



Separation of Labeled Gold Nanoparticles (GNPs) by Capillary Electrophoresis Review of the Literature

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ABSTRACT

Nanoparticles (NPs) are particles ranging in size up to hundreds of nanometers and possess unique characteristics such as a large surface area to volume ratio and special chemical properties. With applications in advanced chemistry, physics, medicine, and material science, their distinctiveness has particularly impacted the field of separation sciences. Recent developments have explored NPs in various applications like microchip technologies and surface coatings, and various types such as zeolite, carbon nanotubes, and latex have been utilized for separation purposes (Sardar et al., 2019; Sýkora et al., 2017; Sperling et al., 2018; Brust et al., 2015). This review highlights the essential role of NPs in separation sciences, showcasing their versatility and relevance across diverse fields.

Keywords: Nanoparticles (NPs), Separation Sciences

INTRODUCTION

Nanoparticles, also shortened as NPs, are particles with various dimensions that vary from unit to unit and up to hundreds of nanometers. NPs have also struck curiosity in the field of separation sciences and have been a key topic in advanced chemistry, physics, medicine and material science, to mention a few. The interest has been associated with NPs special features and chemical properties (Sardar et al., 2019). Generally speaking, NPs are about materials that have a spherical shape and include a large surface area to volume ratio as well as other unique characteristics derived from the quantum size effect. On the whole, the usefulness of nanostructures materials has played a key role in separation science, including applications in microchip technologies. According to Sýkora et al. (2017), nanoparticle serve as either a dynamic capillary surface or permanent use cases on surface coatings. Recent developments in the use of nanoparticles in separation science have been explored over time, and new applications are detailed from time to time (Sperling et al., 2018). Besides, several kinds of nanoparticles and nanostructures have been applied for separation reasons, such as zeolite, carbon nanotubes and latex, to mention a few (Brust et al., 2015). Thus, the uniqueness of nanoparticles has played an essential role in separation sciences, and has been leveraged in various fields in physics and chemistry as illustrated in this review article.

GNPS AND CAPILLARY ELECTROPHORESIS

The separation introduced entails endeavors of capillary electrophoresis (CE) initiated in the late eighteenth century. Initially, experiments were conducted in U tubes, with both the gel and free solution trials being conducted simultaneously. In the early 1930s, Tiselius Arnes, a chemistry enthusiast, first demonstrated the capability of electrophoresis through the

separation of protein molecules in free solutions (Iqbal et al., 2017). Therefore, and over time developments were made as this continued to be of interest to many researchers, and new technics were further developed.

GNPs can also be assessed from the separation point of view. For instance, the materials have been used extensively for low-molecular-mass compounds and their separation. The first material that looked into the separation details of GNPs was first published in 2001. According to the authors, an aqueous for of gold colloida dispersions were prepared via the use of citrate procedures that depended on the reduction of AuCl_4^- . Also, two different forms of GNPs species were applied as additives to BGE to produce a pseudostationary model (Tseng et al., 2015). In the first phase, untouched citrate stabilized GNPs of about 15 nm alongside capillaries are treated with poly (diallyldimethylammonium chloride) also known as PDADMAC. The process also leverages the use cases of an acetate buffer with a pH of 5. The second part uses sodium 3-mercaptopropionate GNPs of about 5 nm and are then synthesized alongside untreated fused silica (FS) capillaries. In the last case, a phosphate buffer of a pH of 6.4 is used as a BGE (Chen et al., 2019). Moreover, structural isomers of aromatic bases and acids are then used as key analytes to determine the effect of GNPs during separation. Overall, the processes imply that GNPs can be used as additives but in a variety of ways.

The changes in the inner capillary wall equipped with homogenous and positively charged layer of the PDADMAC and the silanol class can further be stabilized by EOF models, and providing constant migration times but for toluic acids and aminophenols, to mention a few, even in cases without GNPs in BGE (Hu et al., 2018). Furthermore, PDADMAC that have been modified can cause efficient separation with additional and symmetrical high points or peaks. Therefore, the passing of citrate-stabilized GNPs via capillaries that have been modified using PDADMAC can lead to electrostatic adsorption, but for the negatively charged GNPs and on walls that are positively charged.

Considering the adsorbed layer of the GNPs that has been stabilized using citrate is negatively charged, the process is marked by a reversal process to the cathode. Experiments have also demonstrated that the low concentration of GNPs in BGE is essential in occupying a substantial area of the accessible adsorption sites, on the available layers (Kitagawa and Otsuka, 2014). Moreover, the presence of GNPs in BGE shifts both mobility of the BGE as well as the observed or apparent movement of the analytes. Substantial changes during separation selectivity are observed at parts with reduced concentration (Hsieh et al., 2016). Thus, it is essential that GNPs that have stabilized with citrate are seen as successful otherwise, although failure cases are due to the poor stability of BGE and GNP.

Other cases such as metabolic pathways are used to maintain life functions, and they also involve catalysis of certain enzymes. The malfunction in such applications, such as overproduction, underproduction, or mutation of a single pivotal enzyme can cause diseases. Besides, enzymes are essential elements of research and development, such as the clinical diagnosis of diseases (Jarvas et al., 2020). Moreover, an accurate, efficient, and rapid procedure to determine kinetics, activities and the inhibition of enzyme is, therefore, a notable step toward the comprehension of reactions in cells that have been catalyzed, with further use cases being about drug development and the treatment of diseases. Moreover, Liu et al. (2016) first tested

and monitored alkaline protease functions using capillary electrophoresis (CE), which has also since become one of the most powerful tools for examining enzymatic reactions.

Additional separation processes exist, but CE has since proved its superiority because of its elevated separation efficiencies and sensitivity. CE requires a small sample and can be analyzed rapidly. Lastly, it uses various detection nodes. The last decade has also been marked by rapid development and research, including the aspects of enzyme assays, screening of inhibitors and proteome analysis (Tang et al., 2014). Generally speaking, enzyme assays that are associated with CE can either be offline and online and can be assessed in terms of enzyme kinetics and the examination of enzyme activity toward substrates.

MICROCHIP CAPILLARY ELECTROPHORESIS AND DNA SEPARATION

The separation of labeled gold nanoparticles using capillary electrophoresis has been assessed over a long time. It entails the elements of separation and the role of nanotechnology in the field under analysis. Electrophoresis has also been defined as the process through which ions migrate under the influence of an applied electric current (Kašička, 2014). The ions undergo forces equal to the product of the strength of electric charge applied and net charge. Capillary electrophoresis separates ions based on their charges and electron mobility. The literature review sums up the influence of GNPs in separation science, such as the case of DNA molecules and the overall and important use cases (Tian et al., 2015). The method suggests the use of other technologies in the field, such as hydrodynamic flow during separation. CE is also marked by vast literature regarding these experiments, but there are not many scientists that have attempted to separate labeled gold nanoparticles (GNPs) by capillary electrophoresis. Most scientists have focused more on molecules forgetting about the gold nanoparticles. Drag force or viscosity seriously affects the results and, as such, must be taken into consideration. It has been argued that drag force is a product of translational friction (f) and velocity. ($\mu = q/f = q/6\pi\eta r$), where η is the viscosity of the solvent, f is EP as a result of Stokes law, while r is the atomic radius (Liu et al., 2019). However, the parts of CE are more comprehensive than initially discussed.

The mentioned elements can further be assessed by looking into some key processes. For instance, it is challenging to fill capillaries, and, hence, low-viscosity sieving matrices that have additives such as mannitol and urea can be used for DNA separation. Oishi et al. (2017) also tested DNA separation by applying the services of PEE equipped with GNPs. The separation of DNA can be conducted for strands that range from 8 to 2176 base pairs (bp) and can be done in a short time. Low-viscosity PEO solution provides faster DNA separation while offering good resolution compared to processes that use high-viscosity PEO. The processes can also be improved to boost resolution and reproducibility of DNA strands that has been presented using select separation channels on a poly (methyl methacrylate) (PMMA) dish coated using PEO and GNPs (Yang et al., 2017). Other works performed by Hong et al. (2019) have also demonstrated that the relative sized on GNPs compare to buffer solutions and PEO are pivotal parameters that play an essential role in DNA separation. The use of pH values, PEO, and the concentration of GNPs has been an essential part of the investigation and has also been used in the separation of various sized of DA strands. Thus, the growth in reproducibility relative to the standard deviation has been excellent for all migration periods of DNA fragments of a given size.

The rule of different charges attracts while similar charges repel the charge. When a medium is exposed to an electric current, suspended particles in the electrolyte are attracted to the opposite charge electrode. However, there are vicious forces that act against this movement. Upon stability or equilibrium, two opposite particles, forces, or solutes move with equal and constant velocity. This velocity is hinged upon many factors like the voltage, dielectric constant, medium viscosity, zeta potential, or the applied electric field (Drioli & Lidietta Giorno, 2015). One key issue is that the result of the experiment fully relies on more so the current strength. Electroosmotic flow (EOF) is a result of the use of high voltage current to the electrolyte-filled duct (Eshkaftaki, and Ghasemi, 2018). Moreover, the stream occurs when buffer turns through a silica tube with a pH of more than three, and the silica gel lose the positively charged hydrogen atoms to become SiO^- . Furthermore, negatively charged capillary wall advances a dual-layer of cations. Besides, the inner layer is immobile while the outside coating freely moves lengthways through the silicon duct. The applied electronic charges force the motion of cations to go towards the cathode, thus generating an influential backflow (Micro Drops, 2016). Also, the equation governs EOF; $\mu_{\text{EOF}} = (\epsilon/4\pi\eta) E\zeta$. EOF works best when particles have a large zeta potential between cation layers because of the principle that a large diffusion cation layer slogs more particles towards the cathode, where there is low opposition from the adjacent solution.

CAPILLARY ELECTROPHORESIS IMPROVEMENTS

There are six available techniques of Capillary Electro separation and their improvements: capillary gel electrophoresis (CGE), capillary zone electrophoresis (CZE), capillary electrochromatography (CEC), micellar electrokinetic capillary chromatography (MEKC), capillary isotachopheresis (CITP), and capillary isoelectric focusing (CIEF). They can either fall under discontinuous or continuous systems (da Silva et al., 2012). Continuous systems have backend electrolytes that act through the duct as a buffer. They can later be segregated into either Kinetic and steady- state progressions. Discontinuous systems maintain the sample in distinct zones separated by different electrolytes (LibreTexts, 2020). Others such as Micellar Electro Kinetic Capillary Chromatography (MEKC) entail the separation method founded on the segregation of solutes between the solvent and micelles. They are collections of surfactant particles that coagulate when surfactants are added to solutions above normal micelle absorption. In addition, the coagulants have negatively charged polar thus easily attracted to the anode (Rosenblum et al., 2017). The development happens due to the application of an electric current. Since the electroosmotic flows to the cathode, they pull the micelles to the cathode as well. However, the process is not fast. Specifically, hydrophobic molecules spend most of their time in the micelle, while hydrophilic molecules quickly migrate to the water solvent (Micro Drops, 2016). MEKC is affected by factors such as surfactants concentration, additives, capillary wall polymer coating, and pH.

GNPs have also been used in other applications, such as for detection and diagnostic purposes. One of the applications is known as Sol-Particle Immunoassay (SPIA), which has been in development for decades. It was first suggested by Leuvering et al. (2018), and the purpose was for the detection of materials that are associated with gold nanoparticles accessing aggregation reaction among other macromolecules such as proteins. According to the authors, color shifts in solution for uv-visible (vis) spectrophotometer is from red to purple or blue (Jazayeri, et al., 2018). Therefore, the color changes in SPIA techniques can be presented to fight against various antigens and detection. Some of the materials that have been examined using the procedure

include human chronic gonadotrophin hormone also known as HCG, which is conducted through conjugated gold nanoparticles (Shallan et al., 2013). During the measurement of HCG using SPIA in urine, the gold nanoparticles that measure up to 40 nm and conjugated anti-HCG are used to allow agglutination of HCG- anti-HCG (Choi et al., 2018). Thus, it demonstrates a shift in spectrum absorbance of the nanoparticles. The whole exercise is faster at elevated concentration of HCG color shifts, specifically from red to purple, implying that the process is more of a colorimeter. Overall, the method is widely used because of its robustness, and can also be applied to detect HCG hormones.

FUNCTIONALIZED GOLD NANOPARTICLES

Additional work done by Zhao et al. (2020) has since determined that colorimetric detection over the functions of enzymes, such as their inhibitory elements can be performed for S-Adenosylhomocysteine Hydrolase, also referred to as SAHH. The enzymes can lead to the hydrolysis of SAH to homocysteine as well as adenosine. It would also imply that the inhibition applied for parasitic diseases could also deteriorate to immunodeficiency diseases and genetic issues (Zhao et al., 2020). Other methods used are expensive and cumbersome, such as high-performance liquid chromatography with capillary electrophoresis and fluorescence. The methods are leveraged to determine the performance of the enzymes. Nevertheless, fluorosurfactant- capped AuNPs (FSN-AuNPs) do not function optimally in their space because of their susceptibility to cysteine and homocysteine (Tiwari et al., 2018). However, the action of SAHH can be inhibited, implying that the hydrolysis process can also be inhibited to adenosine. Also, the aggregation of gold nanoparticles does not occur homocysteine is absent. Thus, the procedures are yet to be fully investigated, implying that more work can be dedicated to activity and inhibition of SAHH.

Further cases have suggested the use of CE alongside laser-induced fluorescence (LIF) as a robust tool for DDNA sequencing as well as the evaluation of PCR products and services. Kang et al. (2020) have suggested that the use of the system has been successful because it uses uncross-linking and entangled polymer solutions that offer superior features over cross-linking gels (2020). Some of the advantages are low viscosity, ease of preparation and flexibility. Some of the most used and powerful polymer solutions used for the process include those produced from polyethylene oxide or PEO, polyacrylamide and hydroxyethylcellulose (HEC), to mention a few. The polymers demonstrate self-coating features; hence, any cumbersome coating activities are stopped and the issue associated with coating inconsistencies and capillary fouling and eliminated (Han et al., 2017). Nonetheless, elevated pressure implies that processes are required to fill capillaries alongside highly viscous polymer solutions to offer higher sieving capabilities, and elongated DNA read length. Overall, the use cases imply that there some issues associated with filling capillaries.

SEPARATION SCIENCE AND LINK TO CAPILLARY ELECTROPHORESIS

In other cases, the effective separation of long-stranded DNA plays an essential role in genome works and is performed by using standard procedures such as pulsed field gel electrophoresis. However, it is not a robust method because it is slow, and takes a long time to complete, with worse cases taking several days (Li et al., 2015). While CE, which as mentioned previously uses an entangled polymer solution, is efficient in the separation of DNA, it is not application in the separation of long strands of DNA that are more than 1000 bp since electrophoretic mobility ceases to depend on molecular size as well as DNA that remain in the sieve matrix. Lin et al.

(2019) have given their suggestions to overcome the problem, including a case where CE-based techniques are applied and tested with different success rates. One of the key examples is the use of ultra-dilute polymer solutions, a development that has also been used by other researchers as mentioned above. The solutions are then used alongside pulsed-field CE. However, recent developments have been marked by the use of nanofabricated materials such as microfabricated models of obstacles, DNA prisms, asymmetric obstacle arrays, and entropy trap arrays (Wang et al., 2016). The arrays have also been used to address the time delay issue. Nevertheless, the techniques require expertise to develop and execute and have been termed as one of the most challenging separation systems when compared to their rivals such as using super-dilute polymer solutions.

CURRENT USE CASES OF CAPILLARY ELECTROPHORESIS

Guihen has developed a process for the separation of double-stranded DNAs through the use of CE that is under a high field of up to 270 V/cm. The model also applies the services of ultra-dilute hydroxyethyl cellulose, HEC with a concentration that is under the overlap threshold (Guihen, 2017). The concentration is marked by the interaction of polymers, which negatively influence bulk solution features such as viscosity. Niazi et al. (2016) have also suggested another separation mechanism named transient entanglement mechanism that is marked by DNA polymers, which drag polymer molecules as long as they interact during migration. The method has also been lauded for its ability to demonstrate dynamic formation and deformation in DNA conformation. After the development of the mechanism, a variety of ultra-dilute polymer solutions have been prepared and applied for the separation of elongated strands of DNA. Besides, Geiger et al. (2017) have also developed newer separation methods that leverage the features of CE. One of the methods has been used to showcase the presence of electroosmotic flow (EOF) as well as the separation of DNA strands that measure up to 23.1 kbp. The separation exercise introduces CE and PEO introduced in the review, and then it is applied on a capillary via EOF using pressurized means. Other methods have also been suggested by Huang et al. (2017). Specifically, the previous method is rapid, but it does not support the separation of even longer DNA strands. Therefore, GNPs come in play because they help the separation of long-stranded DNA. On the whole, it is superior over the earlier forms of separation because it can help separate long strands of DNA.

The separations mechanisms have also been explored by Chiou et al. (2017) over time. Similar to the transient entanglement process, other methods are based on a DNA molecule, which then is intertwined with polymers adsorbed by the GNP but for a short period. During the intertwining, the DNA collides with GNP, mainly during electrophoretic separation (Chiou et al., 2017). Afterwards, the GNP are mostly neutral; hence, they are capable of resisting the flow and slow movement of the DNA (Desiderio et al., 2020). The process can then be compared to free linear polymers, which then reveals that the polymers are adsorbed by the GNPs, although they are stiffer and less elongated because they depend on the polymer chain length and have a likelihood of deforming during flow (Thang et al., 2016). However, the case of deformation is only arrived at as an assumption, but it is supplemented by DNA separations using GNPs that have been adjusted to allow the action of neutral polymers and their shorter versions. However, the latter are not observed in bulk solutions, but only to some extent. In other cases, the modifications are not successful under varied conditions. Nonetheless, because of the robust intercalation between adsorbed elements on GNPs and DNA, the overall disengagement period

between of the two materials is relatively extended. Thus, the process is still subject to slow separation, and could be honed to cut separation times.

CONCLUSIONS AND SUGGESTIONS

Generally speaking, some suggestions have been made about the extended separation time for the intertwined GNPs and DNA. Some of the reasonings have suggested that the resolving power of the separation exercise drops with increasing levels of free ethidium bromide (EtBr), especially on the bulk section. More critically, the presence of heavier GNPs could affect linear polymers, implying that it can offer a notable capability in sowing down entangled DNA elements. Using the said model, gold nanoparticle or polymer composites may be able to play the same role as streptavidin, which offers extra friction in the end parts of CE solution. Besides, since extended DNA fragments have a higher chance of linking up with additional GNPs based on the size and conformation of DNA, then the drag forces are more robust for longer DNA elements relative to the shorter ones. Thus, the ability of the long DNA fragments to move is reduced than that of shorter fragments.

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