Field-Flow Fractionation with Atomic Spectrometric Detection for Characterization of Engineered Nanoparticles

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1 INTRODUCTION

Engineered nanoparticles (ENPs) have been applied in various applications: biomedical, consumer products, electronic devices, and sensors. Field-flow fractionation (FFF) is an interesting nonchromatographic technique for size characterization of materials with nanometer range. Various subtechniques of FFF including flow, sedimentation, and electrical are described with some selected applications reviewed. Moreover, FFF can be used via off-line and on-line with many elemental detection techniques: GFAAS, ICP-OES, ICP-MS, and SP-ICP-MS to provide more information in term of quantification and element-specific detection. In this article, applications of FFF with atomic spectrometric detection for environmental and biological samples and consumer products and food-related samples are discussed.

2 ENGINEERED NANOPARTICLES

ENPs have been increasingly used in our daily life. Therefore, suitable analytical techniques for ENPs characterization are of great demands. Choices of analytical techniques for nanoparticle (NP) characterization are various. Selection of proper analytical techniques depends on the information sought. FFF is a technique of choice when the particle size information is required.

This article is categorized into six parts. In the first part, the applications of ENPs are reviewed. The second part describes the principle of FFF techniques and summarizes the applications of FFF for size characterization of ENPs. The third part describes the principle of various atomic spectrometric techniques by showing some selected applications of the techniques to ENPs. The fourth part discusses about the hyphenation between FFF with atomic spectrometric detection, with selected applications in biological, environmental, and industrial samples reviewed. The fifth part consists of the applications of FFF with atomic spectrometric detection for ENPs. The concluding remarks are given in the sixth part.
of ENPs exist and can be categorized into three classes. The first class is the carbon-based materials such as carbon nanotubes (CNTs), fullerenes, and nanowires. The second class is inorganic NPs including metal nanoparticles: silver nanoparticles and gold nanoparticles; metal oxide nanoparticles: CeO$_2$, SiO$_2$, TiO$_2$, and ZnO NPs; quantum dots (QDs): CdSe and CdS. The last class is polymer and dendrimer-based NPs.

In this article, only inorganic NPs are discussed. Metal NPs are fabricated from elemental metals to produce particles in the nanometer scale with new chemical and physical properties. Examples of metal NPs include gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), copper nanoparticles (CuNPs), and platinum nanoparticles (PtNPs). Metal oxide NPs are NPs of metal oxide such as silicon dioxide (SiO$_2$), titanium dioxide (TiO$_2$), zinc oxide (ZnO), and iron oxide (Fe$_2$O$_3$/Fe$_3$O$_4$). Metal oxide NPs are often used as coating and compost agent in various material and devices. QDs are 1–10 nm of particles made from semiconductor materials. QDs show unique electronic and optical properties owing to the electrons transfer as quantum confinement in small limited area fixed by their nanosize. For optical property, QDs absorb wide spectral range and emit the light in ultraviolet to infrared regions, which depend on their size and elemental compositions form core. QDs are used as bioprobes such as bioimaging in medical application. In addition, QDs are used in electronic application such as solar cell, optical sensor, light-emitting diode (LED), telecommunication device, and quantum computer.

Applications of inorganic NPs are various as shown in Figure 1. In this article, applications of inorganic NPs in biomedical, consumer products, electronics, and sensor are summarized.

2.1 Biomedical Application

Nowadays, people concern much about health problems including cancers, tumors, infectious diseases, and antibiotic-resistant problems. Since the beginning of twenty-first century, nanotechnology has been of interest for health and treatment applications using their benefits to the treatment of human diseases. Various types of ENPs were used in medical application. Regarding the inorganic NPs, the use of silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), metal oxide NPs, and many types of QDs has been reported in the applications as antibiotic, cancers and tumors treatment, cell imaging and biomarker, drug delivery, and nanocoating medical device such as catheter, tube, and dressing. Inorganic NPs are easy to synthesize and can be readily functionalized, and they are biocompatible. Consequently, they have been used for cellular delivery, targeted delivery, and controlled release.\(^{(3-6)}\)

2.1.1 Gold Nanoparticles

Gold NPs were used as cancer marker and therapy.\(^{(7-9)}\) Surface-modified AuNPs were used to deliver gene and drug to the target cells.\(^{(3-6)}\) In addition, the use of AuNPs, with and without stabilizers, as an antibacterial agent was reported and it was proved that AuNPs could be used as an alternative for the development of new antibacterial drugs to combat resistance problem.\(^{(10,11)}\) Moreover, AuNPs were used in biosensing applications for diagnostic purposes. Springer et al.\(^{(12)}\) created novel biofunctionalized surface-modified AuNPs (bio-AuNPs) to detect carcinoembryonic antigen, a biomarker of cancer of tumor, in human blood plasma. In addition, Zhang et al.\(^{(13)}\) developed AuNPs for selective and sensitive sensing of prion protein sensing.

2.1.2 Silver Nanoparticles

Silver NPs are well known for their resistance to the bacterial cell both Gram-negative and positive bacteria.\(^{(14,15)}\) They are often used in medical application to inhibit bacterial growth that causes infectious diseases. Synthesis of AgNPs is aimed toward using green methodology to be nontoxic to provide stable particles with narrow size distribution. Examples included the synthesis of AgNPs using cysteine as reducing agent and cetyltrimethylammonium bromide (CTAB) as stabilizing agent. These synthesized AgNPs were
tested for their antibacterial properties with *Escherichia coli* O157:H7, and high antibacterial efficiency was obtained as reported by Paredes et al.\(^{[16]}\) Another investigation was reported by Thomas et al.\(^{[17]}\) to study antibacterial property of biosynthesized AgNPs and AgNPs combined with antibiotics. Both AgNPs exhibited inhibitory effect against *Staphylococcus aureus*, *Vibrio cholerae*, *Salmonella typhi*, *Salmonella paratyphi*, and multidrug-resistant biofilm-forming coagulase-negative *Staphylococcus epidermidis* 73, 145, and 152. In addition, AgNPs were applied to use as wound treatments, by which Tian et al.\(^{[18]}\) demonstrated that AgNPs could heal wounds and reduce inflammation in the animal model. In addition, AgNPs were coated on medical devices as antibiofilm to inhibit dispersion of bacteria in medical activity such as catheters\(^{[19–22]}\) or orthopedics and dentistry for prosthetic implantation.\(^{[23]}\) For therapeutic purpose, the use of AgNPs as tumor and cancer treatment was also reported, by which AgNPs possessed antiangiogenic properties to block growth of tumor cell\(^{[24,25]}\) and AgNPs could damage cell membrane and disturb into cell leading to cancer cell death.\(^{[26–29]}\) Future interest included the modification of AgNPs surface to be selective to cancer cell and nontoxic to normal cell.

### 2.1.3 Zinc Oxide Nanoparticles

Zinc oxide NPs were used for wound healing, cell imaging, cancer therapy, and drug delivery. In 2013, Sudheesh Kumar et al.\(^{[30]}\) fabricated bandage from β-chitin hydrogel and ZnO NPs composites to enhance antibacterial and speed up the wound healing process. Depending on the concentration of ZnO NPs, the composite bandages showed in vitro antibacterial and antifungal activities against *Candida albicans*, *E. coli*, and *S. aureus*. They also studied cell viability using human dermal fibroblast (HDF) cells and found that higher concentration of ZnO NPs resulted in reduction of cell viability. In addition, composite bandages were studied in vivo for their antibacterial activity and wound healing using Sprague Dawley rats. The wound treated with the composite bandages was healed faster with high collagen deposition. Furthermore, the composites of ZnO NPs with chitosan gel and gentamicin antibiotic were prepared to offer cutaneous healing with controlled release of antibacterial agent.\(^{[31]}\) The use of regenerated bacterial cellulose (RBC) combined with ZnO NPs was also demonstrated for wound dressing with biocompatibility and nontoxicity to cell.\(^{[32]}\) In addition, ZnO NPs were used as biomedical therapeutic\(^{[33,34]}\) and imaging agents.\(^{[34,35]}\) The cytotoxicity of ZnO NPs depended on size, shape, and their concentration. Zn\(^{2+}\) released from ZnO NPs and reactive oxygen species (ROS) species caused cytogenetic damage and induced apoptosis of cancer cell.\(^{[35–38]}\)

Other metal oxide NPs include manganese oxide (MnO) and iron oxide (Fe\(_2\)O\(_4\)). With surface modification, they were used as biomedical imaging and drug delivery applications.\(^{[39,40]}\) Iron oxide NPs showed unique properties such as superparamagnetism, and they were used in bioseparation. Furthermore, the applications of iron oxide NPs included multimodality imaging, therapy, biophotonics, diagnostic, and drug delivery agent. Combination with specific targeting agent on the surface of NPs was reported to solve the problem of specificity lacking.\(^{[41–44]}\) Moreover, as antimicrobial activity, AgNPs, AuNPs, SiO\(_2\) NPs, TiO\(_2\) NPs, and ZnO NPs were studied and used in dentistry as control of oral infections.\(^{[45–47]}\)

#### 2.1.4 Quantum Dots

QDs were useful as fluorescence probes owing to their unique optical properties such as photoluminescence, high photobleaching threshold, and excellent chemical stability. In addition, QDs functionalized with targeting agent were also applied in biomedical field to function as cell imaging, biomedical sensor, and biodiagnostic. The use of QDs as a probe for liver cancer cell\(^{[48]}\) and tumor monitoring\(^{[49]}\) was reported. In addition, the QD-loaded micelles were used as cancer therapeutic and imaging agents in mice model.\(^{[50]}\)

#### 2.1.5 Nanoparticle-Encapsulated Platinum

NP-encapsulated platinum was interested for its therapeutic application as cancer treatment agent, because platinum compounds such as cisplatin have shown anticancer property toward germ cell tumors and bladder, ovarian, testes, lung, head, and neck cancers. However, they exhibited unfavorable pharmacokinetic profile, short half-life in blood system, and toxic side effects to liver, kidney, and nerves system.\(^{[51–55]}\) In order to attain enhanced efficiency against cancer with lower dose, targeting, and reduced side effect, development of platinum drug encapsulated in NPs for cancer therapy was studied. Encapsulation of prodrg or other Pt complexes in polymer as drug carrier, which could target, control release, minimize dose with low toxic side effect was considered.\(^{[53,55–58]}\)

Dhar et al. encapsulated Pt(IV) complex: c,t,c-Pt(NH\(_3\))\(_2\)(O\(_2\)CCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\))\(_2\)Cl\(_2\) as cancer prodrug agent, which generated cisplatin after reduction in cell, using poly(D,L-lactic-co-glycolic acid)-b-poly(ethylene glycol) (PLGA-b-PEG) to form NPs. This was to deliver the drug to prostate cancer cell. The test was carried out in mouse and rat models with the result

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shown that the developed drug showed higher anticancer efficiency than that of the cisplatin conventional drug. The lower dose of drug was required, and the drug residence in blood was prolonged.\(^56\)

\subsection{2.2 Consumer Products}

Inorganic NPs have been applied to various consumer products. In textile industry, inorganic NPs (silver, copper dioxide, silicon dioxide, and titanium dioxide) were used as coating materials on the textile fibers.\(^59,63\) TiO\(_2\) and SiO\(_2\) NPs were coated on cotton textile surface to enhance self-cleaning.\(^59\) Fabrication of antibacterial, conductive, and super hydrophobic textiles was possible by coating of AgNPs.\(^64\) ZnO NPs coated silk fabrics showed UV blocking, self-cleaning, and antibacterial activity against \textit{E. coli} and \textit{S. aureus}.\(^65\) AuNPs were coated on cotton and silk fabrics to protect UV radiation and provide antimicrobial ability.\(^66\)

In cosmetic and sunscreen products, nanomaterials (gold, silver, titanium dioxide, and zinc oxide) were used as ingredients to show protections of acne and dermatitis, UV radiation, dark spot, blemish, and freckles.\(^67–69\)

In food and beverage industries, NPs were used for various purposes. AgNPs, TiO\(_2\), and ZnO NPs were used as antimicrobial agents and UV blocker and used for maintaining freshness and nutrient in food storage and in packaging. They were also used in bake wares, chopsticks, kitchen tools, and cutting boards as sterilizing agents to prevent digestive diseases. NPs of copper, gold, iridium, palladium, platinum, silica, silver, and zinc were added in beverage as supplements to promote human health and also for antibacterial protection.\(^67,70,71\) Silica NPs were added in food as anticlumping and anticingking agent in powder food products such as milk powder, chocolate powder, coffee creamer, pancake and cake mix, and instant soups.\(^72\)

In personal care products such as toothpaste, soap, shampoos, and spray, nanomaterials such as silver, titanium dioxide, and zinc oxide were added as antibacterial and antifungal agents to neutralize odor and prevent oral and skin infection.\(^67\)

In paint, pigment, building, and furniture materials, metal oxide NPs such as titanium dioxide, silicon dioxide, indium tin oxide (ITO), and zinc oxide were used for self-cleaning, antifogging, UV protection, and antibacterial and antifungal purposes.\(^67,73–77\)

In addition, home and electronic appliances were coated with nanomaterials as disinfectant and purificant. These appliances include air conditioner, iron, vacuum cleaner, refrigerators, computer equipment, water purifier, and hair dryer and roll.\(^67\)

\subsection{2.3 Electronic Devices}

Owing to the physical properties, size, structure, surface area, and morphology, and chemical properties, electrical, optical, semiconductivity, and mechanical properties, NPs were applied in various electronic-related devices. For examples, NPs were used as electrode materials in solar cell to enhance efficiency of solar cell such as light-harvesting efficiency, electron injection efficiency, and electrons collection efficiency.\(^78–80\) Another example is the use of NPs as anode and cathode materials in lithium-ion batteries and electrodes in super-capacitors because NPs exhibited enhanced capacitance, long cycle life, high power, and high-energy density.\(^78,81,82\) Furthermore, NPs were used in electronic devices such as computers, transistors, televisions, robots, mobile phones, and LED for the purpose of downsizing of the devices and providing lightweight.\(^81,83,84\)

\subsection{2.4 Sensors}

ENPs have been widely used as sensor, owing to their low cost and simple preparation. Moreover, they are less toxic, eco-friendly, chemically stable, with fast response, high sensitivity, selectivity, and simple detection.\(^85\) For example, AgNPs were applied to detect Ba\(^{2+}\), Cr\(^{3+}\), Hg\(^{2+}\), anions, and organic molecules: glucose, triptans, tryptophan, pesticides, melamine, and quaternary ammonium surfactants.\(^85–92\) AuNPs were used for detection of Ag\(^{+}\), Cd\(^{2+}\), Cr\(^{3+}\), Hg\(^{2+}\), NO\(_2\)\(^–\), and NO\(_3\)\(^–\).\(^93–97\) Moreover, AuNPs were modified as electrochemical sensor of organic molecules.\(^98,99\) NPs of metal oxide (Cu\(_2\)O, Fe\(_2\)O\(_3\), MoO\(_3\), SiO\(_2\), SnO\(_2\), TiO\(_2\), WO\(_3\), and ZnO) were used as gas detection (C\(_2\)H\(_2\), CO, VOCs, H\(_2\), H\(_2\)O, H\(_2\)S, NO\(_2\), ammonia, and ethanol)\(^63,99–102\) and humidity sensor.\(^103\) Metal oxide NPs functionalized with organic ligands were developed as luminescent ion probes for detection of Cu\(^{2+}\).\(^104\) QDs were used as luminescence probe, owing to their broad absorption and narrow emission spectra, resistance to photobleaching, and long fluorescence lifetime.\(^105\) The surface modification of QDs gave high sensitivity and selectivity for ion detection.\(^106\) CdSe/CdS QDs were functionalized using diethylidithiocarbamate for Cu\(^{2+}\) detection.\(^105\) CdS:Eu QDs with L-cysteine capping were used as Hg\(^{2+}\) detection.\(^107\) CdTe QDs capped by mercaptopropionic acid (MPA) were used as Ag\(^{+}\) detection.\(^108\) CdTe QDs capped by glutathione were used as Cr(VI) fluorescence probes.\(^109\) CdSe QDs capped by 2-mercaptoethanol were used for Ba\(^{2+}\) detection.\(^110\)
FFF is a nonchromatographic flow-assisted hydrodynamic separation technique. In FFF, an open channel is used instead of a column, and the external physical force is applied to drive separation. Thus, nonspecific interaction between sample and column materials, which normally occur in other chromatographic techniques, is avoided. Many subtechniques are available depending on the field applied to cause separation. If the cross flow is used, the technique is called flow field-flow fractionation (FIFFF). With centrifugal field force, the technique is called sedimentation field-flow fractionation (SdFFF). These two subtechniques are quite common. More details regarding the FFF theory are described elsewhere.\(^{111–113}\) In this article, only the general principles and the applications of FFF for ENPs characterization are discussed.

The FFF separation principle is illustrated in Figure 2. During sample introduction, mixed particles are introduced into the FFF channel, the perpendicular external field is applied to the channel, causing particles move toward accumulation wall. Then, a counteracting diffusive force drives the particles back toward the center of the channel. The diffusive force directly relates to the diffusion coefficient and the hydrodynamic diameter by which smaller particles can move faster than bigger particles. Therefore, the smaller particles are lifted away from the accumulation wall at a higher position than that of the bigger particles. As the flow profile of carrier liquid is parabolic by which the maximal velocity is in the middle of the channel, the particles are then carried downstream through the channel at different speeds and exit the channel at different times.

In a general system set-up, ultraviolet/visible spectrophotometer (UV/VIS) is used as a detector to detect the eluted particles. Nonetheless, various types of other detectors can be used depending on the purpose of the analysis. For example, inductively coupled plasma-optical emission spectrometry (ICP-OES) or inductively coupled plasma mass spectrometry (ICP-MS) is used for element detection, and dynamic light scattering (DLS) is used for size characterization. These two types of detectors can be used both on-line and off-line modes. Transmission electron microscope (TEM) and scanning electron microscope (SEM) can be used as off-line detection system to observe the size and morphology of the particles.

In FFF, separation mechanism can be achieved in normal or steric modes, depending on the particle size and the field condition used. In the normal or Brownian mode, particle sizes of samples are negligible when compared to the diffusional cloud. With the normal mode, smaller particles elute earlier than the bigger particles. Generally, particles of \(\sim 1–1000 \text{ nm} \) are separated in this mode. The steric mode is considered for separation of particle sizes larger than 1 \( \mu \text{m} \). With this size range, the particle sizes are not negligible when compared to the diffusional cloud. The larger particles protrude from the accumulation wall toward the upper part at a higher position than that of the smaller particles. Then, larger particles elute before the smaller ones. Thus, NPs are generally separated in the normal elution mode.

### 3.1 FFF Subtechniques

The perpendicular external field can be of various kinds, resulting in various FFF subtechniques, as illustrated in...
3.1.1 Flow Field-Flow Fractionation

FIFFF (or F4) is the most commonly used subtechnique. With FIFFF, a perpendicular secondary flow is applied as the perpendicular external field. Depending on where the secondary flow is generated, FIFFF can be divided into two types: symmetric flow field-flow fractionation (SF4) and asymmetric flow field-flow fractionation (AF4).

In SF4, the carrier flow rates at the inlet and the outlet of the channel are identical. The cross flow is generated by another HPLC pump that propels liquid through the top permeable ceramic frit and the bottom membrane. In AF4, the carrier flow rates at the inlet and the outlet of the channel are not equal. The top wall of the channel is impermeable, and the cross flow is generated by an excess flow rate at the channel inlet, making the carrier flow rate at the outlet smaller than that at the inlet.

3.1.2 Sedimentation Field-Flow Fractionation

SdFFF was developed for the separation and size determination of particle in the submicrometer to micrometer scale size range. Similar to other FFF subtechniques, separation in SdFFF is carried out in a thin flow channel under an applied field directing perpendicular to the channel flow. The type of force applied to the particles in SdFFF is a centrifugal acceleration generated by rotating the circular channel.

3.1.3 Electrical Field-Flow Fractionation

ElFFF is a technique, which can separate analytes on the basis of their electrophoretic mobility and size by electric field as external field. The ElFFF separation channel is consisted of solid graphite blocks as channel walls and also acting as electrodes that are separated by Mylar spacer. Two modes of separation are considered including normal ElFFF and cyclical electrical field-flow fractionation (CyElFFF). In the normal ElFFF, the constant direct current field is used to provide a perpendicular electric field across the flow channel that can separate particles in the basis of ratio between electrophoretic mobility and the size of particles. In the
CyElFFF, cyclical electrical field is applied instead of the steady direct current field. The cyclical electrical field causes particles to oscillate across the channel width. Separation in CyElFFF is theoretically based on the difference in electrophoretic mobilities.\(^{(117)}\)

### 3.2 Practical Considerations for Successful FFF Experiment

Several practices and precautions for experimental FFF were nicely overviewed by Moon and Myers.\(^{(118)}\) In order to be successful in FFF experiment, several things need to be considered, i.e. carrier preparation, start-up process, sample overloading effect, and channel maintenance. Carriers used in FFF experiment should be free of particulate material and dissolved gas. Bubbles should all be removed from the channel. All carriers should be filtered through 0.2 μm filter to provide particle-free carrier liquid. Ionic strength should be carefully controlled, owing to the fact that high ionic strength aggregation might occur. The channel should be flushed daily using carrier liquid introduced by a channel flow rate of 2–3 mL min\(^{-1}\) for an hour to stabilize the baseline. It is recommended to add an antibacterial carrier liquid within the FFF channel when the FFF channel is not used for an extended time. As the separation in FFF occurs in a very thin region (cloud layer thickness), very large amount of sample materials can cause insufficient room for particles to reach and establish equilibrium. This sample overloading subsequently affects retention level and hence physicochemical information obtained from the FFF experiment. To check the presence of sample overloading, for every unknown sample, several runs should be made with different sample loads to verify that retention times obtained from different amounts of sample injected are the same. Further, the FFF channel should be occasionally cleaned to remove all the materials that adhere to the accumulation wall over time. Excessive accumulation of sample materials can lead to a disruption and blockage of the channel flow path. Once this happens, the FFF channel should be opened up and the FFF accumulation surface should be gently rubbed and cleaned.

### 3.3 Applications of FFF for Engineered Nanoparticles

Using the Scopus database searching for the keywords on ‘FFF’ and ‘nanoparticles’ in recent two decades (1994 and 2004), the total numbers of 221 publications were found, as summarized in Figure 4. It is clearly seen that before the year of 2000 the report on the application of FFF for nanoparticles was not available. Nonetheless, the numbers of publication related to FFF and nanoparticles increased significantly in recent decade. Some selected applications of FFF to ENPs are summarized as follows:

Baalousha et al.\(^{(119)}\) investigated the interactions between unpurified manufactured iron oxide NPs (∼7 nm, pH ∼2) and standard Suwannee river humic acid (SRHA) under a range of environmentally relevant conditions. Increasing the pH from 3 to 5, iron oxide...
NP shifted to larger size and extensive aggregation was observed with the increased pH and reached a maximum at approximately pH 8.5. The adverse effect was observed with addition of SRHA, whereby aggregation was observed with lowering pH values of 4–5, which was also affected by SRHA concentration. Both pH and SRHA concentration affected on the structure and aggregation mechanism of these aggregates.

Cumberland and Lead\textsuperscript{(120)} employed SF4/UV/VIS along with DLS and TEM to study the effects of pH, dissolved organic carbon, and calcium concentration for size distribution of 15-nm citrate-stabilized silver nanoparticles (AgNPs). Increasing the pH from 5 to 8 at low ionic strength (10\textsuperscript{−3} M of Ca(NO\textsubscript{3})\textsubscript{2}) caused the increase in size of AgNPs. However, AgNPs were not stable at pH 5 in high ionic strength (10\textsuperscript{−2} M of Ca(NO\textsubscript{3})\textsubscript{2}) at which loss of AgNPs peak was observed. In case of low ionic strength, adding the humic substance resulted in the reduction in AgNPs size, whereas at high ionic strength, the AgNPs peak disappeared almost completely, which was most likely due to aggregation.

Sermseri et al.\textsuperscript{(121)} employed SF4/UV/Vis for size characterization of α-tocopherol-induced enlargement of AuNPs. α-Tocopherol played the role as catalyst for citrate reduction of AuCl\textsubscript{4}− resulting in larger AuNPs. This catalytic effect also depended on the incubation time and concentration. Longer incubation time and higher concentration of α-tocopherol resulted in larger AuNPs.

Cho and Hackley\textsuperscript{(122)} optimized the measurement conditions for analysis of AuNPs using AF4 coupled online with multiangle light scattering (MALS) to give the radius of gyration and with DLS to give the hydrodynamic size, and UV/Vis detectors to observe the elution of the particles. The mixture of 10–60 nm AuNPs and the mixture of AuNPs functionalized with polyethylene glycol and their unconjugated AuNPs were fractionated.

Römer et al.\textsuperscript{(123)} incubated the monodisperse 7-, 10-, and 20-nm citrate-stabilized AgNPs in the Daphnia magna exposure media as used in (eco) toxicity studies. In the undiluted media, rapid aggregation of all AgNPs was observed. However, dilution of the media by a factor of 2, 5, or 10 could minimize aggregation. However, the smallest NPs were unstable under all media conditions. The authors concluded that dilution by ~10 times of standard media could reduce the aggregation of AgNPs without affecting the viability of the test organism.

Calzolai et al.\textsuperscript{(124)} used nuclear magnetic resonance (NMR) for analysis of citrate stabilized-AuNPs (5–60 nm) before and after fractionation by AF4. They found that the original synthetic AuNPs contained an excess of citrate; however, the free citrate was not present in the fraction from AF4. Then, it was possible to identify the presence or absence of free citrate in the various AuNPs samples.

Gigault et al.\textsuperscript{(125)} demonstrated the use of AF4 for fractionation of positively charged gold nanorods (GNRs). The critical parameter was the components of carrier liquid. A mixture of ammonium nitrate and CTAB at different molar ratios enabled separation of GNRs with high recovery. Moreover, GNRs of different shapes could be fractionated. The fractionation depended on the aspect ratio (length divided by diameter) and a steric-entropic contribution, by which the higher aspect ratio eluted earlier.

Kim et al.\textsuperscript{(126)} demonstrated the application of SdFFF for separation of bimodal mixtures AgNPs in the sizes range about 100 nm. The types of carrier liquid were studied and water with 0.1% FL-70 provided a good resolution. Separation could be speeded up by exploiting a flow programming, where the flow rate was linearly increased during separation, without losing much in resolution.

Böhmer et al.\textsuperscript{(127)} set-up an in vitro digestion models mimicking mouth, stomach, and intestine for determination of physicochemical properties of AgNPs. A separation technique, AF4, was coupled with two different detection methods: SAXS and DLS. In saliva fluid, most AgNPs were not aggregated to larger nanoparticle size as shown by AF4 results. Owing to strongly acidic stomach and basic intestinal environment, hydrodynamic sizes of AgNPs became larger with DLS detection. With SAXS data, only small portion of AgNPs were aggregated and formed dimeric stage.

Cardot et al.\textsuperscript{(128)} employed SdFFF to fractionate polydisperse TiO\textsubscript{2} colloidal suspension. The collected fractions were analyzed for the size distributions by electron microscopy (EM) that showed sizes between 0.2 and 0.4 μm. Further, they performed the reinjection of the collected fraction by both direct injection and preconcentration before injection. The particle size of the collected fractions appeared accurately.

Tadjiki and Deering\textsuperscript{(129)} applied SdFFF to fractionate the unlabeled silica nanoparticles in the size of 70 nm, which were extracted from human endothelial cell lysate and rat lung tissue. Quantifications were obtained by considering from the area under the fractogram. The subsequent work was carried out by fractionation of a mixture of nanosized (70 nm) and submicrometer (250 nm) silicon dioxide particles added to mammalian tissue.\textsuperscript{(130)} They also used fluorescence microscopy and TEM for particle-treated cell culture samples in order to allow comparison of the SdFFF results.

Contaldo and Argazzi\textsuperscript{(131)} applied SdFFF in order to study size distributions of AuNPs that were prepared by citrate reduction method to the particles sizes around 12–65 nm. The size of AuNPs depended on the ratio of citrate/gold(III) by which the particles size decreased in the citrate/gold(III) ratio of 1 : 1 to 3 : 1 and then increased.
from 5 : 1 to 10 : 1 and passing through a plateau region in between.

Gigault et al.\(^\text{(132)}\) demonstrated the fractionation of many kinds of nanomaterials including Fe\(_3\)O\(_4\) and AgNPs (50 and 10 nm, respectively) by CyElFFF. Different operating parameters were investigated including the voltage, frequency, and flow rate of carrier liquid.

Somchue et al.\(^\text{(133)}\) showed the applicability of EIFFF for separation and characterization of AuNPs stabilized by citrate and tannic acid. The effective field and plate height were calculated by varying the applied DC voltage and flow rate. With the same particle size, particles with lower electrophoretic mobility eluted earlier than those with higher electrophoretic mobility. For particles with the same stabilizing agent, particles with smaller size eluted earlier than the bigger particles.

Tasci et al.\(^\text{(134)}\) demonstrated that using biased cyclical electric fields, by which the duration of the positive cycle voltage was applied longer than the negative cycle voltage, were able to separate nanoparticles smaller than 50 nm. They were able to separate a mixture of 15- and 40-nm AuNPs in high resolution by varying the voltages, frequency, and the magnitude of percentage duty cycle. A theoretical analysis to accomplish these separations was also given.

Rasouli et al.\(^\text{(135)}\) showed the applicability of gravitational field-flow fractionation (GrFFF) for separation and characterization of polydisperse submicrometer TiO\(_2\) powder into two groups: spherical particles with an average diameter of 0.31 mm and ellipsoidal particles with a 0.45-mm hydrodynamic diameter. Electrolyte and surfactant characteristics in the carrier phase and the sample concentration strongly affected on the elution peaks.

4 ELEMENT DETECTION OF ENGINEERED NANOPARTICLES

Various analytical methods are available for element detection of ENPs. However, this article focuses on atomic spectrometric techniques, such as graphite furnace atomic absorption spectrometry (GFAAS), ICP-OES, ICP-MS, and single-particle inductively coupled plasma mass spectrometry (SP-ICP-MS), which are widely used as quantitative detection of ENPs as either on-line or off-line coupling to FFF. The brief principles of each technique and their applications on ENPs are summarized.

4.1 Graphite Furnace Atomic Absorption Spectrometry

GFAAS is a powerful atomic spectroscopic technique based on electrothermal atomic absorption spectrometry (ETAAS) in a graphite furnace. GFAAS differs from flame atomic absorption spectrometry (FAAS) by the use of much higher atomization temperature (up to 3000 K). The operation in GFAAS determination starts by dispensing a known volume of sample into a graphite tube (3–5 cm in length and a few millimeters in diameter) through a tiny hole in the center of the tube wall. Both ends of the tube are open to allow the light from the radiation source to pass through and for the removal of sample constituents after the analysis. The sample is then subjected to electrical heat controlled by a multistep temperature program including drying, pyrolysis, and atomization. The limit of detection (LOD) of GFAAS is 10–100 times better than FAAS.\(^\text{(136,137)}\) Two examples of GFAAS for detection of ENPs are summarized as follows:

For GFAAS detection, Gagné et al.\(^\text{(138)}\) stated that the particle size of ENPs affected on the sensitivity of detection. In their study, the effects of atomization temperatures were examined on Ag of different sizes (20, 60, and 80 nm) at the same nominal Ag concentration of 10 mg mL\(^{-1}\). The dissolved Ag (0.15 nm) was also investigated for comparison purpose. The increase in the molecular size of Ag led to increased atomization temperatures: ionic Ag readily atomized at 1400 ± 25°C, whereas 20-, 60-, and 80-nm nano-Ag readily atomized at 1550 ± 30°C, 1600 ± 20°C, and 1700 ± 33°C, respectively.

Hartmann et al.\(^\text{(139,140)}\) developed cloud point extraction (CPE) method for the extraction of ionic silver species, silver nanoparticles, ionic gold species, and gold nanoparticles with further detection by ETAAS. Separation of ionic silver species was achieved by addition of EDTA as a ligand to chelate silver ion, whereas silver nanoparticles (AgNPs) in environmental samples were extracted using Triton X-114 to form cloud. For gold species, Triton X-114 was used as a collecting phase for AuNPs, whereas sodium thiosulfate was used as a complexing agent for ionic gold species.
spectrometer is used to separate and quantify the ions of different elements.\(^{(142)}\) Two applications of ICP-OES and ICP-MS for detection of ENPs are given as examples as follows:

Helfrich and Bettmer\(^{(143)}\) applied liquid chromatography (LC) and gel electrophoresis (GE) coupled to ICP-MS for the characterization of synthesized AuNPs. The LC-ICP-MS approach was optimized for monitoring the formation of citrated-stabilized AuNPs. With GE-ICP-MS, the \(\text{Au}^{3+}/\text{S}^{2+}\) ratios in AuNPs covered by mercapto succinic acid (MSA) were determined. These ratios were used for further characterization of the nanoparticles. In addition, electrospray ionization-mass spectrometry (ESI-MS) was applied as a complementary technique for detection of molecular components of AuNPs.

Geertsen et al.\(^{(144)}\) performed the systematic study based on the ICP-OES and ICP-MS measurement of TiO\(_2\) NPs suspensions. Sample treatment was examined and the measurement was performed in the concentration range from 10 ppb to 30 ppm. Soft sonication was used during sample treatment, and internal standard addition was used during measurement. The procedure was applied to detect titanium in Seine River water with the total amount of 48.7 ppb titanium found. The result was in good agreement with the result of the reference method.

### 4.3 Single-Particle Inductively Coupled Plasma Mass Spectrometry

SP-ICP-MS provides information about particle size distribution and particle number concentration. In SP-ICP-MS operation, sample needs to be very diluted and the sample introduction flow rate is set to be relatively slow to attain very low particle number concentration. A very short dwell time (10 ms or less) is acquired for each reading. The intensity from each reading is plotted individually as a function of time. The intensity is related to particle mass and hence particle diameter, whereas the frequency of the pulses is directly related to the number concentration of the particles.\(^{(145)}\) A brief concept of SP-ICP-MS is illustrated in Figure 5.

In 2003, Degueldre and Favarger\(^{(146–148)}\) reported the first application of SP-ICP-MS for the study of model colloids (rutile, alumina, and goethite) and natural clay (montmorillonite). Thorium colloid particles or thorium sorbed on clay colloids in water were analyzed. With the plasma design used in their experiment, thorium colloids down to 10 fg and gold colloid suspension in water of sizes ranging from 80 to 250 nm were detectable. The size detection limit was around 25 nm corresponding to 0.15 fg colloids.

Hu et al.\(^{(149)}\) proposed a highly sensitive immunoassay based on SP-ICP-MS using AuNPs with an average

![Figure 5](image-url)  
**Figure 5** Schematic diagram representing the concept of SP-ICP-MS.
diameter of about 20, 45, and 80 nm serving as model tags. The antibodies tagged with AuNPs were quantitatively detected based on the good correlation between the frequency of transient signals and the concentration of antibodies. The smallest detectable size of AuNPs tags was approximately 15 nm. The developed protocol was applied for a competitive immunoassay of α-fetoprotein with the linear range 0.016–6.8 μg L⁻¹ (between 20% and 80% inhibition). The limit of quantification was 0.016 μg L⁻¹ (20% inhibition, IC₅₀) with a relative standard deviation of 4.2% (20% inhibition, 4 replicates) for α-fetoprotein.

Pace et al. reported a practical guide on how to count and size nanoparticles using SP-ICP-MS. The developed protocol was used for characterization of mono-dispersed AgNPs. Furthermore, the same group of the authors also assessed the sizing capabilities of SP-ICP-MS for four AgNPs dispersions (nominal diameters of 40, 60, 80, and 100 nm) compared to DLS, differential centrifugal sedimentation (DCS), nanoparticles tracking analysis (NTA), and transmission electron microscopy (TEM). With SP-ICP-MS, size characterization of AgNPs together with particle number concentrations was possible. The accuracy obtained from the developed SP-ICP-MS was similar to the other commercially available techniques.

Mitrano et al. demonstrated the use of SP-ICP-MS to detect and quantify two products containing AgNPs. The first product was AgNPs with precisely manufactured size and shape, and the second product was a commercial health product containing AgNPs. Dissolved and particulate silver (Ag) could be differentiated. The developed SP-ICP-MS was applied to two wastewater samples containing Ag concentrations at nanograms per liter level. AgNP was found at 100–200 ng L⁻¹ in the presence of 50–500 ng L⁻¹ dissolved Ag.

Reed et al. reported the feasibility of SP-ICP-MS for detection and size characterization of metal-containing ENPs such as Ag nanowires, TiO₂, ZnO, and CeO₂. The particle size distributions obtained from SP-ICP-MS were in good agreement with those from SdFFF.

Gray and coworkers applied SP-ICP-MS to investigate ENPs in various biological tissue samples including, beef, Daphnia magna, and Lymbriculcus variegatus. The tissues were extracted by alkaline digestion procedure before SP-ICP-MS detection. From the results, Ag could be separated from AgNPs of 60 and 100 nm particles by extraction procedure. The authors mentioned that this established method could be applied to a wide range of tissues.

Tuoriniemi et al. investigated the potential of SP-ICP-MS for detection of AgNPs in waste water treatment plant effluent sample. To minimize the size detection limit, the shortest possible dwell time of 0.1 ms was used. The authors commented that it would be interesting to adapt the developed concepts for simultaneous multielement detection.

5 HYphenation BETWEEN FFF WITH ATOMIC SPECTROMETRIC DETECTION

Coupling between FFF with atomic spectrometric detection can be as either off-line or on-line, as illustrated in Figure 6. With off-line detection, the fraction from FFF is collected for further detection by atomic spectrometric techniques. The element fractogram is not a continuous plot. However, with on-line detection, the eluted fraction is introduced directly into the sample introduction part of the atomic spectrometric techniques, and therefore, the element fractogram is a continuous plot.

5.1 FFF with ETAAS

Although ICP-MS is extremely sensitive and is considered as a speedy way to acquire analytical information, the limited availability of ICP-MS and its relatively high equipment cost reduced its broad applicability. As an alternative approach, ETAAS has been used as an element detector after size separation. Electrothermal AAS also offers good sensitivity and slurry analysis capability. Nonetheless, most ETAAS instruments are not equipped with simultaneous multielement analysis features. Therefore, this can limit the use of ETAAS as compared to ICP-MS. Yet, when the information of only a few elements is sought, ETAAS can be quite useful.

In 1995, a group of researchers from Italy and Spain first introduced ETAAS as an off-line detection for SdFFF of clay analysis. Aluminum and Si were determined quantitatively, and the limits of detection were 63.6 and 212.4 ng for Al and Si, respectively. Two years later, the same research group, together with Beckett, extended their work to the elemental characterization of water-borne river particles (Po river). The first on-line SdFFF–ETAAS was reported in 2001 for the analyses of Fe in a synthetic model colloid and a reservoir sediment and Cu in a soil sample. Those applications were limited to the particle size of <1 μm. Applications of GrFFF and split flow thin cell fractionation (SPLITT) with ETAAS were reported. In the GrFFF experiment, size separation was tested for 5- and 10-μm HPLC silica particles coated with a thin layer of goethite. With SPLITT fractionation, the applicability range was extended to 25-μm particle size.
5.2 FFF with ICP-OES
In practice, ICP-OES offers advantages over ICP-MS and ETAAS in some circumstances. For instance, ICP-OES is capable of determining major elements, e.g. K and Ca, which are difficult to be determined even with high-resolution ICP-MS. For minor and trace constituents, however, the higher sensitivity of ICP-MS or ETAAS is often required. One might argue that ETAAS is only more sensitive than the ICP-radial view-OES but not the ICP-axial view-OES. The classical ICP-axial-view-OES suffered greatly from matrix interferences, which might make the technique less attractive. Nonetheless, with ICP-axial view-OES, matrix interferences are significantly reduced and hence could improve detection limits of many elements, the FFF-ICP-OES should also be considered, as it provides multielements detection capability with lower cost than FFF-ICP-MS. Some of the literatures reported the use of the FFF-ICP-OES.\(^\text{(160,161)}\)

5.3 FFF with ICP-MS
Optical detectors (spectrophotometric and light-scattering detectors) have been generally used to detect the fractionated materials eluted from the FFF channel.\(^\text{(162)}\) However, this detector type gives information only on the size distribution of the macromolecules or colloidal materials that interact with light. To obtain information about the chemical composition of the colloids or macromolecules in different size ranges, element-specific detectors (e.g. atomic absorption, X-ray fluorescence, or inductively coupled plasma spectrometries) must be used. Practically, only less than 1 mg of sample is required for fractionation in carrier stream flows of 1–2 mL min \(^{-1}\). High sample concentration may cause overloading effects in the FFF channel. With low sample concentration (e.g. < 0.5 mg mL \(^{-1}\)), however, very sensitive analytical techniques must be used. As ICP-MS provides excellent sensitivity, low detection limits, extended linear dynamic range, and multielement analysis with limited interferences,\(^\text{(163)}\) ICP-MS is an ideal element-specific detector for FFF.\(^\text{(164)}\) In addition, slurry atomization from solid-phase particulate matter can be achieved in the plasma source.\(^\text{(163)}\) At the same time, FFF adds a dimension of selectivity to ICP-MS measurement by separating the individual elemental species into different size fractions. The combination of the two techniques offers size-based elemental speciation in a single run. Furthermore, the interface between the FFF system and the ICP-MS instrument is rather straightforward owing to the compatibility between the flow rates generally used in the FFF separation and the ICP-MS sample uptake rate. Therefore, no major instrumentation modification is needed to couple FFF directly to ICP-MS.

FFF-ICP-MS can be applied in numerous fields. As can be seen in Figure 4, the applications of FFF to nanoparticles were not available before the year of 2000. Therefore, the applications of FFF-ICP-MS before the millennium were mostly related to environmental samples but not ENPs. The analyses of natural suspended particulate matter, soil, and clay minerals by SdFFF-ICP-MS\(^\text{(161,165–167)}\) and by FlFFF-ICP-MS\(^\text{(168,169)}\) were described. Applications
of FFF-ICP-MS to biological and industrial materials were also reported.

5.3.1 Biological Applications

Although several biological applications of FFF were reported as reviewed by Levin, only one application of FFF-ICP-MS to biological samples was reported before the millennium. In 1993, Barnes briefly predicted that FFF-ICP-MS should be an alternative technique for elemental speciation in biomedical samples. The idea was also suggested in the review on analytical plasma source mass spectrometry in biomedical research in 1996. A feasibility study of FFF-ICP-MS was first reported for protein standards. In this preliminary work, the effect of the FIFF cross flow rate was examined for separation of a carboxy anhydrate and alcohol dehydrogenase mixture. Preliminary studies with FIFF-ICP-MS were applied to several protein standards including metallotheoninein, carboxy anhydrate, ceruloplasmin, alcohol dehydrogenase, and thyroglobulin. Cadmium was detected in metallotheoninein; Cu and Zn in carboxy anhydrate, alcohol dehydrogenase, and ceruloplasmin; and I in thyroglobulin. As the coupling between FFF and ICP-MS was quite simple and FFF was capable of protein fractionation, FFF-ICP-MS was expected to be a valuable tool for speciation of metal binding proteins.

5.3.2 Environmental Applications

FFF-ICP-MS provides size-based elemental speciation information. This approach was applied successfully to various environmental and geological samples. In general, elemental concentration across size distribution information is obtained. This information can be important and useful to gain insight into metal transport and fate. Brief findings of FFF-ICP-MS experiments on environmental applications are summarized in the following sections.

5.3.2.1 Aquatic Samples In 1993, Murphy et al. investigated changes in elemental composition as a function of particle sizes of suspended particulates from the Darling River. Atomic ratio distribution plots were illustrated for various pairs of elements (Al, Mg, Rb, and Si). All the element atomic ratios with Si showed substantial decrease with larger particle sizes. This might be due to an increase amount of SiO2 fractions with increased particle size. The Mg:Al ratio showed significant decrease with increased particle sizes, whereas the Rb:Al ratio was almost constant throughout the whole particle size range (0.08–0.45 μm). These findings suggested that Mg and Rb were not present in the same proportion.

The effect of colloidal surface coatings on the adsorptive behavior of orthophosphate in river was investigated. The surface adsorption density of orthophosphate increased with increased particle size.

Hassellöv et al. applied SdFFF-ICP-MS to study trace metal adsorption processes onto aquatic colloids. The elements investigated included Cd, Cs, Cu, La, Pb, and Zn. Adsorption experiments were conducted with various amounts of metal loadings and at different pH conditions. The goal was to examine whether the adsorption occurred at a certain size range. Experiments at different pH distinguished between surface complexation (pH dependent) and ion exchange adsorption (pH independent). The aims were to get insightful information on the uptake processes, the transport, and fate of trace metals in aquatic systems.

Early FFF-ICP-MS studies were reported for SdFFF. In 1999, the first application of FIFF-ICP-MS was described by Hassellöv et al. for elemental size characterization of colloids in natural water. Twenty-eight elements in a small freshwater creek in Sweden were determined, and the results of six selected elements were illustrated. In their experiment, an on-channel preconcentration procedure allowing large volume sample introduction was used to provide preconcentration factor of about 1000 times. Different distribution patterns were observed for each element, indicating their dissimilar behaviors in aquatic environment. According to Hassellöv et al., colloidal nickel was mainly associated with the carbon and possibly with the smaller iron fraction. Lead was associated with the larger iron-based colloids, whereas La was bound to both the organic and inorganic colloids. Molybdenum coemerged with the void peak, suggesting that Mo occurred as dissolved molybdate ions, which were partially retained in the channel during the preconcentration step by charge repulsion from the membrane surface.

Similar investigations using an on-channel preconcentration FFF before ICP-MS detection were applied to characterize colloidal samples in sewage water from Amherst wastewater treatment plant (WWTP). Three types of water, including influent sewage water, sewage after primary treatment, and effluent water, were tested for 10 different elements. A 1.0-mL aliquot of wastewater samples was introduced into the FIFF channel instead of the typical injection volume (20 μL). With this, preconcentration factor of 50-fold was obtained. The entire volume of sample was loaded through the back end of the channel using focusing flows. Then, the cross flow stream was introduced, so that the sample could reach steady-state equilibrium. Reasonable trends of decreasing elemental and colloidal concentrations as the water treatment process proceed were achieved.
In addition, elemental distribution patterns also changed along the course of the treatment.

5.3.2.2 Clay Minerals, Soil, and Sediment Samples
Murphy et al.\textsuperscript{176} studied the changes in chemical composition of clay minerals kaolinite and illite, as a function of particle size by plotting appropriate element atomic ratio distributions. Atomic ratio distribution plots were illustrated for Si:Al, Mg:Al, and Rb:Al in an illite sample. Those atomic ratios were constant across the entire size distribution showing that the illite sample had a uniform composition. The authors further suggested the use of a tracer element, so that the size distribution of one component could be singled out from a mixture. Plots of atomic ratio against particle size for appropriate elements were constructed to monitor the changes in elemental composition as a function of particle size.

In 1999, Ranville et al.\textsuperscript{165} examined the applicability of SdFFF-ICP-MS to the analysis of horizon soils collected from Mountain Bold in South Australia. They used a 1 mmol L\textsuperscript{-1} sodium pyrophosphate solution with 0.02% sodium azide as a carrier liquid for SdFFF with 100 ng mL\textsuperscript{-1} In as an internal standard for ICP-MS to correct for noise and drift. Attempts to determine Si ($m/z = 28$), another major element present in the sample, were unsuccessful owing to spectral interferences from diatomic species ($N_2^+$ and NO$^+$). They compared the results of direct slurry with digested sample nebulization. Disagreement between the two approaches occurred when particles of larger than 1 μm were introduced into the ICP-MS, indicating that either the transfer of particles through the spray chamber or the atomization of the particles in the plasma was incomplete. Yet, the results for particles smaller than 1 μm by the two sample introduction techniques agreed, confirming the quantitative nature of direct particle analysis by ICP-MS for colloidal samples.

Schmitt et al.\textsuperscript{178} investigated the influence of natural organic matter on the adsorption of Al, Fe, Pb, and Zn onto clay minerals. Aggregation of clay particles decreased in the presence of natural organic matter and at high pH values.

The scope of FFF-ICP-MS was further extended not only to study elemental size distribution but also to determine the distribution of potentially available heavy metals within the colloidal fractions (0.05–1 μm) in Cu- and Pb-contaminated soils.\textsuperscript{167,179} The metal bioavailability was assessed using a selective extraction. To identify the exchangeable, reducible, or complexed target phases, diluted acetic acid, hydroxylamine hydrochloride, or ethylene diamine tetraacetic acid (EDTA) disodium salt, respectively, was used as extractants. Size distributions of Al, Cu, Fe, Mn, and Pb in colloidal fractions were characterized before and after EDTA extraction. With these chemical pretreatments, the authors were able to identify which size fractions of soil colloids contained the largest fraction of potentially bioavailable heavy metals. The element atomic ratio distributions (i.e. Cu:Al, Fe:Al, Mn:Al, and Pb:Al) were used to follow the changes in soil colloid chemistry.

Elemental size distributions were characterized for river and estuarine sediment core samples collected from two sites in New Jersey.\textsuperscript{180} Sediment samples were extracted using sodium pyrophosphate. Distributions of analyte elements as functions of hydrodynamic diameters and core depth levels (depth profile fractograms) were represented as the three-dimensional surface plots. Patterns of these two samples were significantly different by which the size distributions of Cape May sediments were slightly broader than those of Hackensack sediments. Differences in humic acid sizes found in two sediments probably were due to different types of humic acids or aggregate formation.

5.3.2.3 Humic Substances
Humic substances are well known for their ability to bind and form complexes with metal ions. Flow FFF coupled with ICP-MS enables the simultaneous characterization of molecular weight distribution of humic acid macromolecules and investigation of heavy metals bound to them. Size characterization of trace metals (Al, Cu, Cd, Pb, and Zn) complexed to soil-, peat-, and compost-derived humic acids was reported.\textsuperscript{169} Furthermore, physical parameters such as the diffusion coefficient ($D$) and hydrodynamic diameter ($d_h$) were determined. For all humic acids studied, fractograms were found to be monomodal with good reproducibility. The molecular weights at peak maximum ($M_p$) for all humic acids studied were about 3850 Da and their $M_p$ ranged from 3950 to 3790 Da indicating a very small variation in molecular sizes. The diffusion coefficients of humic acids varied from $1.66 \times 10^6$ to $1.72 \times 10^6$ cm\textsuperscript{2} s\textsuperscript{-1}. The study demonstrated how the FFFF-ICP-MS could be used not only to acquire elemental speciation and molecular weight information under gentle separation conditions presumably without perturbing the humic molecules but also to obtain the important physical and chemical information about the mobility characteristics of humic substances. Moreover, possibilities of using FFF-ICP-MS to study the aggregation of humic acids in the presence of divalent metal ions were also suggested.\textsuperscript{169,181}

Crude isolation of humic substances from the sediment samples was also investigated.\textsuperscript{180} By adjusting the pH of sediment extracts, humic and fulvic acids were isolated. Size distributions of Fe, Ni, and Pb in extracted fulvic and humic fractions were characterized. Distinct peaks of fulvic ($d_p \sim 3$ nm) and humic acids ($d_p \sim 5$ nm) were obtained, providing evidence that sediment extracts

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contained both fulvic and humic components. Humic acids were well resolved from the void peak. Under the operating conditions used, fulvic fractions partly coeluted with the void peak. The observation of two distinct peaks of fulvic and humic acids provided clear proof that FIFFF was capable of separating humic substances. Individual peaks at 3 (fulvic) and 5 nm (humic) after chemical isolation of these two macromolecules by pH adjustment confirmed their coexistence in the sediments.

5.3.3 Industrial Applications

Flow FFF-ICP-MS was applied to study elemental size distributions of chemical mechanical polishing slurries to demonstrate the scope of the technique with industrial materials. Particle size information, including size distribution, minimum and maximum particle sizes, average and median diameters, polydispersity, and breadth of distribution, were characterized for 18 alumina and silica slurry samples. Iron, Pb, Ti, and Zr were also detected by ICP-MS after on-line size separation by FIFFF to evaluate the presence of coexisting elements with alumina and silica polishing slurries. By knowing the exact geometry of FIFFF channel, experimental retention time can be converted into hydrodynamic diameter \( d_h \) without standards of known diameters to calibrate the FIFFF channel.

Mixed mode retention (normal and steric modes) might occur in the separation of these chemical mechanical polishing slurries. Steric inversion is the point where particles of larger size elute earlier than the smaller components. This steric inversion, which is usually taken place at around 1 \( \mu \)m, could lead to inaccurate particle size information. Nonetheless, to avoid steric effects, sample filtration was necessary before sample injection to remove particles of larger than 500 nm. However, particle size distribution of chemical mechanical polishing slurry might be changed upon sample pretreatment. To obtain accurate and reliable size information, independent methods (e.g. light scattering) might be used to verify the analytical results obtained.

Considering the particle size limitations with ICP sample introduction, small diameter particulates (<8 \( \mu \)m) can be introduced directly into the plasma as long as the amount of the solids injected is relatively small. With the particle diameter of larger than 8 \( \mu \)m, plasma energy might not be sufficient to evaporate and decompose the sample matrices. Therefore, applicable particle size range is limited between 2 and 500 nm, when the normal-mode FFF separation with direct ICP-MS detection is used. Nonetheless, for submicrometer-sized industrial particles, the steric-mode FFF separation with electrothermal vaporization (ETV)-ICP-MS might be considered. On the basis of other FFF reports, despite its limited documentation, numerous applications of FFF to the characterization of industrial products were carried out. Most of those applications were of proprietary materials and hence were not reported in the scientific literature. The proposed FFF-ETV-ICP-MS or FFF-ETV-ICP-OES provides the potential for process control applications of raw and processed materials (e.g. cement, nanoparticles, and pigments).

6 APPLICATIONS OF FFF WITH ATOMIC SPECTROMETRIC DETECTION FOR ENGINEERED NANOPARTICLES

The use of FFF coupled with atomic spectrometric detection has been reported. Some researchers examined the advantages and disadvantages of the technique compared with other techniques. The analytical features of the techniques were evaluated. The hyphenated techniques of FFF with atomic spectrometric detection were found useful in various applications for detection of ENPs in food, consumer products, and biological and environmental samples.

Hagendorfer et al. placed an on-line DLS detector between AF4 and on-line ICP-MS in order to determine the mass and number size distributions simultaneously without the need of either size or mass calibration. The results showed a good size characterization in AgNPs containing products although the samples have different degrees of polydispersity. This proposed method was shown to be more reliable than using the batch-DLS and clearly faster than using TEM. However, the limitation of this method was due to poor sensitivity of the on-line light-scattering detector for nanoparticles smaller than 10 nm. Then, higher concentration was required for injection in order to obtain reliable results for such small particles.

Mitran et al. compared the advantages and limitations of SP-ICP-MS and AF4-ICP-MS for silver nanoparticles detection. SP-ICP-MS was considerably more sensitive than AF4-ICP-MS (ng L\(^{-1}\) vs \( \mu \)g L\(^{-1}\), respectively) and offered the unique ability to differentiate dissolved and nanoparticulate fractions of total metal. AF4-ICP-MS could detect a much smaller NP size (2 nm vs 20 nm for SP-ICP-MS) and provide better size resolution.

Geiss et al. described a method based on AF4 with ICP-MS and UV/VIS detection. Prechannel injections were developed to measure size and mass of nanoparticles by simultaneously injection several sizes and concentrations of AgNPs standard reference materials. Comparing to postcolumn with ionic standard solution, a series of standards could be analyzed under exactly the same conditions. However, the limitation of this method was...
due to the lacking of AgNPs with different sizes and concentrations.

6.1 Environmental and Biological Samples

Songsilawat et al.\(^{188}\) used SF4/UV/VIS with off-line electrothermal atomic absorption spectrometry for size characterization of AgNPs in the aquatic system. Upon incubation of three types of AgNPs (9 nm of citrate, 19 nm of pectin, and 45 nm of alginate-stabilized AgNPs) with natural waters, i.e. tap water, seawater, and ground water, rapid changes in particle size of AgNPs were observed. Citrate-stabilized AgNPs were the least stable in comparison with that of pectin stabilized and alginate-stabilized AgNPs, respectively. The results suggested that the surface property was the key factor that controlled the stability of AgNPs in aquatic system and humic acid was found to prolong the stability of AgNPs in the environment.

Poda et al.\(^{189}\) developed an SF4–ICP-MS method for the characterization of AgNPs mixtures and applied to AgNPs suspensions and those in biological tissue. They spiked the polyvinylpyrrolidone (PVP)-coated AgNPs to freshwater sediments for 2 weeks. Then, the freshwater oligochaete Lytechinus variegatus was left in the sediment for 28 days. After that, the freshwater oligochaetes were removed from the sediment and AgNPs were extracted from these tissues which were then analyzed by FFF-ICP-MS. The size of AgNPs increased from approximately 31–46 nm. The increase in AgNPs size might be due to the removal of PVP coating by biological mechanisms or abiotic reactions in the soil exposure medium resulting in destabilized AgNPs.

Hoque et al.\(^{190}\) applied AF4 for size characterization of AgNPs in aqueous matrices, lakes, river, and untreated wastewater, collected from a municipal WWTP. Off-line ICP-MS was used in order to quantify AgNPs. The fractionation of a mixture of AgNPs standards (20, 40, and 60 nm) showed a well-resolved fractogram. AgNPs were not detectable in the surface water; however, they were detected in the untreated wastewater in the size of 9.3 nm (The method detection limit was 0.80 ng mL\(^{-1}\)). The size of 9.3 nm was measured by comparing the retention time with the particle size calibration curve. However, this value was not corresponded with the value obtained using the Stokes–Einstein equation to calculate the size, which yielded the size of 3.2 nm. This error might be due to the use of an inappropriate value for viscosity in the Stokes–Einstein equation.

Gondikas et al.\(^{191}\) examined several methodological approaches to detect TiO\(_2\) nanomaterials released from sunscreen products into the Old Danube Lake (Vienna, Austria) and able to identify TiO\(_2\) NPs stemming from sunscreens in the suspended matter of the lake using EM. Bulk analysis of suspended particulate matter clearly showed an increase in Ti-containing particles during the summer season.

Schmidt et al.\(^{192}\) connected the ICP-MS with AF4-MALS-DLS in order to measure the amount of AuNPs in the sizes of 10–60 nm after fractionation. The LOD of 0.02–0.4 ng Au was obtained, but the LOD increased when the particle sizes were larger. Further, they applied this system to characterize AuNPs in livers of rats after intravenous injection. The livers were solubilized in tetra methyl ammonium hydroxide (TMAH). The bovine serum albumin (BSA) was used for stabilization in the TMAH medium to prevent the aggregation of AuNPs. The soluble AuNPs from rat livers could not be fractionated, owing to their elution in the non-Brownian (steric) elution in AF4. TEM results indicated that AuNPs were associated with undissolved portion, which remained in the liver tissues.

6.2 Consumer Products and Food-Related Samples

Contado and Pagnoni\(^{193}\) showed the ability of SF4 for fractionation of titanium dioxide particles in the range 0.1–0.2 μm and proposed an extraction method for determining the size and amount of titanium dioxide particles in a commercial sunscreen product (with sun protection factor of 50). The fractions of TiO\(_2\) were collected after fractionation by SF4 and measured the amount of TiO\(_2\) by ICP-OES.

Contado and Pagnoni\(^{194}\) reported the use of ICP-MS for nano- or micro-TiO\(_2\) particles determination in commercial cosmetic formulations. Square wave voltammetry (SWV) and ICP-OES were employed to determine the amount of TiO\(_2\) in six foundation creams sold in Italy and the United States. SsDFF and FIFFF were exploited to characterize the sizes of the particles contained in the foundations by analyzing aqueous slurries obtained from solvent extraction procedure. The higher amount of TiO\(_2\) was found in the sample commercialized in the United States with the TiO\(_2\) declared as ~11% w/w, whereas all samples commercialized in Europe (Italy) had a lower TiO\(_2\) content of approximately ~8% w/w.

Samontha et al.\(^{195}\) determined the size distributions of TiO\(_2\) in sunscreen products. They used hexane for removal of organic components before fractionation by SsDFF. ICP-MS was used in order to determine the concentrations of TiO\(_2\). The concentrations of TiO\(_2\) analyzed by both on-line SsDFF-ICP-MS and off-line SsDFF-ICP-MS after acid digestion were in good agreement, indicating that ICP-MS could atomize and ionize the TiO\(_2\) particle without the need for acid digestion of the samples. The obtained size distributions of TiO\(_2\) were larger than 100 nm in most sunscreen
samples and concentrations of TiO₂ were higher for the products of higher sun protection factor values.

Nischwitz and Goenaga-Infante\textsuperscript{(196)} compared and optimized two extraction methods for titanium dioxide nanoparticles analysis in sunscreen samples using AF4-ICP-MS (steric elution mode). The first method was applied for particles that were resuspended by tip sonication before defatting by hexane. The second method was applied for particles that were defatted first and then the residue was suspended in water without any sonication. The authors suggested that using hexane for defatting first followed by reextraction by bath sonication offered clear advantages in terms of simplicity, relatively low cost, and high compatibility with the FFF conditions. Further, they presented a novel approach by spiking with aluminum-labeled titanium dioxide reference particles for studying the effect of extraction and separation conditions in real sample matrix.

Kim et al.\textsuperscript{(197)} demonstrated the use of SP-ICP-MS for the analysis of size distributions and concentrations of two types of TiO₂ nanoparticles, rutile and anatase, after fractionation by SdFFF. The results suggested that SP-ICP-MS could be a powerful tool for broad size distribution analysis of nanoparticles when combined with a particle separator such as SdFFF.

López-Heras et al.\textsuperscript{198} proposed the method based on AF4-ICP-MS for size characterization and element quantification of rutile titanium dioxide nanoparticles (TiO₂ NPs) in cosmetic and food products. Size characterization was carried out using particle size calibration curve constructed from polystyrene latex standards and compared with the size observed by TEM. However, one problem for quantification was the differences in nebulization efficiencies between NPs and the ionic standard solutions. They solved this problem using the titanium standard in the form of rutile TiO₂ NPs. The results were in good agreement with the quantity of Ti analyzed by FIA-ICP-MS. Moreover, using tip sonicator method for preparing NPs dispersions provided better linearity of concentration calibration curve, as opposed to the ultrasonic bath method.

Contado et al.\textsuperscript{(199)} demonstrated the use of SdFFF for size fractionations of four types of SiO₂ available in the market as additives in food and personal care products in the size range 7 nm to 9 μm. TEM and photon correlation spectroscopy (PCS) were also used for detection. The content of SiO₂ in different powdered foodstuffs was determined by GFAAS that showed the concentration in the range 0.006–0.35% (w/w).

Bolea et al.\textsuperscript{(200)} reported the development of a method for size characterization and quantification of AgNPs by AF4 coupled with ICP-MS. They found that the PES membrane and a mobile phase containing an anionic surfactant such as SDS at pH 8 were the optimal conditions for the characterization of AgNPs. The method was applied for the analysis of AgNPs in two consumer products: a strong antiseptic and dietary supplement. The sizes obtained by this system were in good agreement with those obtained by TEM.

Loeschner et al.\textsuperscript{(201)} demonstrated the application of AF4-ICP-MS for characterization of AgNPs in chicken meat. AgNPs were extracted from chicken meat by enzymatic digestion using Proteinase K and subsequently introduced into the AF4. Similar size distributions were observed in the digestive meat and aqueous suspension of AgNPs used for spiking into the meat. No dissolution of AgNPs in the preparation step was observed. Further, offline single particle ICP-MS was used for determination of the number-based particle size distribution.

M-M et al.\textsuperscript{(202)} investigated the changes in the size distribution of selenium nanoparticles (SeNPs) in the environment of gastrointestinal conditions by on-line SF4-ICP-MS. The pectin, mixed alginate/pectin, ovalbumin, and β-lactoglobulin-stabilized-SeNPs (the particle sizes are 64, 37, 30, and 23 nm, respectively) showed different size changes in both enzymatic and nonenzymatic media. However, SeNPs in all types of stabilizing agents were still in nanometer-sized range although they were incubated in the gastrointestinal condition.

Grombe et al.\textsuperscript{(203)} used AF4-ICP-MS as a confirmation method for characterization of silica nanoparticles that were used as reference materials in synthetic tomato soup. Silica nanoparticles were isolated from tomato soup by heating the soup for 30 min at 50°C, homogenization in a glass beaker (Ultra Turrax, IKA-T10; 30 s at 20,000–25,000 rpm), removal of the organic materials by acid digestion and stabilization of the remaining particle suspension by pH adjustment, and probe sonication before fractionation by AF4.

Heroult et al.\textsuperscript{(204)} investigated the application of AF4 with multiple detectors for size characterization of silica nanoparticles in coffee creamer. The probable parameters affecting the change in particle size changing from the original size were examined. These included the coffee creamer matrix components, extraction method, and cooking. The combination of AF4 with ICP-MS and TEM/EDAX was proved essential to provide reliable information of nanoparticle size in the complex food matrix.

Peters et al.\textsuperscript{(205)} applied AF4-ICP-MS and single-particle ICP-MS to characterize TiO₂ particles in several products: 7 food grade materials (E171), 24 food products, and 3 personal care products. Size distribution between 60 and 300 nm was found for all seven food grade materials. Approximately 10–15% and 5–10% of particles with particle sizes smaller than 100 nm were detected in all food grade, food, and personal care products. The authors mentioned that size limits of TiO₂ detection were in the
range 20–50 nm. In term of concentration, 0.02–9 mg TiO$_2$/g product was detected in 24 of 27 food and personal care products.

7 CONCLUDING REMARKS

Owing to the expanding applications of ENPs and their properties depend greatly on size, the analytical techniques used for size characterization of ENPs are necessary. FFF has been increasingly used for particle size characterization of nanoparticles. Hyphenation between FFF and atomic spectrometric detection adds the specificity for the detection. The element-specific detection is particularly useful when the samples contain mixed ENPs, such as AuNPs and AgNPs. With some size characterization techniques, DLS, TEM, only the information on the overall particle size are gained. Nonetheless, with the use of FFF coupled with atomic spectrometric detection, it is possible to differentiate the particle sizes of AuNPs and AgNPs in the mixture. Furthermore, adding the dimension on element-specific detection to the FFF size separation facilitates the characterization of ENPs in complex matrices containing natural nanoparticles. Therefore, FFF with atomic spectrometric detection should be considered as a convenient and effective tool for ENPs characterization.

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ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AF4</td>
<td>Asymmetric Flow Field-flow Fractionation</td>
</tr>
<tr>
<td>BSA</td>
<td>Bovine Serum Albumin</td>
</tr>
<tr>
<td>CNT</td>
<td>Carbon Nanotube</td>
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<tr>
<td>CPE</td>
<td>Cloud Point Extraction</td>
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<tr>
<td>CTAB</td>
<td>Cetyltrimethylammonium Bromide</td>
</tr>
<tr>
<td>CyElFFF</td>
<td>Cyclical Electrical Field-flow Fractionation</td>
</tr>
<tr>
<td>DCS</td>
<td>Differential Centrifugal Sedimentation</td>
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<tr>
<td>DLS</td>
<td>Dynamic Light Scattering</td>
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<tr>
<td>EDTA</td>
<td>Ethylene Diamine Tetraacetic Acid</td>
</tr>
<tr>
<td>EElFFF</td>
<td>Electrical Field-flow Fractionation</td>
</tr>
<tr>
<td>EM</td>
<td>Electron Microscopy</td>
</tr>
<tr>
<td>ENP</td>
<td>Engineered Nanoparticle</td>
</tr>
<tr>
<td>ESI-MS</td>
<td>Electrospray Ionization-mass Spectrometry</td>
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<tr>
<td>ETAAS</td>
<td>Electrothermal Atomic Absorption Spectrometry</td>
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<tr>
<td>ETV</td>
<td>Electrothermal Vaporization</td>
</tr>
<tr>
<td>FAAS</td>
<td>Flame Atomic Absorption Spectrometry</td>
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<tr>
<td>FFF</td>
<td>Field-flow Fractionation</td>
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<tr>
<td>FIFFF</td>
<td>Flow Field-flow Fractionation</td>
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<tr>
<td>GE</td>
<td>Gel Electrophoresis</td>
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<tr>
<td>GFAAS</td>
<td>Graphite Furnace Atomic Absorption Spectrometry</td>
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<tr>
<td>GNR</td>
<td>Gold Nanorod</td>
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<tr>
<td>GrFFF</td>
<td>Gravitational Field-flow Fractionation</td>
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<tr>
<td>HDF</td>
<td>Human Dermal Fibroblast</td>
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<tr>
<td>ICP-MS</td>
<td>Inductively Coupled Plasma Mass Spectrometry</td>
</tr>
<tr>
<td>MALS</td>
<td>Multiangle Light Scattering</td>
</tr>
<tr>
<td>ICP-OES</td>
<td>Inductively Coupled Plasma-optical Emission Spectrometry</td>
</tr>
<tr>
<td>ITO</td>
<td>Indium Tin Oxide</td>
</tr>
<tr>
<td>LC</td>
<td>Liquid Chromatography</td>
</tr>
<tr>
<td>LED</td>
<td>Light-emitting Diode</td>
</tr>
<tr>
<td>LOD</td>
<td>Limit of Detection</td>
</tr>
<tr>
<td>MPA</td>
<td>Mercaptopropionic Acid</td>
</tr>
<tr>
<td>MSA</td>
<td>Mercapto Succinic Acid</td>
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<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<tr>
<td>NP</td>
<td>Nanoparticle</td>
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<tr>
<td>NTA</td>
<td>Nanoparticles Tracking Analysis</td>
</tr>
<tr>
<td>PCS</td>
<td>Photon Correlation Spectroscopy</td>
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<tr>
<td>PLGA-b-PEG</td>
<td>poly(D,L-lactic-co-glycolic acid)-b-poly(ethylene glycol)</td>
</tr>
<tr>
<td>PVP</td>
<td>Polymethylpyrrolidone</td>
</tr>
<tr>
<td>QD</td>
<td>Quantum Dot</td>
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<tr>
<td>RBC</td>
<td>Regenerated Bacterial Cellulose</td>
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<tr>
<td>ROS</td>
<td>Reactive Oxygen Species</td>
</tr>
<tr>
<td>SdFFF</td>
<td>Sedimentation Field-flow Fractionation</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning Electron Microscope</td>
</tr>
<tr>
<td>ScNP</td>
<td>Selenium Nanoparticle</td>
</tr>
</tbody>
</table>
FIELD-FLOW FRACTIONATION WITH ATOMIC SPECTROMETRIC DETECTION

SF4 Symmetric Flow Field-flow Fractionation
SP-ICP-MS Single-particle Inductively Coupled Plasma Mass Spectrometry
SPLITT Split Flow Thin Cell Fractionation
SRHA Suwannee River Humic Acid
SWV Square Wave Voltammetry
TEM Transmission Electron Microscope
TMAH Tetra Methyl Ammonium Hydroxide
UV/VIS Ultraviolet/Visible
WWTP Wastewater Treatment Plant

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