Flow-based System: A Highly Efficient Tool Speeds Up Data Production and Improves Analytical Performance

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In this review, we cite references from the period between 2015 and 2020 related to the use of a flow-based system as a tool to obtain a modern analytical system for speeding up data production and improving performance. Based on a great deal of concepts for automatic systems, there are several research groups introduced in the development of flow-based systems to increase sample throughput while retaining the reproducibility and repeatability as well as to propose new platforms of flow-based systems, such as microfluidic chip and paper-based devices. Additionally, to apply a developed system for on-site analysis is one of the key features for development. We believe that this review will be very interested and useful for readers because of its impact on developing novel analytical systems. The content of the review is categorized following their applications including quality control and food safety, clinical diagnostics, environmental monitoring and miscellaneous.

Keywords Flow-based system, microfluidic chip, paper-based device, food control and safety, clinical diagnostic, environmental monitoring

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1 Introduction

In both modern life science and physical science laboratories, high-throughput sample handling is usually required for the purpose of efficiency. For example, within the space of analytical chemistry, the number of samples is huge and an oversized number of must be performed to determine the appropriate conditions for analysis. Up to now, laboratory automation or semi-automation has attracted a huge amount of

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attention to answer the requirements. A flow-based system is taken into account in every one of the foremost vital breakthroughs in the recent history of laboratory development. Moreover, the copious and varied advancements of automation technologies have conjointly generated a profound impact on the performing arts of analytical laboratories, wherever several manual tasks have currently been partly or utterly replaced by automatic and labor-saving instrumentation. Automation not only provides a reduction in human error and laboratory expenses but is also predominant in economic times as laboratories. Therefore, it is challenged for limited budget resources.

Flow-injection analysis (FIA) was introduced in 1975 by Ruzicka and Hansen. This system has become a necessary tool to design many modern analytical methods for various applications because of both its miniaturization advantages and the challenge of instrumentation for flow-injection analysis, such as decreasing the volume of the reagent and the sample, diminishing the volume of waste that could cause polluting, increasing the diffusion of the sample into the stream of the reagent and promoting repeatability of the methodology, robustness of the system and ease to automate or implement in an application.

Such benefits obtained from FIA are leading to the continuous development of new methodologies to fulfill the completeness system for detection. Sequential injection analysis (SIA) is the next generation of FIA which was discovered in 1990. This approach can fully automate sample manipulation that arises simple manifolds leading to the unique requirements of analysis process. For SIA, a selection valve and a bi-directional pump are the main parts employed to draw up the small volumes of the sample and the reagents and to propel them through a mixing coil to a detector. SIA has shared many characteristics with FIA; however, the concept in practice of SIA is different from FIA. The strong point of SIA is simpler hardware. It consists of one pump, one valve, and one carrier stream. In addition, this system is also more efficient in reducing the reagents and minimizing waste. It contains a simple and universal manifold of ease. Thus, different chemistries can be implemented in one manifold. Because of its advantages, there is no doubt that there have been hundreds of articles published based on the SIA concept. Moreover, batch injection (BIA), multi-commuted flow injection analysis (MCFIA), all-injection analysis (AIA), multi-syringe flow injection analysis (MSFIA), multi-pumping flow injection analysis (MPFIA), and simultaneous injection effective mixing (flow) analysis (SIEMIA) have been proposed, respectively.3,5 Nevertheless, FIA and SIA are still the most widely used techniques because there are no complicated instruments.

As can be seen, there are several hundred research papers published every year based on the flow technique and applications found in different fields. This indicates that it is a very important and vital area of analytical chemistry and related fields. Aside from optimization of the sample processing methods and devices, a very significant trend of research involves improving the detection methods. In this case an increasing importance is observed for current achievements of nanotechnology.

Another trend of flow analysis involves the miniaturization of measuring devices. Microfluidics became a major device in a variety of applications such as medical diagnostics and environmental analysis.8,9 Up to date, new instrumental constructions are focused on the design of paper-based devices,10 which are simple for mass-production and inexpensive platforms leading to be highly potential applications.

Such a very important flow-based system for the development of a modern analytical chemistry can be considered as an important part of flow chemistry. The reminiscence for five years ago concerning the development of flow-based systems for chemical and biological analysis and its progress in recent years is the main topic of this review. The outline of this review will be categorized based on their applications.

2 Application of Flow-based System for Quality Control and Food Safety

The analysis of food ingredients or contaminants is very important to provide safety because it is certainly absolute that products are safe for consumers. For food suppliers, food safety quality assurance is the first priority that is needed to be proceeded as the risk of product recalls, or warnings. These results can have a serious detrimental effect on business, brand and even ultimate outcome. Therefore, as any food or beverage products enter supply, they are subjected to sampling to comprehensive screening and testing them to ensure the regulatory and process compliance. These requirements lead to the development of analytical methods to meet the needs of users. From literature reviews, it was found that the novel methods obtained for quality control and food safety are based on optical and electrochemical detection. Therefore, the review is sequentially focused on detection methods commonly used in flow-based systems.

A flow injection analysis system employing spectrophotometric detection is still being developed to obtain a simple and fast assay for the determination of acidity in different types of wines using pH indication in an alkaline solution11 and for determining nitrate and nitrite in a variety of commercial baby foods in Fiji.12 Next, in 2019, we found the development of automated flow-based spectrophotometry for the determination of arsenic in drinking water.13 In this work, a gas-permeable membrane was used for the first time to develop a flow analysis (FA) system for the automatic detection of arsenic. In the same year, flow-based spectrophotometry was established to develop a

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procedure for the determination of sialic acid in milk using a flow-batch analysis with direct heating.\textsuperscript{14} It presents advantages of low cost, easy operation and less time for analysis compared to chromatography. In addition, Manthong \textit{et al.}\textsuperscript{20} proposed a FIA system using PEDD for the determination of antioxidant ins commercial fruit juice and instant tea products. Thongsaw \textit{et al.}\textsuperscript{25} reported on the use of SPE-FI-CVAAS for mercury detection, and applied it to freshwater fish samples. Another example is the development of flow-based spectrophotometry for immunoassays.\textsuperscript{17} They reported a continuous flow-ELISA based on the sequential injection mode for the determination of zearalenone. They are successful to reduce the analysis time from 5 h to 18 min compared to the traditional ELISA.

For using fluorescence spectrometry, we found 2 publications. First, the authors proposed a simple, non-chromatographic and green method based on flow injection UV photochemical or ultrasonic vapor generation atomic fluorescence spectrometry (AFS) for the determination and speciation analysis of mercury.\textsuperscript{18} Besides rapidness and high sensitivity, this work described a greener and relatively safe method. It can be useful for the determination of total and inorganic mercury. Finally, they also mentioned gaseous mercury hydrides that can even be directly atomized by using only UV radiation, and this can be used for mercury speciation analysis, but after chromatographic separation. In 2018, a new low-pressure flow injection chromatography (FIA-C) system with fluorescence detection was developed for the toxicological control of glibenclamide in beverages was presented.\textsuperscript{19} The advantage of this work is to determine glibenclamide in the high content of caffeine. Their proposed system combined a strategy for the separation of both compounds, and reported the relation between the high content of caffeine and the decrease of the fluorescent signal. Based on the convenience to incorporate spectrophotometric devices into microfluidic systems, we also found the development of microfluidic colorimetry for the detection of methanol from a mixed ethanol-methanol water solution.\textsuperscript{20} The proposed device has been successfully applied for the detection of methanol concentrations in commercial fruit wines. In addition, the combination of a microfluidic chip and immunosassay was proposed for the sensitive detection of alternariol monomethyl ether by UV spectroscopy and smart phone imaging in 2019.\textsuperscript{21} Under the optimal conditions, the proposed immunosassay was able to detect AME as low as 12.5 pg/mL for UV spectroscopy, and 200 pg/mL for smart phone imaging. This finding offers a good idea for making on-site analysis with simple operation.

For flow-based chemiluminescence, this mode is a superior detection method for flow injection, sequential injection, multicommuted flow, multi-pumping and microfluidic systems due to the simple instrumentation and high sensitivity involved. The optical system used requires no external light source, which not only simplifies the instrumentation, but also reduces noise, which in turn lowers the detection limit. \textit{He et al.}\textsuperscript{22} developed a novel flow-injection chemiluminescence analysis method to detect a fluorescent whitening agent (2,20-[1,10-biphenyl]-4,40-diylidene)-bis-benzensulfonic acid disodium salt (CBSS)) for the first time. \textit{Yan et al.}\textsuperscript{23} also proposed flow-injection chemiluminescence analysis for the determination of potassium bromate in flour as well. Their method is sensitive and convenient, and could be comparable to previous techniques.

For a sequential injection system, \textit{Chaiyasing et al.}\textsuperscript{24} reported on the use of a SIA method for the rapid and sensitive determination of fluoroquinoline residues, including norfloxacin, ciprofloxacin and enrofloxacin, in fish samples using eosin Y as a reagent. The last is that Alarajf \textit{et al.}\textsuperscript{25} proposed a new sequential chemiluminescence strategy for monitoring the caffeine content in soft and energy drinks. They reported on the use of nano-metal oxides as a catalytic reagent to traditional reagents to increase the sensitivity and selectivity.

Next is the development of multicommuted flow and multi-pumping based chemiluminescence detection. In 2016, a novel multicommuted flow method was described for the determination of total polyphenol using nanocolloidal manganese(IV) as an enhancer.\textsuperscript{26} The proposed system showed better selectivity, a higher degree of automation of the analytical procedure and a significant reduction of the reagent consumption and waste generation. \textit{Lara-Ortega et al.}\textsuperscript{27} demonstrated the capability of multicommuted chemiluminescence flow injection analysis (MCFIA-CL) for the determination of olive oil. They claimed that the proposed method offers a faster, safer, and more environmentally friendly procedure than the respective official or classical method. Besides, we found the use of a concept of multicommuted flow system for the preparation of sample before detection by ICP-MS to determine the cadmium content in tobacco samples.\textsuperscript{28}

For combining chemiluminescence to a multi-pumping flow system, \textit{Vakh et al.}\textsuperscript{29} proposed an automated and miniaturized chemiluminescence method for screening for fluoroquinolones in milk samples. The presented method demonstrated the possibility to be a good tool for available and cost-effective point-of-need screening fluoroquinolones. In 2019, a multi-pumping system was designed as a new assay for β-galactosidase activity\textsuperscript{30} based on the determination of p-nitrophenol formed in the reaction of enzyme-catalyzed hydrolysis of p-nitrophenyl-galactotyranosides. The method provided a high sample flow-throughput.

For microfluidic chips, chemiluminescent-based carbon dots, quantum dots and metal nanoparticles were developed for the determination of nitrite,\textsuperscript{31} food allergens,\textsuperscript{32} organophosphorus pesticides,\textsuperscript{33} foodborne bacteria\textsuperscript{34} and salmonella.\textsuperscript{35} An example for microfluidic chip is demonstrated in Fig. 1.

Another interesting idea is the development of a lateral flow assay for the rapid and quantitative detection of toxins and virus in food samples. \textit{Zhao et al.}\textsuperscript{36} developed a lateral flow assay for the rapid and quantitative detection of aflatoxin B1 in crops using a competitive up-converting phosphor technology. \textit{Wu et al.}\textsuperscript{37} and \textit{Xu et al.}\textsuperscript{38} demonstrated the use of lateral flow using aptamer and immunosassay techniques for the detection of zearalenone in corn and maize, respectively. They were successful to improve sensitivity of detection. Moreover, \textit{Chavan et al.}\textsuperscript{39} used a lateral flow chip to enhance the performance in detecting on infectious pancreatic necrosis virus, which is a remarkable problem for salmon fish farmers. Such a high technology, now a smartphone-based lateral flow imaging system, was proposed for the detection of food-borne bacteria \textit{E. coli} O157:H7.\textsuperscript{40} The obtained results suggests that a smartphone-based reader provided sufficient sensitivity for the detection of \textit{E. coli} in ground beef and spinach food matrices.

Next, we focused on the attraction of integrating an electrochemical detector into a flow-based system due to its inherent portability and easy fabrication of the micro or nanoelectrodes. The instrumentation costs for this technique are also the lowest compared to others. From literature reviews, modified electrodes and the amperometric mode are the most popular for coupling to flow-based systems. Starting from 2015, \textit{Rodriguez et al.}\textsuperscript{41} proposed the use of an antimony film electrode as an amperometric detector for a sequential injection analysis for determining azo dyes in food samples. \textit{Casella and co-worker}\textsuperscript{42} demonstrated the use of an IrOx modified electrode as an electrocatalyst toward the oxidation of semicarbazide (SEM). The proposed amperometric method appears to be an
appropriate analytical detection method for the determination of SEM, and it is more simple and inexpensive than the detection based on mass spectrometry coupled with liquid chromatographic separations. Samphao’s group developed a biosensor-based flow to determine glucose in glucose syrup, honey samples and in an energy drink. They fabricated a new electrode using the immobilization of glucose oxidase onto Au seeds decorated on core Fe₃O₄ nanoparticles. Next year, Sağlam et al. also proposed a biosensor-based flow for the determination of glucose. They employed a glucose oxidase-quantum dot modified pencil graphite electrode as a sensor. They received a lower limit of detection than previously. Another application for a glucose sensor has been reported by Vargas et al. The strategy involves on-line microdialysis sampling coupled with a continuous flow system with amperometric detection at an enzymatic biosensor. The method can perform a straightforward sample preparation leading to low-cost and reduced assay time. Amatatongchai and coworkers reported a simple amperometric flow system for the determination of sulfite using a carbon nanotubes-PDDA-gold nanoparticles modified glassy carbon electrode. An enhancement of the sensitivity compared to a bare glassy carbon electrode was obtained. A cyclometalated Rh(III)-complex/CNTs modified glassy carbon electrode was integrated with the FIA system to monitor nitrite reported by Hallaj et al. Based on the performed experiment it is anticipated that a fabricated sensor could be applied to the determination of nitrite in food samples successfully with moderate increased speed. Another nitrite sensor was described by Promsuwan and coworkers. They reported an electrochemical sensor based on a screen-printed carbon electrode (SPCE) modified with silver microcubics-polyacrylic acid/poly vinyl alcohol (AgMCs-PAA/PVA) for nitrite determination by using a flow-injection amperometric system. The obtained sensitivity was lower than previously, however, it is high sufficient for application. Since the screen-printed technology came to play an important role, we found the development of a screen-printed carbon electrode modified by graphene nanoribbons-ionic liquid-cobalt phthalocyanine composites for the determination of fenobucarb using FIA as a tool for increasing the reproducibility and sample throughput. In 2020, a flow-injection analysis method with amperometry was developed using a reduced graphene oxide (RGO)-based sensor to determine ascorbic acid in food beverage samples. The main advantages of this method were the high analytical frequency and the minimum sample preparation step, thus avoiding the use of expensive operation.

Lastly, Deroco’s group presented a simple flow-injection analysis coupled to multiple-pulse amperometry for simultaneous determination of sunset yellow and aspartame using a borondoped diamond electrode. The method is simple and fast, with a high speed of 120 determinations per hour, being an attractive option for routine work.

Another interesting design is the combination of an analytical flow system and low-pressure chromatography for the analysis of niacin by amperometric detection. The manifold comprised a monolithic column and a boron doped diamond electrode. In comparison to the traditional HPLC for niacin determination, this method displays a simple configuration and low cost as well as fast and easy assembling.

For a microfluidic chip, electrochemical detection is ideal for integrating to a microchannel. Jiang et al. created a novel cell-to-cell electrochemical microfluidic chip for the qualitative and quantitative analysis of food allergen. This finding provides a...
general example of rapidly prototyped low-cost biosensor technology. In addition, a microfluidic aptasensor for the detection of bio-toxin, okadaic acid was introduced last year by Ramalingam et al.54 The screen-printed carbon electrode (SPCE) modified by a phosphorene-gold nanocomposite was a sensor. Electrochemical measurements were performed using differential pulse voltammetry. The application was applied to on-farm assays in fishing units.

For the last point, as we knew very well that paper-based devices are a new platform for analytical detection. A simple and low-cost continuous-flow electrochemical paper-based analytical device (PAD) was presented55 in 2020 by Henry’s group. They utilized polycaprolactone (PCL) as a TPE binder to create our continuous-flow electrochemical μPAPDs. As a proof of concept, the proposed system was used to determine caffeic acid (CA) in tea samples. The use of paper substrates involves easy-to-make electrodes that do not require external mechanical pumping systems or complicated valves. Therefore, this proposed idea could be a new alternative platform to design a simple device for various applications.

3 Application of Flow-based System for Clinical Diagnostics

The main goal to create microfluidic systems is to systematize all analytical processes into one microdevice that can carry out sequential sampling, sample pretreatments, analytical separations, chemical reactions, analyte detection and data analysis processing. As a result, the development of a miniaturized platform and detection mode with high sensitivities and high signal-to-noise ratios, fast response times and multiplex functions for microfluidic systems is an important role. There are numerous studies that integrate various detection schemes with microfluidic platforms, which can be categorized into optical detectors and electrochemical detectors. Subsequently, integrated microfluidic systems with optical and electrochemical detection modes for clinical diagnostic are summarized in Table 1 and Table 2, respectively. An example for microfluidic chip with optical detection is shown in Fig. 2.

Besides, regarding the development of a microfluidic system for clinical diagnostic, there are other platforms for a flow-based system, including the use of a basic flow-injection system and optoelectronic devices for the determination of dialysate urea nitrogen,92 automated flow-based plasmonic ELISA for detection of biomolecule and small contaminants,93 Based on simple flow-injection amperometric detection, we found the concept of a lateral flow assay for the determination of HIV-1 DNA,96 thyroid-stimulating hormone,97 DNA quantification for phenylketonuria diagnostic,97 C-reactive protein,108 exosomes,110 and a scrub typhus biomarker.111 For using paper as a substrate for creating caffeic acid (CA) in tea samples. The use of paper substrates involves easy-to-make electrodes that do not require external mechanical pumping systems or complicated valves. Therefore, this proposed idea could be a new alternative platform to design a simple device for various applications.

4 Application of Flow-based System for Environmental Monitoring

Environmental analysis is a strategic plan that describes the process concerning the determination of all components, which has a high potential on the arranging the organization. Environmental analysis or environmental screening provides critical information concerning the creating process that is not only used to control the quality of environment, but also directly affects human beings. Significant changes, events and trends could be monitored on a regular basis in order to make timely adjustments to the strategic plan. The advantages of a flow-based system lead to an important part for development of analytical methods for environmental biomarkers. In addition, in 2020, Teshima et al.116 reported on the development of testing methods for water quality by flow analysis.

Flow injection analysis (FIA) and sequential injection analysis (SIA) coupled with the optical mode is finding increased use in environmental analysis because of its promising challenge to increase sensitivity and sample throughput. In 2016, Wang et al.117 developed the FIA system for the determination of nitrate plus nitrite using vanadium(III) as new reductant and recorded the absorbance at selected wavelengths. Next, an on-line flow-injection spectrophotometric method coupled with supported liquid membrane enrichment was developed to determine trace Hg(II) in water at the micro-molar level.118 Yanaga and colleagues119 developed a FIA system hybrid micr-gas unit for the simultaneous determination of formaldehyde and ozone. The use of FIA can improve the vapor of formaldehyde in the presence of ozone. Using a similar concept for the hybridization of a gas flow reactor and FIA, Chaisiwamongkhol et al.120 demonstrated a new flow system for investigation the efficiency of synthesized TiO₂ photocatalysts for NO₂ degradation followed by monitoring NO₂ emission which is a serious environmental problem worldwide.

Regarding spectrophotometric FIA, Liang et al.121 established the system to determine ammonia nitrogen in water using a NH₃–o-phthalaldehyde (OPA)–Na₂SO₃ reaction to produce a rose red product. Denna et al.122 described the selective determination of copper(II) in a river-water system using a polymer inclusion membrane (PIM) via a continuous-flow system.

For using the chemiluminescence mode, toxic organic and inorganic substances were highlighted as target analytes for developing method. In 2018, Murillo Pulgarin et al.123 reported on a method for the simultaneous measurement of carbaryl and 1-naphthol in soil. Furthermore, in 2019, Asghar et al.124 presented the new assay for the determination of manganese(II) using a surfactant as enhancer signal obtained and Zhang et al.125 exhibited the method based on “turn off-on” for the simultaneous determination of iodide and mercury contaminated in water samples.

As mentioned, the SIA is a powerful fully automated system that is easy to control by a computer. Therefore, there is no doubt to see that many research groups published their work by using SIA. Sklenářová et al.126 proposed a SIA system as a speed tool for monitoring aluminum content in water samples. Falkova et al.127 applied their developed SIA coupled with IR for the determination of petroleum products in water. Machado et al.128 used SIA for the determination of NO₃ in natural water. They presented a concept of a greener method for inline nitrate reduction in the SIA system. Giakisikli et al.129 reported on the integrated SIA for determination of ammonium in recycled water produced on a board in a manned space mission because SIA provided the specifications for fully on-line monitoring in
under the space condition. Next, Lin and co-workers\textsuperscript{130} described the automatic and sequential determination of multi-nutrient elements in natural water samples. They received a high sample throughput and can be applied for various kinds of nutrient elements in natural water samples and wastewater. They were the first group to transfer the chromotropic method to a microfluidic CM platform. Moreover, lab-in-syringe and SIA systems were proposed for speciation analysis\textsuperscript{135} and lab-on-valve sequential injection ELISA for the determination of carbamazepine.\textsuperscript{136}

The microfluidic platform still becoming important for developing new methods for environmental applications. Starting from 2015, Cogan et al.\textsuperscript{137} progressed a miniaturized microfluidic colorimetry for direct measurements of nitrate in natural water samples and wastewater. They demonstrated the use of aqueous-phase microfluidics (ATPM) for the selective extraction of bisphenol A in aqueous samples before injection to HPLC.

| Analyte | Sample | Linear range | Detection limit | Ref. |
|---------|--------|--------------|----------------|------|
| Blood glycated hemoglobin (HbA1c) | Blood samples | 0.46 - 1.85 g dL\textsuperscript{-1} | 0.65 g dL\textsuperscript{-1} | 56 |
| The total hemoglobin (Hb) | Patient-mimicked serum | 1 μM - 10 μM | 15 FM | 57 |
| Cancer antigen (CA125) | Serum | 0 - 30 kU L\textsuperscript{-1} | 0.16 kU L\textsuperscript{-1} | 58 |
| HER2 | Human plasma samples | 0 - 1 U mL\textsuperscript{-1} | N/A | 59 |
| Epithidymis protein 4 (HE4) | Glutamate | N/A | 12.5 - 250 mg dL\textsuperscript{-1} | 60 |
| Eotaxin-1 | Glutamate | N/A | 3.2 HAU | 61 |
| Immunoglobulin-E (IgE) | Glutamate | N/A | 0.032 HAU | 61 |
| Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) | Glutamate | N/A | 3.2 HAU | 62 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
| Glutamate | Glutamate | N/A | 0 - 20000 pM | 20 pM | 63 |
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This finding represents potent candidates for multipathogen detection in various approaches.

| Analyte                              | Sample                                           | Linear range       | Detection limit       | Ref.  |
|--------------------------------------|--------------------------------------------------|--------------------|-----------------------|-------|
| Human cartilage chitinase-3-like protein 2 (hYKL-39) | Synovial fluids and cell lysates                  | 0.1 – 1000 μg L⁻¹ | 0.074 μg L⁻¹          | 81    |
| 4-Aminophenol (4-AP)                  | Pharmaceutical paracetamol (PA) formulations      | 50 - 500 μM        | 15.68 μM              | 82    |
| Naproxen (NPX)                        | Tablets                                           | 1.0 – 1000.0 μM    | 0.29 μM               | 83    |
| Melanoma cells                        | Peripheral blood mononuclear cells (PBMC)         | 10 – 9000 cells/10 mL | N/A                  | 84    |
| Different circulating tumor cells (CTCs) | Patient blood samples                            | 100 – 25000 cells/mL | N/A                  | 85    |
| Uric acid (UA)                        | N/A                                              | 5.0 – 1000.0 μM    | 1.1 μM                | 86    |
| Hydrochlorothiazide (HCZ)             |                                                  | 5.0 – 750.0 μM     | 1.1 μM                |       |
| Ascorbic acid (AA)                    |                                                  | 100.0 – 2500.0 μM  | 6.8 μM                |       |
| Epinephrine (EP)                      |                                                  | 100.0 – 2500.0 μM  | 5.3 μM                |       |
| Glucose                              | Urine sample                                     | 0.1 – 40 nM        | 0.03 nM               | 87    |
| IgG antibodies anti-Toxocara canis (IgG anti-T. canis) | Human serum samples                              | 0.33 – 75 ng mL⁻¹  | 0.10 ng mL⁻¹          | 88    |
| C-reactive protein (CRP)              | Serum and preterm neonatal plasma samples         | 1 – 100 μg mL⁻¹    | 0.40 μg mL⁻¹          | 89    |
| miRNA-197                             | Human serum samples                              | 1.28 – 87 nM       | 1.28 nM               | 90    |
| Sandwich assay                        |                                                  | 4.05 – 84 nM       | 4.05 nM               |       |
| Competitive assay                     |                                                  |                    |                       |       |
| Dopamine                              | Plasma samples                                    | 0.05 – 130 nM      | 0.034 nM              | 91    |
| Norepinephrine                        |                                                  | 0.055 – 130 nM     | 0.037 nM              |       |
| Epinephrine                           |                                                  | 0.055 – 130 nM     | 0.037 nM              |       |
| 3,4-Dihydroxy-l-phenylalanine         |                                                  | 0.06 – 125 nM      | 0.039 nM              |       |
| 5-Hydroxytryptamine                   |                                                  | 0.06 – 125 nM      | 0.039 nM              |       |
| 5-Hydroxyindoleacetic acid            |                                                  | 0.07 – 120 nM      | 0.041 nM              |       |
| 5-Hydroxytryptophan                   |                                                  | 0.07 – 120 nM      | 0.044 nM              |       |

Fig. 2 Schematic illustration of the SERS-based microdroplet sensor for a wash-free magnetic immunoassay. The sensor is composed of five compartments with the following functions: (i) droplet generation and reagent mixing, (ii) formation of magnetic immunocomplexes, (iii) magnetic bar-mediated isolation of immunocomplexes, (iv) generation of larger droplets containing the supernatant for SERS detection and (v) generation of smaller droplets containing magnetic immunocomplexes. Reprinted from Ref. R. Gao, Z. Cheng, A. J. deMello, and J. Choo, Wash-free Magnetic Immunoassay of the PSA Cancer Marker Using SERS and Droplet Microfluidics, Lab on a Chip, 2016, 16, 1022, with permission from the Royal Society of Chemistry.
proposed by Liu and colleagues.\textsuperscript{140} Cr(VI) was used as a model analysis. This method can eliminate additional sample conditioning as well as reduce sample consumption and the analysis time. Besides, Yoosefian \textit{et al.}\textsuperscript{141} presented the concept of a photothermal lens and microfluidics for the femtomole detection of 2,4,6-trinitrotoluene.

A miniaturized fiber-optic colorimetric sensor\textsuperscript{142} and a wavelength-ratiometric fluorescent quantum dot pair\textsuperscript{143} were built on microfluidics to detect small ions such as nitrite and copper, respectively. Now, a portable microfluidic surface-enhanced Raman scattering\textsuperscript{144} was proposed to detect uranyl ions as low as \(7.2 \times 10^{-13}\) M. For gaseous species, microfluidics can be adapted for the on-line determination of formaldehyde.\textsuperscript{145} They can reduce the response time and improve the compactness of the system. Moreover, a microchip biosensor based on immunoassay was developed for the rapid detection of \textit{Legionella pneumophila} in surface water,\textsuperscript{146} and for fast screening of tetracyclines in environmental and food samples.\textsuperscript{147}

Not only the use of only a flow-based system as a tool for detection, but also a flow-based system/spectrometry hybrid and a flow-based system/chromatography hybrid were developed. For a flow-based system/spectrometry hybrid, they are popular for the developed method to quantify metals.\textsuperscript{148–152} For a flow-based system/chromatography hybrid, they were found to be a part of sample preparation before moving into a chromatographic system. Applications can apply to organic and inorganic compounds.\textsuperscript{153–156}

The development of advanced manufacturing is a necessary part to design modern analytical tools. Therefore, 3D printing has become a new choice for working in analytical fields. Calderilla \textit{et al.}\textsuperscript{157,158} proposed a 3D printed device for the automated speciation of iron and Cr(VI) using the multisyringe flow-injection analysis. The group of Mattio\textsuperscript{159} demonstrated a 3D-printed flow system for the determination of lead in natural water samples. Yamashita \textit{et al.}\textsuperscript{160} demonstrated the use of the 3D printing technique for the fabrication of a FIA manifold for phosphate determination in water. Lastly, Ceballos \textit{et al.}\textsuperscript{161} exhibited the use of a 3D printed device for uranium(VI) extraction using flow-through magnetic-stirring assisted system. These findings met portability and simplicity requirements for low cost analysis.

Due to well-known benefits of paper, it is becoming interesting material for various analytical platforms. A microfluidic paper-based device is very popular for this field. Many researchers have described this platform for improving their work. Alahmad \textit{et al.}\textsuperscript{162} presented a microfluidic paper-based analytical device for the determination of Cr(III) using chemiluminescence. Zhu \textit{et al.}\textsuperscript{163} reported on a paper-based microfluidics for a highly sensitive and label-free determination of thiram residue using surface-enhanced Raman spectroscopy. Yamada and team\textsuperscript{164} reported on the distance-based detection with color screening. Nickel was used as an analyte for a prototype of concept. Lin and co-workers\textsuperscript{165} illustrated an environment-friendly fabrication strategy for microfluidic paper-based analytical devices, and applied it for bacterial detection. Mako \textit{et al.}\textsuperscript{166} proposed an ultrasensitive detection of nitrite through the implementation of \(N\)-(1-naphthyl)ethylene diamine-grafted cellulose into paper. The device can enhance the performance by around 12.9-fold compared to the typical assay. Last, Zhou \textit{et al.}\textsuperscript{167} presented the use of newly fluorescent ZnSe quantum dots with ion imprinting technology for fabricating a three-dimensional (3D) rotary paper-based microfluidic chip platform. It can be used for the specific and multiplexed detection of cadmium and lead. Therefore, a microfluidic paper-based device showed promising application prospects for the rapid testing of target analytes in the environmental in the future.

For constructing a flow-based system and electrochemical detection for environmental analysis, we classified a group by detection techniques. First is a voltammetric flow sensor. Based on the high sensitivity of stripping voltammetry, thus, this technique is famous for the determination of metals at low levels.\textsuperscript{166–171} The design of a flow diagram is created for single and simultaneous detection based on the objective. The common working electrode material used are modified electrode with nanomaterials and polymers. For other analytes, we found the use of a microfluidic paper-based analytical device for measuring the biotoxicity of pollutants.\textsuperscript{172} Amperometric detection is the most favorite mode for the flow-
based system. The applications can be seen for organic analytes such as organophosphate insecticides, ascobic acid, 2,3-dihydroxybenzoic acid and pyrocatechol and phenol. Applications of inorganic analyte detected by amperometric flow-based system are chlorine, heavy metals (Pb(II), Cd(II) and Cu(II)), manganese and arsenic.

Potentiometric detection can be observed for ion-selective sensors. However, their applications are narrow. Chango et al. developed a simple potentiometric chip-based multipumping flow system for the simultaneous determination of fluoride, chloride, pH, and redox potential in water samples. They can analyze 12 samples per hour. Pol et al. developed automated devices for real-time monitoring by integrating a screen-printed sulfide-selective sensor on a 3D-printed potentiometric microfluidic platform. This appealing device could constitute a new choice for the production of functional monitoring devices. Ding and Lisak demonstrated the application of new materials and sponges for use in microfluidic solution sampling integrated with ion-selective electrodes. They serve as alternatives for microfluidic paper- and textile-based sampling for ion analysis in various environmental (Cd(II), Pb(II) and pH) and clinically (K+, Na+, Cl−) relevant samples based on the selection of the sponge type.

Last is conductivity detection. For this type of detector, it is not generally found in applications. However, it still another choice for the detection of small inorganic molecules. Somboot and the group reported on using a homemade direct current (DC) conductivity detector as an alternative cost-effective detection for determination of dissolved inorganic carbon (dissolved CO2, HCO3− and CO32−) in water. Fifteen injections per hour of the sample throughput can be obtained. In 2019, Li et al. demonstrated an online conductometric flow-through analyzer for ammonia monitoring in the wastewater treatment process (Fig. 3). Membrane diffusion was used to trap gas produced in a received solution before converting to ammonia in the sample solution. They are being successfully applied in real-time ammoniacal nitrogen monitoring at different wastewater treatment stages without any pretreatment. Hence, it is a promising method for ammonia controlling in a water environment.

5 Application of Flow-based System for Pharmaceutical and Biomedical Applications

The measurement of chemical species in pharmaceutical and biomedical samples is a field in which analytical chemistry plays an important role to contribute new procedures of analysis and instrumentation. Therefore, many methods have been developed. Flow-based systems can be coupled to various detection systems, such as a spectrophotometer as exhibited in Fig. 4, which allows for a wide range of analytical devices to be obtained. To complete the review, the application of flow-based systems to pharmaceutical and biomedical applications are summarized in Table 3.

6 Conclusion

The measurement of high-impact target analytes in food, clinical, environmental and miscellaneous samples is an area in which analytical chemistry provides significant roles to contribute new assays of analysis and instrumentation. Many research groups aimed at the monitoring of chemical species in various samples and many methodologies have been developed, investigated and validated. The combination of flow-based systems to analytical techniques leads to enhance the analytical performances in term of the sensitivity, reproducibility and speed of analysis. In addition, such a development of advanced technology in manufacturing also leads to the design of novel analytical platforms without any precedent in history. These findings represent a step forward toward the improving the analytical detection to be highly potential systems for applications. Moreover, these developments remind us of the
excitement in the early step of FIA to the present. The presented systems stand out by their design, portability, and simplicity for cost-effectiveness analysis. We hope they inspire a new generation of researchers to have new ideas and to focus on future work. This will lead to the growing ranks of contributed generation of researchers to have new ideas and to focus on future work. This will lead to the growing ranks of contributed studies that have impacts on analytical chemistry, and become a partner to other techniques.

7 References

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