Chapter 17

Capillary Electrophoresis in Nanotechnologies versus Nanotechnologies in Capillary Electrophoresis

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Additional information is available at the end of the chapter

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Abstract

Nanomaterials are attracting an interest of many researches. All this attention is due the unique physical and chemical properties of nanomaterials differing significantly from the bulk materials mainly due to their size in range of nanometers. Capillary electrophoresis (CE) is a powerful, well-established analytical technique that provides numerous valuable benefits over other separation methods including high-performance liquid chromatography. The connection between CE and nanotechnology can be approached by two strategies: (i) CE analysis of nanomaterials and (ii) nanomaterials for CE improvement. The first perspective focuses on uses of CE as a method for characterization employed during nanomaterial production and modification as well as for monitoring their properties and interactions with other molecules. The second viewpoint deals with applications of nanomaterials for improving CE performance, mainly by enhancing efficiency of separation using nanomaterials as a stationary or pseudo-stationary phase and by enhancing detection sensitivity and/or selectivity in both optical and electrochemical detection. Moreover, applications of nanomaterials for sample preparation before CE analysis will be mentioned. This chapter aims at highlighting the symbiosis of CE and nanotechnology as a combination of modern, progressive field with well-known and reliable analytical method.

Keywords: capillary electrophoresis, nanomaterials, separation efficiency, sensitivity

1. Introduction

The very first nano-scientist was a Roman potter, who made the Lycurgus Cup as the oldest known application of nanomaterials (fifth-fourth century B.C.). This cup was made from so-called "gold-ruby glass" containing tiny gold droplets (5–60 nm in size). Therefore, the glass appeared green in daylight (reflected light), but red when light was transmitted from the inside of the vessel [1]. In spite of the fact that we do not know the name of the potter, which is based on nano-research

without the knowledge of nanoparticles, Richard Feynman opened "nano-window of twenty-first century" with his lecture "There's plenty of room at the bottom". This lecture came to be looked upon as the starting point of nanoscience as we are already living in [2]. In 1974, Taniguchi used the term "Nanotechnology" for the first time. This term was defined as the technology, where dimensions, within the range of 0.1–100 nm, play a key role. At the nanolevel, gravity is less an issue while the strength of materials is a bigger one and also quantum size effect is a key aspect. Due to the unique size-dependent spectroscopic, electronic, and thermal features and also chemical properties, and ability to be functionalized, arising from the small sizes and large surface-to-volume ratio, nanomaterials found their applications not only in electronics, physics, and engineering but also in natural sciences. Although nanomaterials are greatly affecting numerous scientific fields, it can be perceived differently. In chemistry, the range of sizes has been associated with colloid solutions, micelles, polymeric molecules, and also large molecules, or aggregates of number of molecules. Recently, structures such as carbon nanotubes, silicon nanorods, and semiconductor quantum dots have been emerged as particularly interesting classes of nanomaterials. In physics and electrical engineering, nanoscience is most often associated with quantum behavior, and the behavior of electrons and photons in nanoscale structures. Biochemistry and biology is interested in nanostructures such as cells components. The most widely investigated biological structures including DNA, viruses, and subcellular organelles can be considered as nanostructures [3].

1.1. From nano-pottery to modern analytical tools

It is obvious that "nano" influences the whole scientific world including instrumental analytical chemistry. Due to above-mentioned unique properties, not only new approaches and assays are being developed, but also standard techniques have been upgraded and capillary electrophoresis (CE) belongs to the group of these highly affected methods. In 1981, and since then, this powerful analytical technique progressed significantly not only in instrumentation, but also in method development, data acquisition, and processing. The group of applications has also widened markedly. The applications of CE are covering huge number of analytes from inorganic ions [4–8] and organic molecules [9–11] to biomolecules such as proteins [12–14] and DNA [15–17]. The golden era of CE was in 1990s, during the Human Genome Project [18]. The sequencing of the whole human genome was successfully finished in 2006 identifying all 20,000–25,000 genes (approximately) in human DNA and determining the sequences of 3 billion base pairs that make up human DNA.

Next great boom of CE begun due to the micro-total analysis system (μTAS) concept [19]. Due to the relatively simple instrumentation and ease of miniaturization of CE, the fast growth of attention in microfluidics and particularly in chip-based CE [20–23] was observed. Even though CE provides rapid results with high efficiency and resolution, and sample consumption is low; advantages of high number of theoretical plates can be diminished by relatively low sensitivity of commonly used photometric detection systems [24]. Therefore, new approaches improving these weak sites are investigated and the use of nanomaterials is widely tested.

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2. Capillary electrophoresis

Capillary electrophoresis is an extremely powerful microcolumn separation technique, separating molecules based on their mobilities in the electric field. Its main advantages include high separation efficiency, short time of analysis, and low consumption of chemicals.

Classical CE separation takes place in a fused silica capillary with internal diameter of 20–100 μm, where the voltage of up to ±30 kV is applied. The scheme of the setup is shown in **Figure 1**.

Diversity of detection modalities applicable in CE is very wide. Optical detection methods including photometric and fluorimetric detection are probably the most common ones currently used in CE; however, electrochemical detection including amperometric and contactless conductometric detection have unparalleled advantages. Especially for analysis of small inorganic ions, which do not absorb light, electrochemical detection is an alternative to the indirect optical approach. Also, popularity of mass spectrometric (MS) detection coupled to CE increased rapidly in past few decades.

From the very beginning, electromigration methods benefited from the use of certain sieving media, such as paper or gel. Moreover, since the separations have been transferred to capillary and/or chip, the addition of some kind of "stationary phase", sieving media or pseudo-stationary phase increased the number of applications. This step led to rise of several electrophoretic methods such as capillary electrochromatography or capillary micellar electrokinetic chromatography.

Low sensitivity, which is probably the main weakness of CE in connection with the most wide spread detection method—spectrophotometric detection—is caused by the short optical path-length (given by the capillary diameter) and the low sample volume that is injected.

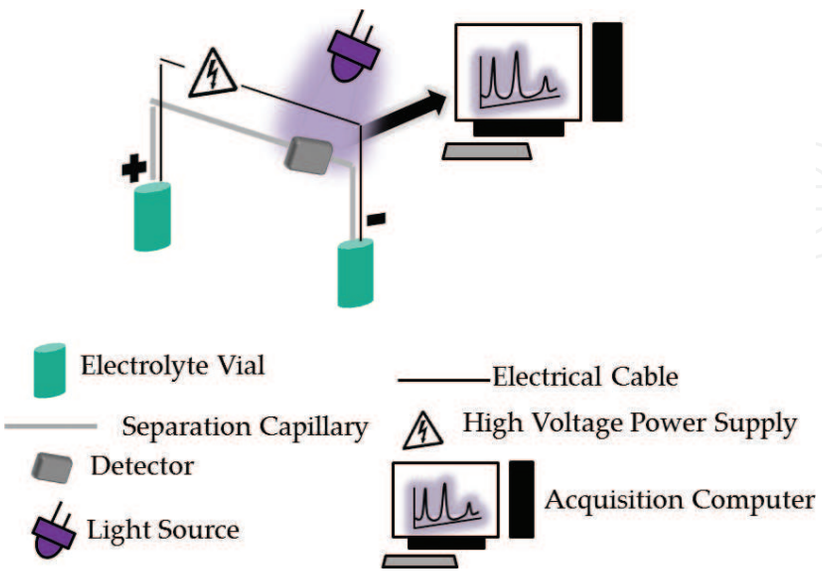

Figure 1. Scheme of CE setup.

Therefore, a preconcentration step is usually used for analysis of relatively diluted sample solutions. The injected sample solution should have low salt concentration to enable the sample stacking process. Otherwise the electro-osmotic flow can be altered, and the unfavorable detector background signal may be observed. Two main methods are used for sample pretreatment and preconcentration: (i) an electrophoretic method and (ii) a chromatographic technique. Electrophoretic techniques are based on differences in the electrophoretic mobilities of the analytes. Four main types of these techniques have been presented: transient isotachophoresis [25, 26], stacking [27–29], sweeping [30–32], and dynamic pH junction [33, 34]. On the other hand, chromatographic techniques rely on analyte sorption on a surface of the stationary phase. Chromatographic techniques allow for loading of large volumes followed by preconcentration on a sorbent and subsequent elution into a small volume of solvent, resulting in lower limits of detection.

For such applications, nanomaterials are excellent candidates because, compared to bulk materials, nanomaterials offer significantly higher surface-to-volume ratios, and therefore provide higher sorption capacity and thus better extraction efficiencies. As an example, may serve the comparison of surface area of carbon microparticles with 60 μm in diameter of (0.01 mm^2) and the surface area of carbon nanoparticles with 60 nm in diameter (11.3 mm^2). Similar to the increase in the surface area, the reactivity is also increased by approximately three orders of magnitude. Not only the surface area, but also the chemical affinity may be beneficial. For example, gold nanoparticles provide excellent extraction power due to their high affinity for thiol-containing compounds.

Similarly, magnetic separation is a method using magnetism for the efficient separation mediated by paramagnetic and superparamagnetic particles. This technique takes advantage of the option of surface modification of magnetic nanoparticles to enable so-called immunoextraction. Such particles may be modified by either antibodies for specific capture of the target analyte or by oligonucleotide fragments having sequences complementary to the desired nucleic acid. Magnetic particles can be immobilized using an external magnetic field and interfering compounds are removed from the solution [35].

3. Capillary electrophoresis for analysis of nanomaterials

The field of nanomaterials (e.g. metal or polymeric nanoparticles and carbon nanomaterials) is one of the most attractive and quickly emerging, while these materials have often valuable properties for various applications. The synthesis, however, is problematic especially from batch-to-batch repeatability point of view and, sometimes, techniques enabling characterization of nanomaterial properties and composition are absent. Even within a single batch, the polydispersity of the particles and the variability of their properties may present insurmountable problem for reliable application [36].

The conventional methods evaluating the size distribution are transmission electron microscopy and/or size exclusion chromatography. However, these methods have disadvantages including high instrumental costs, time consuming and laborious sample preparation, and

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high requirements on an operator, because of interpretation of the results. Therefore conventional or microfluidic CE is a good alternative for characterization of colloids and nanomaterials. Review articles focusing on electrophoretic separation of nanoparticles has been published in 2004 by Rodriguez and Armstrong [37], later by Surugau and Urban [38], Pyell [39], Lopez-Lorente et al. [40], and in 2017 by Aleksenko et al. [41]. Microfluidic format used in nanoparticle separation was reviewed by Salafi et al. [42]. More focused review article about CE analysis of poly(amidoamine) dendrimeric structures was prepared by Shi et al. [43]. Paper summarizing the application of separation techniques (including CE) of gold nanoparticles [44, 45] and QDs [46, 47] analysis are also accessible.

One of the main advantages of nanomaterials is that their surface can be easily functionalized and modified with various molecules potentially applicable for interactions with other molecules. Therefore, CE can (i) monitor the interaction between nanomaterial and analyte, (ii) monitor the interaction between two analytes facilitated by the nanomaterial, and (iii) monitor the interaction between two analytes expressed as a change in the signal of the nanomaterial.

4. Nanomaterials enhancing performance of capillary electrophoresis

4.1. Enhancement of separation

Nowadays, an increasing number of researchers perform CE separations in short capillaries (units of centimeters) instead of microfluidic chips [48, 49]. In such capillaries, fast and efficient separations are carried out without complicated chip preparation requiring expensive facilities (e.g. clean rooms and lithography). Compared with microchip-based high-speed CE systems, short capillary-based high-speed CE systems take advantage of simple structure, easy fabrication, and low costs.

The disadvantage, however, is in lowered resolution connected with short separation length. This obstacle can be solved either by injection of extremely low sample volumes (picoliters) or by additional selectivity given by stationary of pseudo-stationary phases of various natures (e.g. micelles, nanoparticles, nanostructures, etc.), which significantly eliminate the adsorption of highly abundant proteins on the capillary wall [50–53]. Nanomaterials have been proven to be effective (pseudo)stationary phase due to their beneficial properties, such as large surface–to-volume ratio and easy modification. The most commonly used nanomaterials are carbon nanotubes [54]. However, other structures including nanoparticles [55, 56], nanofibres [57], and/or nanorods [58, 59] have been utilized for these purposes. On the other hand, surface-binding method uses interaction between analyte with the surface of fixed nanostructures such as monoliths, nanopillars, immobilized nanoparticles, and/or other nanomaterials. All of these types have already been employed in coupling with in either capillary-based CE or microfluidic CE. Immobilized nanomaterials, either deposited on capillary wall as a thin layer coating or packed within the capillary, are commonly utilized as stationary phases for capillary electrochromatography. The (pseudo)stationary phases enable a broad range of functionalities offering a variety of interactions [60] (**Figure 2**).

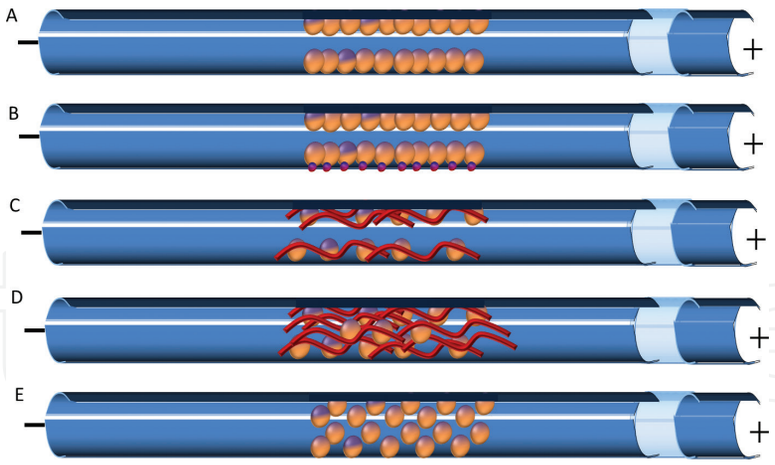

Figure 2. Approaches for separation performance enhancement by nanomaterials. (A) Physically adsorbed opentubular phase, (B) covalently bound opentubular phase, (C) co-polymerized opentubular pahse, (D) full-filling sieving matrix, (E) mobile pseudo-stationary phase.

The efficiency of separation of two compounds is defined as resolution (R_S). It can be affected by alternating the electrophoretic mobility of the analytes and their electrophoretic mobilities. R_S can be calculated according to the equation (1):

$$R_S = \sqrt{N}\frac{\mu_{elA} - \mu_{elB}}{4(\mu_{av} + \mu_{EOF})} \quad (1)$$

where N is the number of theoretical plates, μ_{elA} and μ_{elB} are electrophoretic mobilities of the analytes, μ_{av} is the mean electrophoretic mobility of analyte A and B, and μ_{EOF} is mobility of electro-osmotic flow.

4.2. Enhancement of detection

Laser-induced fluorescence detection is (and most likely will be also in the future) the most sensitive detection technique among the optical detection modes following chemical separation. It has exceptionally low limits of detection (10^{-13} M) [61] and good detection selectivity in cases of sample analysis with rather complex matrices. Simultaneously, this selectivity could be perceived as a limitation because the majority of analytes lacks the desired fluorescent properties, and therefore, derivatization by some fluorescent label is needed.

Optical detection in association with nanomaterials is mainly connected with quantum dots due to their application as a fluorescent labels in laser-induced fluorescence detection [62–65]. An indirect laser-induced fluorescence mode of detection by means of CdTe quantum dots has been demonstrated and therefore determination of small organic acids in food with detection limits in the range of tenths of mg/L was enabled [64]. Moreover, determination of pesticide and antibiotic residues in vegetables [66, 67] and in foods [68] has been described. Chen and Fung presented laser-induced fluorescence detection using immobilized QDs to determine organophosphate pesticides (mevinphos, phosalone, methidathion, and diazinon) in vegetable samples [69]. Detection limits of the method were in the range of tens of μg/kg.

Besides photoluminescence detection, chemiluminescence (CL) and electrochemiluminescence detection are also benefiting from properties of nanomaterials [70]. CL detection is based on measurement of electromagnetic radiation released after excitation of the electron by chemical reaction. The main advantages of CL are in the absence of undesired background signals, improved sensitivity, and wide linear dynamic range. Moreover, no excitation sources and/or optical filters are essential; therefore the instrumentation is simple, robust, and relatively low cost. In such instruments, metal-based nanoparticles can be used as catalysts, reductants, fluorophores, or acceptors of energy. Metal nanoparticles, such as gold, silver, platinum, semiconductors, and magnetic types, provide beneficial properties for CL detection [71].

Electrochemical detection in CE can be carried out in three modes: potentiometric, amperometric, and conductometric. Potentiometric and conductometric detectors provide good sensitivity and on contrary, amperometric detection is selective and can be tuned to the analyte of interest. One of the main differences of this approach compared to the optical detection modes is that the electrochemical detection is mostly performed by off-column, end-capillary, and therefore, in destructive arrangement.

The use of nanomaterials for electrochemical detection covers a remarkably broad field. Due to their electrochemical properties, nanomaterials have been applied for electrochemical analysis of many analytes, comprising of nucleic acids [72–74], proteins [75, 76], secondary metabolites [77, 78], and/or metals [79]. The key roles delivered by nanoparticles include biomolecule immobilization, catalysis of electrochemical reactions, enhancement of electron transfer between electrode surfaces and proteins, biomolecule labeling, and even use as a reactant [80]. In addition to the relatively low financial demands of electrochemical detection in comparison to optical instrumentation, advantages such as the possibility of miniaturization and in-field applications are vital. Number of reviews covering this topic has been published. For example, Pumera and Escarpa [81] summarized the different approaches for constructing nanomaterial-based detectors for conventional CE and microchip electrophoresis and mostly focused on three main types of nanomaterials, that is, carbon nanotubes, nanoparticles, and nanorods, in various designs. The work by Garcia-Carmona focusses on highlighting the electrochemical detection enhancement in CE, chip electrophoresis, and paper-based microfluidic devices [82].

In our opinion, it is highly unlikely that nanomaterials will wholly substitute such well-established approaches as organic dyes for fluorescent labeling. However, nanomaterials offer new options for a broad range of applications. The electrochemical detection particularly benefits from use of nanomaterials that enable increasingly sensitive detection.

5. Conclusion

There is no doubt that nanomaterials are extremely valuable tool for analytical applications enhancing highly the efficiency of extraction techniques, increasing significantly the resolution of separations, and improving greatly the capabilities of detection systems. There are a lot of key features of instruments used for clinical purposes including being easy to use and robust. In spite of the great advantages of capillary electrophoresis, robustness and repeatability of measurements belong to its weaknesses, which represent an obstacle for using of

capillary electrophoretic instrumentation in clinical practice with one exception represented by DNA sequencer. Utilization of nanomaterials in capillary electrophoresis is opening new perspective in the field of clinical usage because these advanced materials can lower detection limits on one side and enhance the separation effectiveness on the other side. Nevertheless, this is at the beginning and waiting for exploration.

From the CE point of view, NMs such as liposomes and dendrimes have abilities to improve the separation part of the CE analysis and QDs, on the other hand, they can significantly improve the detection part. However, there are several members of the nanomaterial family, which can improve both of those—carbon nanotubes and metal nanoparticles. At the same time, CE is an effective technique for NMs characterization, evaluation, and/or observation (**Figure 3**).

The symbiosis of CE and nanomaterials is beneficial not only for analytical chemists and material scientists, but also for biochemists and molecular biologists, because it leads to the development of new, more effective, and more sensitive methods.

The combination with the simplicity of miniaturization is opening the opportunities for portable and point-of-care applicable instrumentation suitable for personalized diagnostics. Moreover the separation power of electrophoretic analysis, even increased by nanomaterial-based stationary and pseudo-stationary phased in combination with advances in microfluidics, promises effective analyses of complex biological samples.

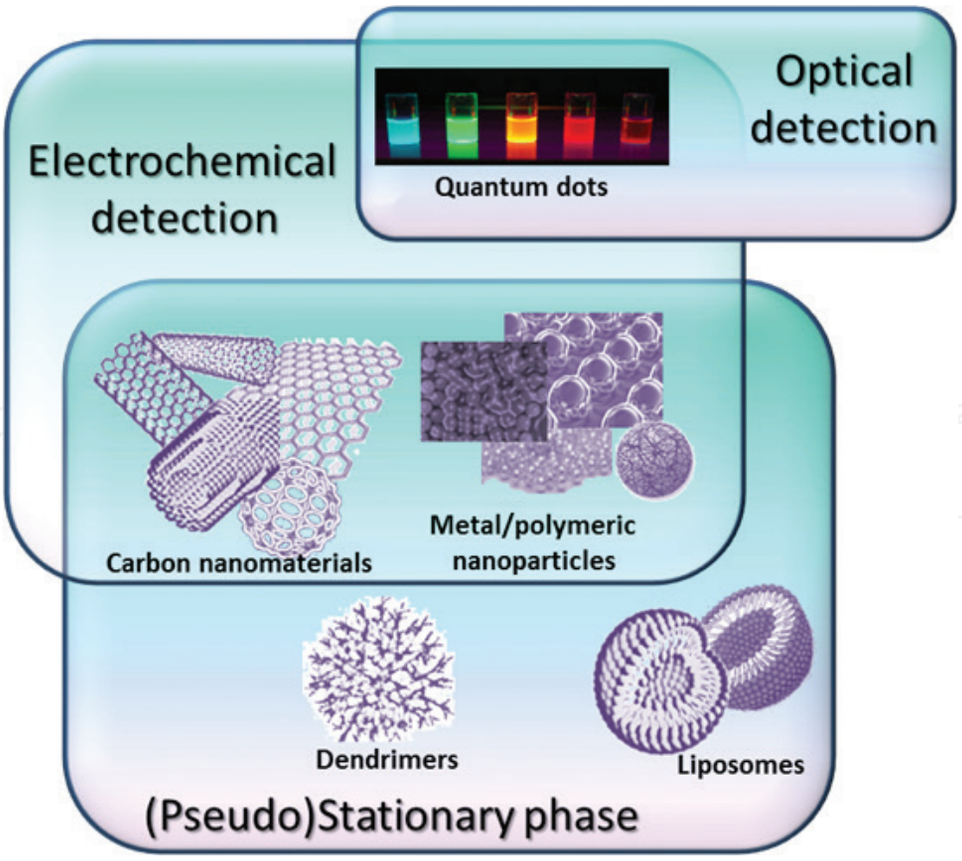

Figure 3. Summary of applications of nanomaterials in capillary electrophoresis.

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