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TRENDS

Nanoparticle: is it promising in capillary electrophoresis?

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Introduction

Separation sciences progress with size. On the one hand, extensive efforts devoted to miniaturization of analytical instruments have significantly promoted the development of this field. On the other hand, wide applications of novel materials with size at the sub-micron level as separation media have offered more and more opportunities for solving separation puzzles. The potential of nanostructured materials, e.g., nanoparticles (NPs), in chromatographic and electrophoretic techniques has gradually been discovered in recent years. NPs usually refer to a kind of nanomaterial with a spherical-like appearance measured in nanometers, sometimes up to 1500 nm, with a large surface-to-volume ratio and other fascinating properties derived from the "quantum size effect". Existing NPs comprise the following [1–3]: fullerene NPs, silica NPs, precious metal NPs, metal oxide NPs, semiconductor quantum dots, and polymer-based NPs (i.e., polymer NPs, molecular micelles, molecularly imprinted polymers, and dendrimers). Surface modification with functional groups and/or molecules is a key procedure to prevent the prepared NPs from aggregation and to control the particle size, and also provide extra selectivity when the NPs are used as separation media. NPs are mostly stabilized by steric exclusion and electrostatic repulsion. A great breakthrough giving deep insight into the structure of nanometer-sized gold particles protected by *p*-mercaptobenzoic acid (p-MBA) has been achieved recently [4]. The prepared NP comprises 102 gold atoms and 44 p-MBAs (Fig. 1). The central gold atoms are packed in a Marks decahedron, surrounded by additional layers of gold atoms in unexpected geometries. The p-MBAs interact not only with the gold but also with one another, forming a rigid surface layer. It is interesting that particle aggregation can be utilized in sensitive detection of particular molecules, which can induce NP aggregation indicated by solution color change and monitored by electron microscopy [5].

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Applications of NPs in capillary electrophoresis

Various NPs have been employed in capillary and chip-based electrophoresis for improved separation with higher efficiency and selectivity and better reproducibility, due to their large surface-to-volume ratio and their favorable surface chemistry. They serve either as inner surface coating in permanent or dynamic mode, or as a pseudo-stationary phase added to the buffer and used in partial filling or continuous filling form. Here, we take gold NPs as an example to demonstrate the applications of NPs in capillary electrophoresis (CE). Citrate-stabilized gold NPs with average diameters of 18 nm and 10 nm have been used as anionic surface coating in normal and chip-based CE, respectively, with poly(diallyldimethylammonium chloride) as the first cationic layer [6, 7]. Self-assembly via S–Au covalent bonding was used to prepare single and multiple gold NP layer-coated capillaries with alkanethiol as the outermost layer exposed to the solution phase for separation

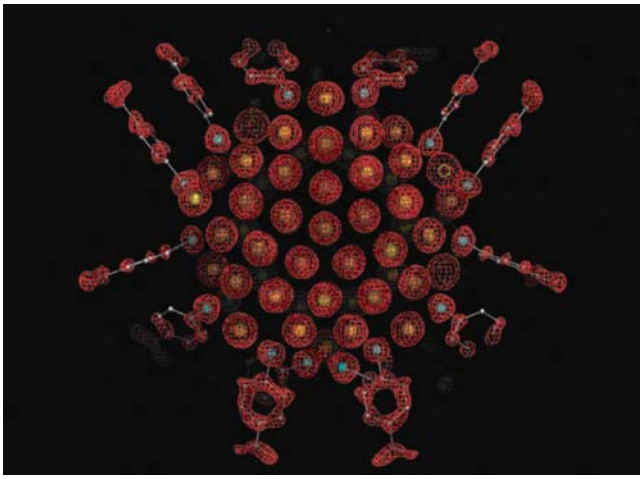

Fig. 1 Electron-density map (*red mesh*) and atomic structure (*gold atoms depicted as yellow spheres, and p-MBA shown as framework and with small spheres [sulfur in cyan, carbon in gray, and oxygen in red]*) of the $Au_{102}(p\text{-}MBA)_{44}$ NP (reprinted with permission from Ref. [4])

of neutral compounds [8, 9]. To further improve the sample loading capacity and stationary-to-mobile phase ratio of gold-NP-coated capillaries, Yang et al. [10, 11] incorporated sol–gel technology into the capillary inner wall processing procedure or used a capillary etched with ammonium hydrogen difluoride. 3-Mercaptopropionate-stabilized gold NPs (5 nm) were successfully utilized as buffer additive for improved separation efficiency and analytical precision for various aromatic amines [6]. Yu et al. [12] reported their achievement in separation of acidic and basic proteins by surfactant-capped gold-NP-filled CE, in which gold NPs served as both dynamic coating and capillary filling solution. Another important application of gold NPs is as a pseudo-stationary phase in the presence of poly(ethylene oxide) (PEO) for double-stranded DNA separation. NP–polymer composites are formed via non-covalent bonding to stabilize the NP and to provide strong interactions with DNA molecules. Gold NPs can enhance the interactions between DNA and PEO adsorbed on the NP surface, and thus improve the sieving ability of PEO but without marked change in its viscosity. In other words, separation efficiency obtained by using PEO of lower viscosity combined with gold NPs is comparable with that provided by more viscous PEO alone, but the analysis is faster in less viscous matrices. Moreover, it is easier to fill and refresh the capillary with less viscous polymer. Figure 2 shows the significant improvement in resolution of DNA fragments in the presence of gold NPs [13]. Recently, sieving matrices for single-stranded DNA based on gold NPs and a quasi-interpenetrating network composed of linear polyacrylamide and poly-*N*, *N*-dimethylacrylamide have been reported [14]. Moreover, gold NPs were used as a modifier of stacking and separation buffers for on-chip trace analysis of DNA with electrochemical detection [15]. Detection sensitivity and reproducibility were further improved by use of a gold-NP-modified microelectrode rather than a bare electrode.

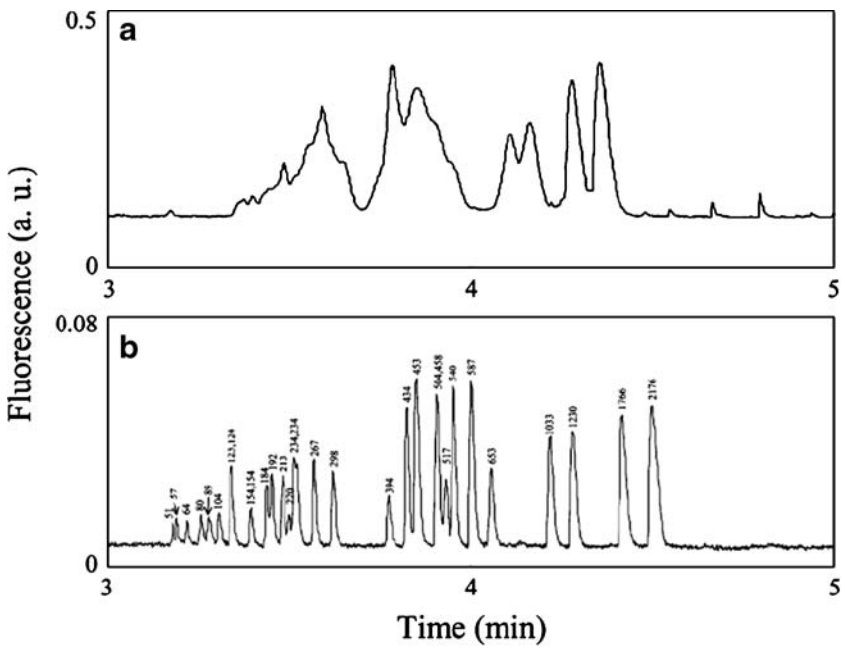

Fig. 2 Separations of 10 μg mL^{-1} DNA markers V (pBR 322/*Hae*III digest) and VI (pBR 328/*Bgl*I and *Hin*fI digest) using (**a**) 0.2% PEO (8 MDa) and (**b**) 0.2% PEO (8 MDa) containing 0.3×56 nm gold NPs. Electrophoresis conditions: PEO was prepared in 25 mmol L^{-1} glycine, pH 9.0, containing 0.5 μg mL^{-1} ethidium bromide; electrokinetic injection at 1 kV for 10 s; separation at 15 kV in a 40 cm long (30 cm to the detector) fused-silica capillary of 365 μm o.d. and 75 μm i.d. (reprinted with permission from Ref. [13])

Challenge and perspective

Basic requirements for NPs suitable for use in CE include [16]:

1. acceptable stability in a variety of electrolytes;
2. discriminating interactions with the analytes;
3. different mobility from that of the electroosmotic flow;
4. equal mobility to prevent band broadening;
5. small mass-transfer resistance;
6. no disturbance on detection; and
7. large surface area.

Among these issues, the negative effect of NPs on detection because of the light-scattering problem in ultraviolet detection and interference with the ionization process in mass spectrometric detection has proved to be the major drawback of NPs for CE application. Although the partial filling technique has been utilized to avoid NPs passing through the detection window together with the analytes, the time-consuming optimization for partial filling is tedious and sometimes resolution is not as good as that for continuous filling. Fluorescence and electrochemical detection may be reasonable choices to overcome the detection problem to some extent. 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. Future studies on NPs and their applications in CE should cover the following topics.

1. Synthesis of smaller, more porous, and more monodisperse NPs for faster mass transfer, higher sample capacity, and narrower band broadening.
2. Design of highly selective interaction sites on the surface of NPs for on-line preconcentration and screening of target compounds such as biomacromolecules and small drug molecules. Immobilization of aptamer and antibody on the particle surface and preparation of surface-imprinted core/shell NPs are promising strategies for separation with high selectivity.
3. Further application of NPs in chip-based electrophoresis for faster separation. In-situ synthesis of NPs in chips will eliminate tedious solution-transfer procedures.
4. Analysis of nanomaterials by NP-based CE techniques. This topic involves classification and characterization of nanoparticles of different sizes, separation and purification of nanomaterials of different shapes (e.g., nanorod, nanotube, nanobelt, and nanocage), and determination of some important properties of interesting nanomaterials.
5. Applications of NPs in highly sensitive detection of a variety of analytes. As mentioned above, fluorescence and electrochemical detection are favorable choices in NP-based CE analysis. Utilizing the fluorescence-quenching effect of NPs towards specific molecules and/or fluorescence resonance energy transfer between NPs and analytes may offer sensitive on-line detection strategies. Some NPs with electrocatalytic activity are suggested for use as electrode modifiers to improve detection sensitivity.

With the development of materials science, more and more novel NPs will be proposed and employed in separation science.

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