



Size-based characterization of nanoparticle mixtures by the inline coupling of capillary electrophoresis to Taylor dispersion analysis



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ABSTRACT

Separation of closely related nanoparticles is still a challenging issue for the characterization of complex mixtures for industrial/research applications or regulatory purposes. In this work, the remarkable separating performances of CE were complemented with the absolute size-based determination provided by Taylor dispersion analysis (TDA) for the characterization of nanoparticle mixtures. The inline hyphenation of CE to TDA was successfully implemented for the baseline separation followed by a size-based characterization of a bimodal mixture containing two closely size-related nanolatexes (70 nm and 56 nm radii). A pixel sensor UV area imager providing three detection points along the capillary was used for a differential measurement of the peak broadening during the Taylor dispersion step. Comparison of this new technique with dynamic light scattering and hydrodynamic chromatography is also discussed.

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1. Introduction

Nanoparticles (NPs) have gained much interest in the scientific community over the last decade due to a wide variety of potential applications, notably in biomedical and material fields. NPs are of great scientific interest as they constitute a unique opportunity to fill the gap between bulk materials and molecular structures [1]. On a medical point of view, drug (or gene) delivery based on NPs allows optimal diffusion in the tissues due to their small size [2].

Conversely, this high level of penetration in the tissues may increase the general toxicity of NPs for most of the applications [3]. From a regulatory point of view, it is therefore essential to be able to measure NPs size from 1 nm to sub-micron range [4,5]. In addition to regulatory/health issues, the development of NP-based industrial applications/formulations requires suitable analytical methods for the size measurement of NP and NP mixtures. Indeed, the distribution of NP size influences rheological and solid-state properties such as transport, atomization, mechanical strength and bulk density [6]. As an example of the importance of NP distribution on the properties of application, bimodal particle size latexes have been

the subject of extensive work [7–13]. It has been shown that the latex dispersions having a well-controlled, bimodal particle size distribution are able to control the dispersion rheology, the film formation characteristics, and the final film properties [7].

Several studies were devoted to NP size characterization by capillary electromigration techniques (see e.g. Ref. [14]). Recently, capillary isotachopheresis (cITP) was used for the separation of silver nanoparticles according to their size [15]. Bouri et al. reported a simple and rapid methodology for the separation and characterization of gold nanoparticles, which differ by only 3 nm in diameter, by capillary electrophoresis–evaporative light scattering detection (CE-ELSD) [16]. The identification and size characterization of nanoparticles in complex media was also reported by using CE coupled to inductively coupled plasma mass spectrometry (ICP-MS) [17].

Several other methods such as atomic force microscopy (AFM) [18], dynamic light scattering (DLS) [19,20], analytical ultracentrifugation (AUC) [21], size exclusion chromatography (SEC) [22,23], asymmetrical flow field flow fractionation (AF4) [24], Taylor dispersion analysis (TDA) [25–29] and hydrodynamic chromatography (HDC) [30,31] were used in the literature for the NP size characterization.

While the application of HDC to NPs separations has, to date, been somewhat limited, AF4 has been used to separate colloids [32], metallic NPs [33] and biological samples [34,35], and is one of

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the most commonly used NP separation techniques. The analysis of NP mixtures by HDC is still a challenge due to the limited resolution inherent to the method [36]. DLS, also known as photon correlation spectroscopy, is one of the most popular non-separation method used to determine the size of NPs [37]. Despite being a powerful and accessible tool, DLS is known to have several drawbacks, which are inherent to the principles of the technique. Indeed, the fact that the intensity of the scattered light is proportional to the sixth power of the radius results in a bias of DLS to larger sizes [38]. A regain of interest in TDA has been recently observed. TDA is an absolute method for the determination of hydrodynamic radius (R_h) based on the dispersion of a sample plug in a laminar flow [39].

Even if recent advances describe the use of TDA for the analysis of sample polydispersity [40], TDA has the disadvantage that it can be easily disturbed by the presence of chromophoric low molar mass compounds (e.g. UV absorbing solvent) in the sample [25]. Moreover, TDA is a separation technique that is only based on dispersion, and not on retention. Chromatographically speaking, TDA has zero selectivity, since all components are unretained. Hinterwirth et al. recently reported an extensive comparative study between DLS, AF4, transmission electron microscopy (TEM) and nanoelectrospray gas-phase electrophoretic molecular mobility analysis (nES-GEMMA) for the characterization of gold NP of different diameters in the range of 13–26 nm [41].

Another alternative, which shows great promise in the ability to accurately characterize nanomolecular mixtures, is the inline coupling of CE to TDA. This method can be considered as a two-steps approach in which an electrophoretic separation is followed by online TDA. TDA allows the inline determination of the diffusion coefficient (D) of each sample zone previously separated by CE. This method was first successfully applied by Le Saux et al. for the individual diffusion coefficient measurements in polymer mixtures [42]. It was next improved on the basis of a differential measurement of the diffusion coefficient using inline two UV detection windows [43]. More recently, inline CE-TDA coupling using a single UV detection point was applied for the fast characterization of individual polyelectrolyte constituents contained in polyelectrolyte complexes [44]. Application of CE-TDA approach for simultaneous measurement of protein hydrodynamic radius and ligand-protein affinity constant was reported by Østergaard and Jensen [45].

In this work, we investigate the inline coupling of CE to TDA for the characterization of NP mixtures. The individual hydrodynamic radii of a bimodal mixture composed of closely related nanolatexes are determined in a single run using CE instrumentation hyphenated with a pixel sensor UV area imager providing three detection points along the capillary. The results obtained by CE-TDA are compared to those derived from DLS and HDC.

2. Experimental

2.1. Reagents and materials

Poly(ethylene glycol) dodecyl ether (Brij-35), sodium tetraborate ($\text{Na}_2\text{B}_4\text{O}_7$) were purchased from Aldrich (Steinheim, Germany). Sodium hydroxide (NaOH) was from VWR (Leuven, Belgium). Deionized water was further purified with a Milli-Q system from Millipore (Molsheim, France). Nanolatexes (1) and (2) (BASF, Ludwigshafen) studied in this work are anionic nanolatexes that were synthesized by seeded emulsion polymerization of styrene, butadiene and carboxylic monomers (acrylic acid, itaconic acid and fumaric acid) in the presence of DPOSNa surfactant. DPOSNa is a mixture of two anionic surfactants (80%, w/w of benzenesulfonic acid, dodecyl-, sodium salt (CAS N° 25155-30-0) and 20%, w/w of benzenesulfonic acid,

oxybis(dodecyl)-, sodium salt (CAS N° 30260-73-2)). The only difference in composition between these two nanolatexes is the level of seed and surfactant, which allows controlling the final particle size. Hydrodynamic radius determined by dynamic light scattering are 71.5 and 54 nm, respectively. The mean electrophoretic mobility of the two nanolatexes in $\text{Na}_2\text{B}_4\text{O}_7$ buffer (35.2 mM, pH 9.2) is $\mu_{ep} = -47.14 \pm 0.95 \times 10^{-9} \text{ m}^2 \text{ V}^{-1} \text{ s}^{-1}$.

2.2. Capillary electrophoresis and Taylor dispersion analysis

CE and TDA experiments were carried out with a 3D-CE instrument (Agilent technologies, Waldbronn, Germany) equipped with a diode array detector. Separation capillaries prepared from bare fused silica tubing were purchased from Composite Metal Services (ShIPLEY, UK). New fused silica capillaries were conditioned by performing the following washes: 1 M NaOH for 20 min, 0.1 M NaOH for 15 min, and water for 10 min. The temperature of the capillary cassette was maintained constant at 25 °C. Samples were injected hydrodynamically. Details on the capillary length, sample injection, applied voltage (CE mode) and pressure mobilization (TDA mode) are given in the figure captions. Inline CE-TDA experiments were also performed using the Agilent apparatus in combination with the Actipix multiple UV detector. For TDA calculation, the temporal variance (σ^2) required for the size (or diffusion coefficient) measurement was calculated by integration of the elution profile on the digitalized data points using Excel software and following Eq. (1) [46]:

$$\sigma^2 = \frac{\sum_{i=n}^{i=m} h_i(t_i - t_d)^2(t_{i+1} - t_i)}{\sum_{i=n}^{i=m} h_i(t_{i+1} - t_i)} \quad (1)$$

where h_i and t_i are respectively the detector response and the elution time for a given data point i of the Taylorgram. n and m are the starting and ending points that are considered for the integration of the Taylorgram. t_d is the average elution time (or the time at the peak apex).

2.3. Multiple UV detection points for CE-TDA experiments

Detection at multiple windows in a looped capillary was carried out with an Actipix D100 UV area imaging detector (Paraytec, York, UK). The detector uses a 9 mm × 7 mm active pixel sensor array made up of 1280 × 1024 individual 7 μm pixels. Pixel binning by a factor 10 in the row dimension parallel to the axis of the capillary gives 128 × 1024 effective pixels. Each column of effective pixels provides zones for both sample and reference, and this self-referencing process ensures good signal-to-noise ratios independent of any fluctuations in light source intensity [47]. The light source was a pulsed xenon light source and wavelength selection was via a 214 nm interference filter with 10 nm band pass (full width at half-maximum). A notch was made in the standard Agilent capillary cassette allowing the capillary to be lead out of the side of the cassette. The capillary was inserted and detection windows aligned in the Actipix Cartridge allowing three-point detection before returning it into the capillary cassette. Three detection windows were placed at 27 cm (1st detection point), 42 cm (2nd detection point) and 57 cm (3rd detection point) windows on a 94 cm fused silica capillary × 26 μm I.D. (365 μm O.D.). Each capillary window was made by burning the polyimide coating on a 1.5 cm width.

2.4. Hydrodynamic chromatography

The determination of the particle size distribution was also carried out by means of HDC using a Particle Size Distribution Analyser (PL-PSDA, Varian Deutschland GmbH) with a cartridge type No. 2

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