms of incubation time and DNA concentration (see Fig. 2). Furthermore, the authors suggest that QDs are incorporated into the major groove of DNA because of the similarity in dimension of this hollow (2.1 nm) with the QD size. This result suggests that the QD-DNA interaction hardly depends on QD size, which has to match the dimension of DNA groove.

CE offers highly valuable help for optimizing engineering NPs in terms of synthesis and surface modification as well as characterizing their conjugates. Nevertheless, one of the weakness points of CE for the characterization of NPs in different complex media is the sensitivity of the detection. To overcome this limitation, different strategies are being studied and will be described in the next paragraph.

New strategies for the improvement of CE-detection sensitivity for the separation of NPs

The strategies developed to improve the sensitivity of detection coupled or integrated on-line to CE instrument are mainly focused on the one hand, on chemical derivatization of the NPs, and on the other hand, on the coupling of CE instrument to new detection systems.

In addition to already developed strategies for the enhancement of CE-detection sensitivity towards NPs, such as metal-enhanced fluorescence method [23] or different stacking strategies for on-line sample pre-concentration [24, 25], other strategies have been recently investigated. For example, in the case of oxide NPs (SiO$_2$, TiO$_2$, Fe$_2$O$_3$, etc.) an interesting strategy based on NP surface coating [26, 27] has been evaluated. The general idea is to
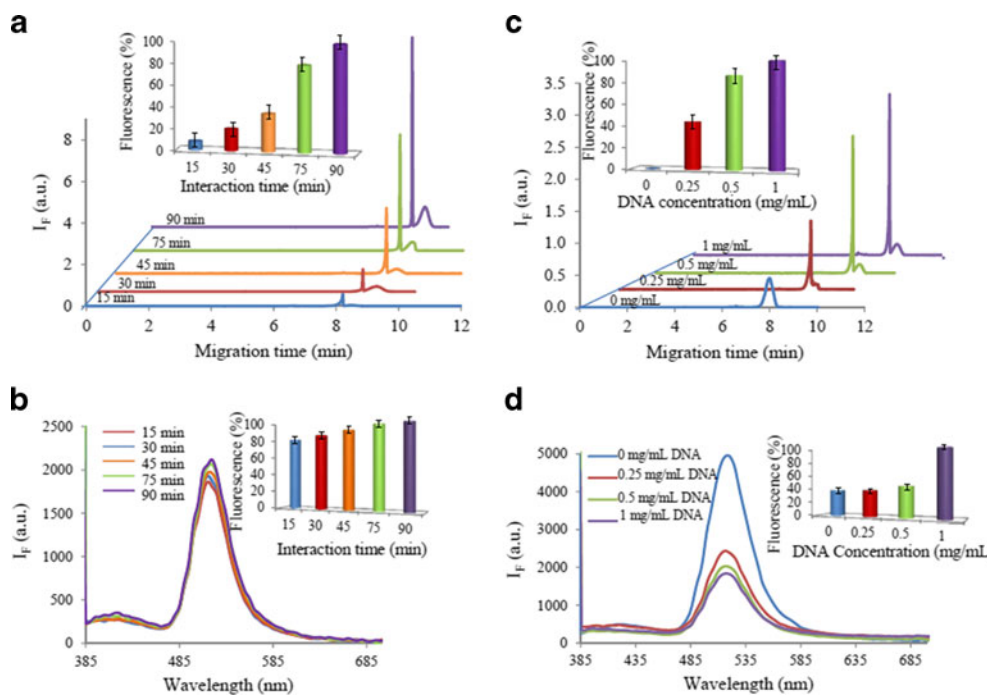
Fig. 2 CE-LIF and fluorimetric characterization of QDs-DNA interaction. **(a)** QDs and DNA (500 µg/mL) time interaction monitored by CE-LIF, inset: the peak height dependence on interaction time (peak 1 – QD-DNA complex, peak 2 – QDs). **(b)** QDs and DNA interaction time monitored by fluorescence spectrometry, inset: fluorescence intensity dependence on the interaction time. **(c)** QDs and DNA interaction with different concentrations of DNA measured by CE-LIF, inset: dependence of created complex peak height on DNA concentration (peak 1 – QD-DNA complex, peak 2 – QDs). **(d)** QDs and DNA interaction with different concentrations of DNA measured by fluorescence spectrometry, inset: fluorescence intensity dependence on the DNA concentration. Reproduced from reference [22] with permission of Wiley

introduce a chromophore that enhances the analytical signal. For such purpose, different polymers presenting chromophores in their structure and different coating strategies were assayed for the surface modification of SiO_2 and TiO_2 NPs. Thus, a direct growth of the polymer from NP surface allowed improving detection sensitivity up to 15-fold depending on the polymer nature. An enlargement of the electron delocalization, by the addition of another polymer layer, could even increase the sensitivity 50-fold. This strategy could be very interesting for trace analysis of NPs in environmental or biological samples.

The other strategy that is being investigated in order to improve sensitivity and resolution of CE detection consists in coupling CE to new detection systems such as dark-field microscopy [28], evaporative light scattering [29], and ICP-MS [30–32]. In this latter case, the challenge emerges from the need to perform an accurate and sometimes quantitative analysis of trace level NPs in different complex matrices enabling the discrimination between metal NPs and the ionic forms of the respective dissolved elements. Some pioneering works [30–32] have employed different CE modes (MEKC and CZE) to perform the separation, identification, size,
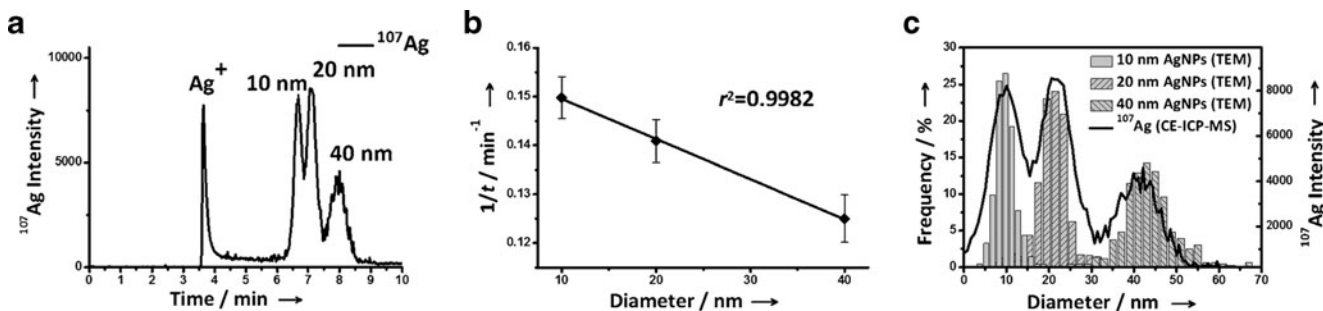

Fig. 3 Illustration of CE-ICP-MS features in terms of speciation and resolution of AgNPs of different sizes in mixture. **(a)** Typical electropherogram of a mixture of Ag^+ and AgNPs of diameters 10 nm, 20 nm and 40 nm. **(b)** Relationship between the reciprocal migration time and the diameter of AgNPs. **(c)** Size distributions generated by CE-ICP-MS and TEM. Reprinted from reference [32] with permission of Wiley

characterization and speciation of different metal NPs (Au, Ag, Pt, and Pd) in different matrices. It should be noted that the type and concentration of the surfactant introduced in the BGE seems to be the key factor to achieve a good resolution capability. Figure 3 illustrates some of these features and shows the agreement between the results from CE-ICP-MS methodology and those from TEM. This methodology seems promising not only for a reliable NP characterization but also for rapid screening of NPs in different samples.

Conclusions and outlook

The applications reviewed here illustrate that CE offer access to a multitude of parameters characterizing NPs either bare or functionalized on their surface with various organic compounds, such as polymers or biomolecules. Nevertheless, there are some critical points to consider when CE is used for the analysis of NPs that could limit its application and reliability. The selection of the BGE (composition, additives, pH, and ionic strength) is not a trivial question because it can affect not only the separation performance but also the colloidal stability of NPs. The lack of reference materials is another issue that has been claimed by other authors before [3]. Finally, the question of detection sensitivity that has been revised here and the reproducibility of the analysis are other challenges to widespread electrokinetic methodologies.

In spite of these limitations and because of the rapid development of CE methodologies and strategies to improve its sensitivity and selectivity and to adapt CE systems to different environments, we can foresee a promising and challenging future for CE in terms of separation and characterization of NPs with various surface chemistries. This would allow a better understanding of the behavior of these materials in suspension in different complex matrix (environmental, biological and physiological samples, and commercial products). In this sense, a new tendency in CE separations concerning the evaluation of the possible undesired and unspecific interactions between the biological media (e.g., proteins) and NPs (i.e., the analysis of the so-called "protein corona") [33–35] should be noted. The great potential of CE for weak interaction characterization will provide highly desired information about the "soft-corona."

Compliance with ethical standards

Conflict of Interest Authors declare not having any conflict of interest in this publication.

References

1. Lapresta-Fernández A, Salinas-Castillo A, Anderson de la Llana S, Costa-Fernández JM, Domínguez-Meister S, Cecchini R, et al. A General perspective of the characterization and quantification of nanoparticles: imaging, spectroscopic, and separation techniques. Crit Rev Solid State Mater Sci. 2010;39:423–58.
2. Pyell U. Characterization of nanoparticles by capillary electromigration separation techniques. Electrophoresis 2010;31:814–831.
3. López-Lorente AI, Simonet BM, Valcárcel M. Electrophoretic methods for the analysis of nanoparticles. Trends Anal Chem. 2011;30:58–71.
4. Sang F, Huang X, Ren J. Characterization and separation of semiconductor quantum dots and their conjugates by capillary electrophoresis. Electrophoresis. 2014;35:793–803.
5. Jones HK, Ballou NE. Separations of chemically different particles by capillary electrophoresis. Anal Chem. 1990;62:2484–90.
6. Petersen SL, Ballou NE. Effects of capillary temperature control and electrophoretic heterogeneity on parameters characterizing separation of particles by capillary zone electrophoresis. Anal Chem. 1992;64:1676–81.
7. Henry DC. The cataphoresis of suspended particles, Part 1. The equation of cataphoresis. Proc R Soc Lond A. 1931;133:106–29.
8. Overbeek JTG. Theory of the relaxation effect in electrophoresis. Kolloide Beih. 1943;54:287–364.
9. Booth F. The cataphoresis of spherical, solid nonconducting particles in a symmetrical electrolyte. Proc R Soc Lond A. 1950;203:514–33.
10. Ohshima H. Approximate analytic expression for the electrophoretic mobility of a spherical colloidal particle. J Colloid Interface Sci. 2001;239:587–90.
11. Radko SP, Chrambach A. Separation and characterization of submicrom and microm-size particles by capillary zone electrophoresis. Electrophoresis. 2002;23:1957–72.
12. Pyell U, Jalil AH, Pfeiffer C, Pelaz B, Parak WJ. Characterization of gold nanoparticles with different hydrophilic coatings via capillary electrophoresis and Taylor dispersion analysis. Part I: Determination of the zeta potential employing a modified analytic approximation. J Colloid Interface Sci. 2015;450:288–300.
13. Pyell U, Jalil AH, Urban DA, Pfeiffer C, Pelaz B, Parak WJ. Characterization of hydrophilic coated gold nanoparticles via capillary electrophoresis and Taylor dispersion analysis. Part II: Determination of the hydrodynamic radius distribution – comparison with asymmetric flow field-flow fractionation. J Colloid Interface Sci. 2015;457:131–40.
14. Kato M, Sasaki M, Ueyama Y, Koga A, Sano A, Higashi T, et al. Comparison of the migration behavior of nanoparticles based on polyethylene glycol and silica using micellar electrokinetic chromatography. J Sep Sci. 2015;38:468–74.
15. Hu Q, Paau MC, Zhang Y, Chan W, Gong X, Zhang L, et al. Capillary electrophoretic study of amine/carboxylic acid-functionalized carbon nanodots. J Chromatogr A. 2013;1304:234–40.
16. Liu L, Feng F, Hu Q, Paau MC, Liu Y, Chen Z, et al. Capillary electrophoretic study of green fluorescent hollow carbon nanoparticles. Electrophoresis. 2015;36:2110–9.
17. López-Lorente AI, Soriano ML, Valcárcel M. Analysis of citrate-capped gold and silver nanoparticles by thiol ligand exchange capillary electrophoresis. Microchim Acta. 2014;181:1789–96.
18. Vorácová I, Klepárník K, Lisková M, Foret F. Determination of ζ-potential, charge, and number of organic ligands on the surface of water soluble quantum dots by capillary electrophoresis. Electrophoresis. 2015;36:867–74.

19. Ramírez-García G, d'Orlyé F, Gutiérrez-Granados S, Martínez-Alfaro M, Mignet N, Richard C, et al. Functionalization and characterization of persistent luminescence nanoparticles by dynamic light scattering, laser Doppler, and capillary electrophoresis. Colloids Surf B: Biointerfaces. 2015;136:272–81.

20. Surugau N, Urban PL. Electrophoretic methods for separation of nanoparticles. J Sep Sci. 2009;32:1889–906.

21. Girardot M, d'Orlyé F, Varenne A. Electrokinetic characterization of superparamagnetic nanoparticle-aptamer conjugates: design of new highly specific probes for miniaturized molecular diagnostics. Anal Bioanal Chem. 2014;406:1089–98.

22. Stanisavljevic M, Chomoucka J, Dostalova S, Krizkova S, Vaculovicova M, Adam V, et al. Interactions between CdTe quantum dots and DNA revealed by capillary electrophoresis with laser-induced fluorescence detection. Electrophoresis. 2014;35:2587–92.

23. Li Y-Q, Guan L-Y, Zhang H-L, Chen J, Lin S, Ma Z-Y, et al. Distance-dependent metal-enhancement quantum dots fluorescence analysis in solution by capillary electrophoresis and its application to DNA detection. Anal Chem. 2011;83:4103–9.

24. Lin K-H, Chu TC, Liu F-K. On-line enhancement and separation of nanoparticles using capillary electrophoresis. J Chromatogr A. 2007;1161:314–21.

25. Cacho C, Markova Z, Sevcik J, Zboril R, Petr J. Study of behavior of carboxylic magnetite core shell nanoparticles on a pH boundary. J Chromatogr A. 2014;1364:59–63.

26. Alsudir S, Lai EPC. Polymer coatings for sensitive analysis of colloidal silica nanoparticles in water. Colloid Polym Sci. 2014;292:1289–96.

27. Alsudir S, Lai EPC. Hydroxypropyl methacrylate interaction and chitosan coating for enhance UV detection sensitivity of colloidal nanoparticles in capillary electrophoresis analysis. J Anal Bioanal Tech. 2015;6:242. doi:10.4172/2155-9872.1000242.

28. Li L, Yu H, Liu D, You T. A novel dark-field microscopy technique coupled with capillary electrophoresis for visual analysis of single nanoparticles. Analyst. 2013;138:3705–10.

29. Bouri M, Salghi R, Algarra M, Zougagh M, Ríos A. A novel approach to size separation of gold nanoparticles by capillary electrophoresis-evaporative light scattering detection. RSC Adv. 2015;5:16672–7.

30. Franze B, Engelhard C. Fast separation, characterization, and separation of gold and silver nanoparticles and their ionic counterparts with micellar electrokinetic chromatography coupled to ICP-MS. Anal Chem. 2014;86:5713–20.

31. Qu H, Mudalige TK, Linder SW. Capillary electrophoresis/inductively-coupled plasma-mass spectrometry: development and optimization of a high resolution analytical tool for the size-based characterization of nanomaterials in dietary supplements. Anal Chem. 2014;86:11620–7.

32. Liu L, He B, Liu Q, Yun Z, Yan X, Long Y, et al. Identification and accurate size characterization of nanoparticles in complex media. Angew Chem Int Ed. 2014;53:14476–9.

33. Wang J, Li J, Teng Y, Hu W, Chai H, Li J, et al. Studies on multivalent interactions of quantum dots-protein self-assemble using fluorescence coupled capillary electrophoresis. J Nanoparticles Res. 2014;16:2487–93.

34. Wang J, Li J, Li J, Qin Y, Wang C, Qiu L, et al. In-capillary self-assembly study of quantum dots and protein using fluorescence coupled capillary electrophoresis. Electrophoresis. 2015;36:1523–8.

35. Matczuk M, Anecka K, Scaletti F, Messori L, Keppler BK, Timerbaev AR, et al. Speciation of metal-based nanomaterials in human serum characterized by capillary electrophoresis coupled to ICP-MS: a case study of gold nanoparticles. Metallomics. 2015;7:1364–70.