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Parallel differential mobility analysis for electrostatic characterization and manipulation of nanoparticles and viruses

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Abstract

The electrophoretic mobility of charged, airborne nanoparticles (NPs) or macromolecules and their specific complexes opens new avenues for their analysis and handling. The newly developed parallel differential mobility analyzer in combination with an electrostatic particle sampler enables not only the characterization of bio-NPs, but even their sampling while preserving their bioactivity (e.g., the enzyme activity of galactosidase). Precondition for the applicability of this technique is a well-defined charging status of the NPs in question. This charge conditioning can be achieved by means of a radioactive source, Po-210, even if the yield in terms of charged particles is low for sub-20-nm particles and the aging of the source influences the size spectra measured. Nevertheless, this technique enables size-defined sampling and enrichment, combined with real-time measurement of the size of both NPs and viruses. Furthermore, it allows determination of the number of attached biospecific antibodies, thereby providing information about the surface coverage of viruses by antibodies.

Keywords

Antibody; Bio-NP; Differential mobility analyzer; Electrophoretic mobility; Electrostatic particle sampler; Gas-phase electrophoretic mobility molecular analyzer; GEMMA; Macromolecule; Nanoparticle; Parallel differential mobility analyzer; Virus

1. Introduction

Real-time measurement of airborne nanoparticles (NPs) and viruses based on techniques utilizing the electrophoretic mobility of a charged particle in a defined electrostatic field appears to be one of the best approaches currently available. Electrophoretic mobility analysis is a technique not only well-suited for size analysis but also for semi-preparative collection of airborne NPs [1–3]. Originally, this method was developed primarily to measure ions in gases and in the atmosphere [4,5].

Rohmann [6] was among the first to utilize this technique for the observation of airborne particles. The idea was then taken up by Liu and Pui [7] and Knutson and Whitby [8] – the modern differential mobility analyzer (DMA) for aerosol particles was created.

The beauty of this technique lies in its simplicity. The usual arrangement comprises co-axial placement of a cylindrical, larger outer electrode and a thinner inner electrode with an electrostatic field between them, which is well-defined by the voltage, V , applied to the inner electrode. Commonly, there is a constant laminar flow of particle-free air coaxial with the electrodes. The introduction of small air flow containing charged NPs between the electrodes results in their movement, which is determined by both the laminar air-flow velocity (v_f) and the drift velocity (v_e) in the electric field (Fig. 1(a)). When the voltage applied to the inner electrode is changed continuously, particles with different, well-defined electrophoretic mobilities corresponding to particles with defined sizes [7,9] will leave the DMA system at the particle-outlet slit placed at the bottom of the inner electrode and may consequently be monitored, analyzed and further manipulated [1,2,10].

Subsequently, numerous designs of DMAs have been reported in the literature [3,7,10–16]. Obviously, the utilization of the electrophoretic mobility technique to measure airborne “nano-species” is being developed and refined. To date, precise measurement of equivalent particle sizes in terms of electrostatic mobility [16] even below 1 nm has been achieved.

The condition *sine qua non* for the utilization of an electrostatic field for NP measurement is a known, well-defined and experimentally repeatable charge level of the particles in question. Ideally, a highly efficient charging process resulting in a single charge per particle, entirely independent of its size and chemical-surface composition, would be desirable. Unfortunately, such results cannot be achieved by any currently known particle-charging method. A number of approaches have been investigated [17–23,25]. However, the most popular method is the diffusion charging of particles in a bipolar ion atmosphere, which can be obtained by means of a radioactive source, typically Po-210 (solid, α -radiation), or Kr-85 (gas, β -radiation). The relative ease of use and the well-defined Boltzmann charge equilibrium [24] is offset by the very low charging probability for particles with sizes smaller than about 20 nm [11,24] and the safety issues associated with radioactive sources. Po-210 is rather easy to handle, but has a relatively short half-life time. Am-241 radiation is a more convenient alternative for the charge-conditioning process due to its comparatively long half-life time. However, because of a certain amount of γ radiation, besides the α radiation (5.48 MeV α particles and 59 keV γ emission), the use of this element is not too well-appreciated for NP-charge conditioning.

A prerequisite for the electrostatic characterization of NPs, as discussed here, is the necessity to aerosolize them. This can be achieved by means of aerosol generation using an electrospray device (Fig. 1a) from NP suspensions and/or solutions [1,26,27]. This technique has proved useful to characterize proteins [1], protein complexes [1,28], DNA [29], dendrimers [30], bacteriophages [31], viruses and virus fragments [1] and inorganic particles [17]. Because electrostatic characterization of aerosols is performed at ambient pressure, this technique offers an opportunity for the measurement, sampling and enrichment of NPs or biomolecules from heterogeneous mixtures without any vacuum and is also very useful as a tool complementing mass spectrometry. Because NPs of a particular size can be sampled and enriched, electrostatic characterization of aerosols can also be used as a micro-preparative device. The latter approach can deliver purified, uniform nanomaterials, which are practical for various biochemical, chemical and nanotechnological tasks.

2. Electrostatic nanoparticle handling

Based on the above mentioned points, a parallel differential mobility analyzer (PDMA) [32] that enables simultaneous characterization of an entire initial NP population together with simultaneous sampling and enrichment of a well-defined specified particle size class was designed and constructed. The PDMA scheme and the outline of operation are shown in Fig. 1(a).

First, the NP sample of interest is aerosolized using an electrospray source, run in the cone-jet mode, followed by charge reduction to mainly singly-charged particles by means of the Po-210 source [19,24]. The second and main part, in which the singly-charged NPs are introduced, comprises two nano-DMAs (nDMA1 and nDMA2) with an identical geometry and operating in parallel under identical hydrodynamic conditions. These nDMAs are built in-house based on an earlier design [12] that was optimized to work in a size range of 0.8–90 nm. The central electrodes of both nDMAs operate with positive high voltage (HV) polarity, thereby analyzing and separating the negatively-charged NP fractions. As a detection device, an aerosol electrometer based on the Faraday Cup (FC) principle is used. It has to be kept in mind that the measurable parameter is the electrophoretic mobility of the particle in question, which may be converted into an equivalent particle size – electrophoretic mobility diameter (EMD) [1,9,30,33].

Spherical inorganic silica particles [Ludox SM30 (SM), HS40 (HS) and AS40 (AS), Sigma-Aldrich], proteins [bovine serum albumin (BSA), enolase, ferritin (FER), β -galactosidase and macroglobulin (MGL), Sigma Aldrich], virus-like particles (VLPs) and synthetic bioorganic NPs in suspension, namely dendrimers (PAMAM) [generation 6 (G6) and 7 (G7), Sigma Aldrich] were used in these experiments. The particles were aerosolized from a diluted (~50 $\mu\text{g/mL}$) aqueous NP solution or suspension using a commercial electrospray aerosol generator (EAG, Model 3480, TSI Inc). As a buffer, an aqueous 20 mM ammonium acetate solution with a pH value of 6.5 was chosen for all particles analyzed. For silica NPs, it was adjusted to a pH value of 9, in order to ensure the negative charge of these NPs in the solution and to prevent aggregation.

The EAG was operated in the so-called Taylor-cone jet mode [34–36], which yields uniform primary nanodroplets with diameters of about 160 nm. This setting was advantageous for the aerosol generation in terms of particle concentration and low abundance of unspecific aggregates. A Po-210 α -radiation source was used in the EAG in order to obtain charge equilibrium [24] on the originally highly and arbitrarily charged aerosolized particles that were produced by the electrospray process. The radioactive source generated a cloud of highly concentrated bipolar ions from surrounding air and solvent molecules. Aerosolized droplets or particles exposed to this cloud eventually collided with ions and thus acquired or lost charges. This process is called bipolar diffusion charging [5,14,24]. Thorough investigations of the functional dependency of charge state on particle size were made [19,37–39]. The bipolar diffusion-charging process (assuming that Boltzmann charge equilibrium has been reached) yields an unambiguous particle-size spectrum from the measured electrophoretic mobility [1,3,11,32]. This size spectrum can even be transformed into molecular mass information of NPs in question [1,2,26,27].

An example of the quality of the measured size spectra [sometimes also called gas-phase electrophoretic mobility molecular analyzer (GEMMA) spectrum] is shown in Fig. 2 for enolase, ferritin and silica particles. Next to the pronounced monomer peak (single molecule or particle, singly charged, “m”), a dimer peak (also singly charged, but containing two molecules or particles, “d”), but with much smaller abundance, was measured. The relative height of the dimer peak to the monomer peak is mainly a function of the concentration of the particles in the spray solvent. Increasing the dilution of the sample decreases the probability of forming dimers. However, as a consequence, the absolute abundance of detected monomers per volume (determined in terms of charges with the FC detector or particles with a condensation particle-counter detector) decreases.

To verify the ability of the PDMA (and other DMAs) to size-characterize NPs and to sample or to enrich specific NPs for micro-preparative applications, it is necessary to remove and to collect the electrostatically-selected size class of NPs from the gas phase after electrostatic size separation. It was reported [40] that many simple mechanical particle samplers have collection efficiencies of less than 10% for particles with sizes below 100 nm. In order to collect those particles by mechanical methods, the use of micro-orifice, special virtual or low-pressure impactors [41,42] is necessary. Another possibility is to utilize an electric field because all electrostatically-classified particles are then charged (in the size range applied in this work, practically all particles are singly charged or neutral [19,24]).

For collecting silica particles, we used the electrostatic NP sampler (ENS) built in-house and shown in Fig. 1(b) [42]. It was operated with a 2-kV deflection voltage applied to a transmission electron microscopy (TEM) grid (BalTec S160, 3 mm diameter, ~20 nm carbon film). The electric field was oriented orthogonal to the air flow that carried the silica NPs and came from the nDMA (nDMA2 separation). Fig. 3(a) shows the TEM image of the silica NPs in the stock suspension before spraying. Visual inspection of this picture may suggest that all particles are of exceptionally similar size. Nonetheless, a PDMA spectrum of this suspension exhibits a broad peak around 17 nm (maximum) with full width at half-height in the range ~13–22 nm, indicating the broad size distribution. Fig 3(b) shows the TEM image of particles collected by the ENS on the TEM grid after the PDMA

classification at 17 nm. Here, all particles are *de facto* of one size. However, due to the limited diffusion-charging efficiency of NPs of this size [17,24], the collecting yield is low. This is easily compensated for by longer collection times (usually only nL/min sample solutions were consumed and several μ L-sample solutions were available). A similar experiment was performed successfully with a tobacco mosaic virus sample [2].

In the case of bio-NPs, it seems advantageous to transfer and to collect them into a liquid environment for further investigations. This is necessary on the one hand to preserve the biological activity of proteins, enzymes and viruses, and on the other hand to enable further characterization steps without a hard impact due to collection process.

Liquid impingers of various designs are traditionally used for collecting μ m and sub- μ m particles from the gas phase [40,43,44,46,47]. However, investigation has shown that the sampling efficiency of such samplers – as their sampling mechanism relies mainly on inertial forces – rapidly drops below 100 nm in terms of particle diameter, which shows that they are not suited to bio-NP sampling [40].

Based on this rationale, another electrostatic NP sampler (liquid ENS) for collecting charged nm-sized particles from gas into liquid (water) phase (Fig. 1(c)) was designed and its sampling efficiency evaluated with proteins, enzymes, inorganic silica particles, and dendrimers in a size range 5–25 nm [44,45].

This in-line liquid ENS (Fig. 1(c)) utilizes a collection liquid to provide a surface for “soft landing” of the particles investigated. The liquid has to offer electrical conductivity and physiological conditions suitable for bio-NPs in order to preserve the biological activity of the sampled biomaterial. We used a 20-mM aqueous ammonium acetate solution with a pH of 6.5. An electrostatic field was applied between the nozzle outlet and the liquid surface by a platinum wire that introduced positive high voltage in the range 0–3 kV to the collection liquid. The liquid itself was contained in a 1.5-mL Eppendorf vial at the bottom of the glass impinger. The size-selected NPs entered the liquid ENS through a nozzle of 4-mm inner diameter. Its exit was located 10 mm above the aqueous surface and thus caused the flow streamlines to follow a sharp turn at the liquid surface and exit the ENS through its outlet (Fig. 1(c)). The collection efficiency of the liquid ENS vs. particle size and voltage applied to the liquid was carefully evaluated [45]. The results are summarized in Fig. 4.

The collection efficiencies of the liquid ENS as a function of NP size for different applied voltages increase with an increase of voltage and a decrease of particle diameter. It is evident that the collection efficiency of an in-line (impacting particles orthogonal to the water surface) liquid ENS operating without the applied electrical field goes towards zero. However, when using relatively small voltages, the sampling efficiency approaches 100%. The data for the different types of NPs also suggest that the electrical collection performance depends on particle diameter only, and not on the particle material.

In addition, an experiment to confirm the presence of collected NPs in the liquid and, in case of enzymes, their biological activity, was carried out by applying an enzyme-activity assay. This approach proves not only the presence of sampled NPs, but also addresses the question

of preserving the biological activity after aerosolization, charge conditioning, electrostatic separation and sampling.

In order to verify the “soft” collection of functional bio-NPs and the preservation of the biological activity, an aerosol containing β -galactosidase was electro-sprayed, and then partly size-separated and sampled in two subsequent experiments. First, the liquid ENS was positioned directly behind the electrospray (with charge conditioning using Po-210) device outlet, and then behind the PDMA classification. The sampling times were 2 h and 28 h respectively, to accommodate the low charging probability of NPs [24]. The relative enzyme activity of the sampled solution compared to the electrosprayed solution was calculated according to following equation:

$$Ac = \frac{\frac{Ab_s}{ti_s}}{\frac{Ab_e}{ti_e}} \times \frac{V_s}{V_e}$$

where: Ac is the relative activity of the sampled-solution related to the electrosprayed solution; Ab is the absorbance of free *ortho*-nitrophenyl- β -galactopyranoside (OPNG) after incubation time for the sampled solution (s) and the electrosprayed solution (e); ti is the time of incubation ((e) just electrosprayed solution and (s) sampled solution); and, V is the volume of the electrosprayed solution (e) and volume of the sampled solution (s), during the sampling process.

The relative activity for both experiments reflects the amount of intact sampled β -galactosidase molecules per intact electrosprayed β -galactosidase molecules and thus directly reflects the sum of losses of β -galactosidase molecules via transmission through the PDMA system and diffusion at tubing walls as well as losses of enzyme activity caused by the electrospray and charge-reducing process and the sampling process.

β -galactosidase enzyme activity was determined with a commonly-used photometric enzyme-activity test protocol, which determines the amount of released *ortho*-nitrophenole from the OPNG at 405-nm wavelength. Incubation time was 15 min for the stock solution and the liquid ENP sampled solution after the electrospray process and 12 h for the sampled solution after the selective sampling procedure.

The relative activity determined for the first experiment of the ENS located for a sampling period of 2 h right after the EAG device was found to be 5.8% and, following the PDMA, 0.04%. This agrees quite well with the diffusion-charging probability of about 5% for NPs of 8 nm using a radioactive source [19,24,37,48]. The fact that only negatively-charged particles were sampled by the positively-charged liquid surface inside the liquid ENS leads to the conclusion that all particles of the investigated fraction were sampled and that the biological activity of the sampled solution was unaffected by the aerosol-generation process.

The value of activity after the PDMA is also very likely to reflect the diffusion losses and maybe the influence of the extended sampling time (loss of enzyme activity). Once again, this demonstrated the low effectiveness of diffusion-driven charging for sub-10 nm particles,

which is unquestionably the weakest point in the otherwise very successful method for the characterization of airborne bio-NPs.

The problem of the methodology described increases with the decay of the activity of the radioactive Po-210 source used for charge conditioning of NPs.

3. Impact of aging of the radioactive source on measured spectra

As mentioned above, probably the most frequently-used radioactive material for the charge conditioning of NPs is Po-210, probably because this material is a pure α -emitter, which decays to a stable daughter isotope Pb-206, that it is inexpensive and not hazardous outside the body. The drawback of Po-210 is its rather short half-life time of 138.4 days.

We looked into the influence of the aging of the Po-210 source on the measured size spectra. Decreasing radioactivity results in reduced concentrations of the generated ions, which are needed for two processes in the EAG:

- (a) to decrease charges on electro-sprayed, drying droplets to prevent their explosion at the Rayleigh limit [49,50]; and,
- (b) to obtain charge equilibrium [24] for the final NPs, enabling their electrophoretic mobility determination.

Consequently, the NP-size distribution entering the electrostatic classification device, (e.g., PDMA or GEMMA) can be obtained.

In order to evaluate the aging effects of the Po-210 radioactive sources, three different sources of identical type but different age were used. Their radioactivities weakened to 3.5%, 10.5%, 22%, 64% and 86% of their initial activities of 5 mCi. The aging effects were evaluated for three different proteins (BSA, enolase and ferritin). Fig. 5(a) shows the changing size spectra of the same material (BSA) caused by the aging of the radioactive source. It is evident that the use of aged radioactive sources increases the amount of doubly-charged and sometimes even higher-charged monomers, eventually dominating the size spectrum (for radioactive Po-210 sources older than three half-life times with reference to the original radioactivity).

Further experiments with enolase and ferritin shown in Fig. 5(b) confirmed the finding. It is evident that in the electrospray arrangement used in this study in order to maximize the amount of monomers, the radioactivity of the α -radiation source used should be about 5 mCi. Otherwise, the advantage of the charge reduction yielding simple size spectra decreases (the problem of deconvolution of multiply-charged high-molecular-weight mass spectra is well known in electrospray ionization mass spectrometry, and unsolved).

4. Characterization of biospecific virus-antibody complexes

Finally, we address the unique possibility of characterizing airborne viruses (human rhinovirus, HRV) and to determine the attachment of specific antibodies (monoclonal antibody mAB-8F5) using the electrostatic sizing technique presented, based on the DMA concept and known as GEMMA. This method can be applied not only to determine the size

of globular viruses [1,51], but also to investigate the surface coverage of viruses with specific antibodies [32]. The HRV was incubated with a specific mAB at different molar ratios and the products of this incubation were size analyzed. Fig. 6 shows the size spectra of plain HRV (peak at 29.8 nm), HRV with complete surface coverage with mAB (peak at 35.6 nm) and an intermediate coverage situation (peak at 34.2 nm). Because no further increase in the measured size beyond the value of 35.6 nm of the HRV-mAB complex was observed upon increasing the concentration of antibodies (or ratio), it was assumed that the surface of the virus was saturated. This observation indicates also that such a biospecific complex can survive the electrospray process and complete passage through the device.

Many viruses and their complexes with antibodies or receptors possess approximately spherical shape. This allows conversion from a measured EMD to the volume equivalent diameter [52]. Measuring the EMD of the antibodies and assuming that the volume of the complex (HRV and mABs) is the sum of the volume of “plain”, antibody-free viruses and that of the attached mABs, one can calculate from the increase in the measured EMD of the virus the number of attached antibodies [32]. This can be done assuming that no significant conformational changes – that might change the volume or density during the attachment process – would occur. Consequently, if the experimentally-determined maximum number of attached antibodies is in agreement with the theoretical prediction, it could be deduced that no conformational changes occur during the attachment process. In the case of the HRV-mAB complex, this was corroborated by an orthogonal method, namely cryo-electron microscopy [53].

5. Conclusions

The electrostatic methods of aerosol science have proved to be an extremely useful tool for a number of applications beyond the original field of research. One could say that electrostatic size classification of airborne NPs was born in aerosol science, but is maturing in analytical chemistry.

The analysis of macromolecules and bio-NPs by electrical means discussed here seems to offers the possibility not only to complement mass spectrometric and liquid-phase separation techniques, but also, because measurements are performed at ambient pressure, to open the way to a wide spectrum of applications. It is also important to realize that non-volatile contaminants (e.g., sodium phosphate or ionic detergents) have to be avoided or may be present in the sample at low concentrations only. Otherwise, the determined particle size is too high. What still limits this technique is the low efficiency of charging processes for NPs available. Once better charging methods in the NP range are accessible, electrophoretic mobility could also be a major preparative tool for nanotechnological applications.

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Figure 1.

(a) Electrostatic aerosol generator with parallel differential mobility analyzer (EAG-PDMA) system, indicating some particle trajectories consisting of scanning nanoDMA (nDMA 1) with a Faraday cup (FC) detector and separation nanoDMA (nDMA 2) for electrostatic sampling; (b) transmission electron microscopy electrostatic nanoparticle sampler (TEM-ENS); and, (c) liquid ENS sampler for collection of bioactive compounds.

Figure 2. Size spectra of enolase, Ferritin and silica particles determined with the parallel differential mobility analyzer (PDMA) system.

Figure 3. Transmission electron microscopy (TEM) images of silica particles (400×400 nm): (a) stock solution of particles before introduction in the parallel differential mobility analyzer (PDMA); and, (b) size-selected (17 nm) and collected silica particles on TEM grid by the electrostatic nanoparticle sampler (ENS).

Figure 4. Sampling efficiency of the liquid-electrostatic nanoparticle sampler (ENS) vs. particle size (derived from different classes of nanoparticles: BSA, FER, monomers of G6, monomers (G7M) and dimers (G7D) of G7 dendrimers, MGL, VLP and silica particles AS, HS and SM) for various applied voltages.

Figure 5.

(a) Changing size spectra of bovine serum albumin (BSA) as a function of the nanoparticle size due to the different age of the Po-210 source in the EAG ($n = 1$: singly-charged particles; $n = 2$: doubly-charged particles; and, $n = 3$: triply-charged particles); and, (b) increasing concentration of doubly-charged ($n = 2$) nanoparticles (Enolase, Ferritin) as a function of age (in term of multiples of the half-life time).

Figure 6.

Size spectra from the gas-phase electrophoretic mobility molecular analyzer (GEMMA) of the human rhinovirus (HRV) showing the increasing antibody (mAB-8F5) attachments indicated by the size changes from the plain virus to a virus with a complete surface coverage by the virus-specific antibody (mAB-8F5).