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Multisyringe Flow Injection Technique for Development of Green Spectroscopic Analytical Methodologies

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ABSTRACT Since its creation, the Multisyringe Flow Injection Analysis (MSFIA) technique has proved to be a highly useful tool for the automation of sample pretreatment procedures prior to spectroscopic detection (UV-vis spectrophotometry, fluorescence, or chemiluminescence). This article reviews the recent applications of the MSFIA technique and how they have contributed to the Green Analytical Chemistry field. These contributions are mainly based on the development of multicommutated analytical methodologies for the minimization of the consumption of reagents, automation and miniaturization of solid phase extraction, reagent immobilization, or in the automation and miniaturization of the required pretreatments prior to separation techniques.

KEYWORDS automated sample pretreatment, Green Chemistry, Multisyringe Flow Injection Analysis, spectroscopic detection

INTRODUCTION

It is a well-known fact that the production of any chemical activity produces some impact just by itself, while a huge number of chemical substances or chemical processes are widely used in increasing the quality of life, but also producing an environmental impact, in some cases of worldwide extension. Concerning these problems in 1990s emerged a new movement called Green Chemistry (GC),^[1] promoting the use of chemistry with the aim of the minimization of the feedstocks and by-products produced in the use of any chemical activity. Green Analytical Chemistry (GAC) is a sub-area of GC, recently reviewed by Armenta et al.^[2] GAC is based on the improvement of analytical methodologies for the determination of target compounds in any area of interest, turning on the classical methodologies in a more environmentally friendly ones.^[3,4] Here it should be pointed out that flow injection (FI)^[5] techniques are a powerful tool for greening classical analytical methodologies. Since their creation (in the 1970s) until now, the first Flow Injection Analysis (FIA) systems^[6] have been improved gradually by the development of the Sequential Injection Analysis (SIA) systems,^[7] the Multicommutated Flow Injection Analysis (MCFIA) systems,^[8] or the

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Multisyringe Flow Injection Analysis (MSFIA) systems.^[9-12] The evolution of flow techniques produces an improvement in the automated handling of fluids, providing an increase in efficiency, accuracy, economy, and quickness, besides other relevant features. The use of these techniques allows the approximation of the classic analytical methodologies, to the principles stated by the GC movement.

This revision is focused in the recent contributions of the MSFIA technique in the automation of analytical methodologies with spectroscopic detection, and how these improved methodologies have contributed to the GC or GAC field.

GREEN ANALYTICAL CHEMISTRY (GAC)

It is a well-known fact that the amounts of waste products generated in a laboratory-scale process are lower than those generated in an industrial-scale process. Nevertheless, it is an important fact that requires consideration due to the high number of hazardous chemicals used, starting for the sample preservation procedures and finishing in the cleaning procedure of the instrumentation used once the analysis is completed. As a representative example, in the use of analytical methodologies for the determination of hazardous substances for the environment, ironically the chemicals used along the analytical methodology often contribute to further environmental problems.

The Green Chemistry movement is based in 12 principles.^[1] Between them, the most applicable to analytical chemistry are the following: (a) waste prevention; (b) use of safer chemicals; (c) design for energy efficiency; (d) reduce derivatives; (e) real-time analysis for pollution prevention; and (f) inherent safer chemistry for accident prevention. If we are talking about the development of analytical methodologies, the expression “Green Chemistry” is usually related to the design of improved methods in which the use or generation of hazardous substances is reduced or completely removed.

The different contributions of the flow techniques to the development of greener analytical methodologies can be established in a priority order^[13]. An ideal analytical methodology from the point of view of GC should be a reagentless procedure. If it is not possible, the next step should be the replacement of hazardous reagents for other more benign

ones. Advantageous characteristics of these two greener alternatives can be increased with the use of FI techniques owing to their intrinsic advantages, such as the downscaling of the different analytical operations that make up an analytical methodology. But when the use of reagents is indispensable and the substitution of these is not a feasible option, the best alternative is the minimization of its consumption. At this point is when the automation of analytical methodologies by means of FI techniques plays its main role in the GC context.

Lastly, if any of the previous options is applicable in a concrete analytical methodology, the use of FI techniques could facilitate the implementation of other alternatives such as the waste recycling (with concomitant reutilization) or the automated treatment of the generated waste products.

MULTISYRINGE FLOW INJECTION ANALYSIS (MSFIA) TECHNIQUE

MSFIA technique is based on the use of a multisyringe burette for the automated handling of fluids into a flow network (FN). The FN is specially designed for the implementation of each concrete analytical methodology. As can be seen in Fig. 1, the multisyringe is composed of a maximum number of 4 syringes of different volumes (usually between 1–10 mL). Syringes are set between a metal bar common to all of them, and a three-way solenoid valve for each one of them. The four syringes are displaced simultaneously and at the same flow rate (only if all of them have the same volume). Each syringe, as can be seen in Fig. 1, achieves four different movements: (a) Pickup in “Off” position (Load solution from a reservoir); (b) Pickup in “On” position (Load solution from the FN); (c) Dispense in “Off” position (Unload solution toward a reservoir); (d) Dispense in “On” position (Unload or inject solution toward the FN). MSFIA technique presents a high flexibility in the automated handling of fluids due to its 32 different combinations for flow management (if four syringes are used). The current versions of the commercialized multisyringe modules have a piston pump of 40.000 steps, which allows a perfectly reproducible flow management at the μ L range (1 motor step = 25 nL of flow displacement, using a 1 mL syringe).

This flexible and precise flow management provided by the MSFIA technique allows the

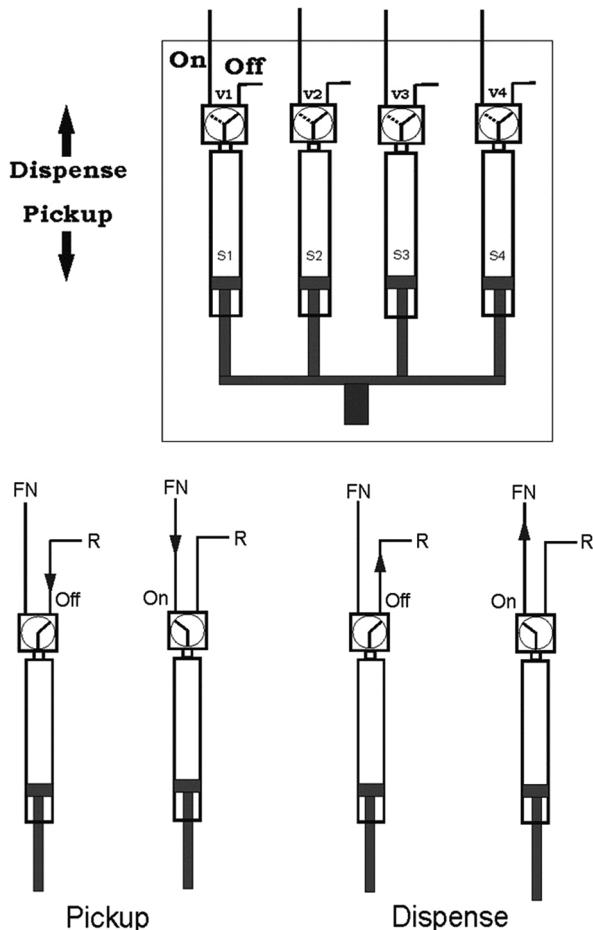


FIGURE 1 (Up) Schematic representation of a typical multi-syringe burette used in MSFIA systems. (Down) Different possibilities of fluid handling allowed by each syringe of a multisyringe burette.

implementation of acknowledged analytical methodologies in a more environmentally benign way. It is produced due to the efficient downscaling of the different pretreatment steps required in each concrete analytical method, such as: sampling, development of chemical reactions, solid- or liquid-phase extraction, membrane isolation (gas diffusion, pervaporation, dialysis), mineralization (UV, chemical, microwave), or separation procedures (capillary electrophoresis, liquid chromatography). Furthermore, the selection of the MSFIA technique for the automation of analytical methods provides other advantageous features in comparison with the other existent flow techniques, such as: (a) robustness similar to SIA technique, avoiding the use of the Tygon® tubes commonly used in FIA and MCFIA systems, thus allowing the use of aggressive reagents (concentrated acids or organic solvents); (b) as in a multicommutated technique, the volumes are

perfectly controlled, obtaining a saving of reagents in comparison with classical FIA systems; (c) the required volumes of sample and reagents can be injected toward the detector following a forward flow scheme as in FIA technique, thus avoiding the usual problems in the development of the reaction product when two or more reagents are used in SIA technique. By this way the injection throughput is increased, and thus the efficiency of the system.

CONTRIBUTIONS OF THE MULTISYRINGE FLOW INJECTION TECHNIQUE AS A TOOL FOR GREENING SPECTROSCOPIC ANALYTICAL METHODOLOGIES

Simple Multicommutated Procedures with Spectroscopic Detection

Several analytical methodologies have been implemented in the MSFIA technique through the use of multicommutated procedures, minimizing by this way the consumption of reagents. These methodologies are based in the precise injection of the minimum amounts of the required reagents to carry out a concrete determination. Some examples that can be found in the recent literature are: (a) the spectrophotometric determination of S^{2-} in waters by the methylene blue method, diminishing the consumption of N,N-dimethyl-p-phenylenediamine (DMPD), $NH_4Fe(SO_4)_2$ and HCl^[14]; (b) the time-based determination using fluorimetric detection of Al^{3+} in drinking waters using 8-hydroxyquinoline-5-sulphonic acid,^[15] or the (c) multicommutated procedure for the spectrophotometric determination of Cl^- in waters^[16] using Fe^{3+} and $Hg(SCN)_2$. In all the previous examples the consumption of reagents is diminished in comparison with FIA systems and in similar levels than in SIA systems but achieving higher injection throughputs than these last ones.

If we study more deeply the concrete case of the spectrophotometric determination of Cl^- in waters based on the $Cl^-/Hg(SCN)_2/Fe^{3+}$ reaction system where the reaction product $[Fe(NCS)(H_2O)_5]^{2+}$ is followed at 470–480 nm, we can appreciate that it is a very useful methodology (easy, cost-effective,

sensitive, reproducible, and quick—overcoat if it is automated). By this reason, the automated version of this methodology is an acknowledged reference method.^[17,18] However, this method presents a serious drawback, that is, the use of considerable amounts of $\text{Hg}(\text{SCN})_2$, a highly toxic reagent. Since the first direct FIA system for this purpose^[19] in the year 1976, the reagent consumption was improved following alternative strategies based on automation such as membrane reagent introduction in 1998,^[20] the $\text{Hg}(\text{SCN})_2$ immobilization in an epoxy resin in 2005,^[21] or the multicommutated MSFIA procedure in 2008.^[16] The consumption of Fe^{3+} and $\text{Hg}(\text{II})$ for the previously commented systems can be seen in Table 1. We can appreciate a progressive reduction in the consumption of $\text{Hg}(\text{II})$ with the concomitant increase of the automation degree. With the MSFIA method^[16] the lowest reagent consumption levels are achieved. The manifold correspondent to this MSFIA system for the spectrophotometric determination of chloride in waters is schematically depicted in Fig. 2.

Another improvement is the combination of MSFIA technique with cold vapor atomic absorption spectrometry (CVAAS)^[22] and cold vapor atomic fluorescence spectrometry (CVAFS),^[23] both for the determination of mercury in water and fish samples (after manual mineralization of the solid sample). In this line must be added the proposed MSFIA systems with hydride generation atomic fluorescence spectrometry (HGAFS) for the determination of inorganic arsenic,^[24] inorganic antimony,^[25] and for the speciation of inorganic selenium^[26] and inorganic arsenic.^[27] On the one hand, as seen in Table 2, the implementation of these methodologies in the MSFIA

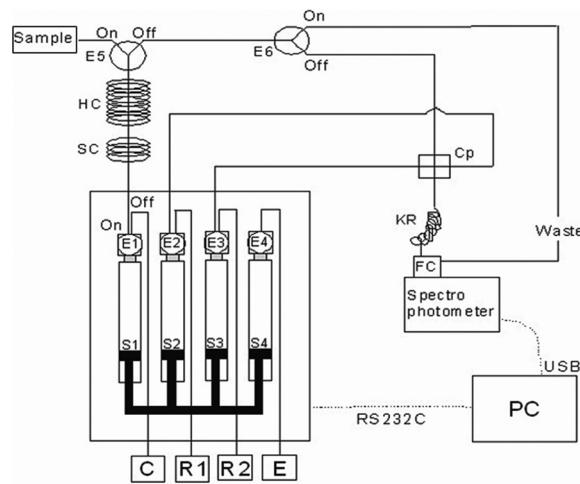


FIGURE 2 Schematic representation of the MSFIA manifold for chloride determination. C: carrier (distilled water); R1: $\text{Hg}(\text{SCN})_2$ reagent; R2: Fe^{3+} reagent; E: empty (not used); S1–S4: syringes; E1–E6: solenoid valves; On–Off: solenoid valves positions; SC: security coil; HC: holding coil; Cp: confluence point; KR: knotted reactor; FC: flow cell.

technique provides a lower consumption of reagents than in FIA systems and a concomitant high efficiency as can be seen in the injection throughput values. On the other hand, the reagent consumption is similar or higher than in SIA systems, but still maintaining a higher efficiency in terms of injection throughput.

Solid Phase Extraction

Another relevant alternative in the implementation of analytical methodologies in a cleaner way, is the use of solid-phase extraction (SPE) instead of the classic liquid–liquid extraction (LLE). An improved and greener way to perform SPE is based on its miniaturization and consequent exploitation in

TABLE 1 Summarized Analytical Performance of Several Flow Systems for the Spectrophotometric Cl^- Determination Based on the $\text{Cl}^-/\text{Hg}(\text{SCN})_2/\text{Fe}^{3+}$ Reaction System

	Ref. 19	Ref. 20	Ref. 21	Ref. 16
Linear range (mg L^{-1})	0–40	0.3–25	2–8	1–40
LOD (mg L^{-1})	–	0.3	0.5	0.2
R.S.D. (%)	–	–	2.2	0.8
Injection throughput (h^{-1})	300	18	100	130
Type of water sample	River	River-pond	Natural	Mineral-tap-well
$\text{Hg}(\text{II})$ (μmg per determination)	680	600	120	45
$\text{Hg}(\text{II})$ consumption	–	1.1 fold lower	5.7 fold lower	15.1 fold lower
$\text{Fe}(\text{III})$ (μg per determination)	7210	11100	50000	335
$\text{Fe}(\text{III})$ consumption	–	1.5 fold higher	6.9 fold higher	21.5 fold lower

* $\text{Hg}(\text{II})$ and $\text{Fe}(\text{III})$ consumptions are referred to ref. [19].

TABLE 2 Comparison of MSFIA Systems with AFS or AAS Detection with Analogous FIA and SIA Systems

Technique analyte	CVAAS mercury 22		HGAFS arsenic 24		HGAFS antimony 25		HGAFS selenium 26	
Reference	SnCl ₂ (mg inj ⁻¹)	IT (h ⁻¹)	NaBH ₄ (mg inj ⁻¹)	IT (h ⁻¹)	NaBH ₄ (mg inj ⁻¹)	IT (h ⁻¹)	NaBH ₄ (mg inj ⁻¹)	IT (h ⁻¹)
FIA	27.5	90	56	45	26–60	40–51	36	48
SIA	0.5	30	0.6	33	—	—	—	—
MSFIA	8	44	0.72	113	0.9	80	0.63	84

IT—Injection throughput.

automated FI systems, besides the direct sensing of the analytical signal in the same surface of the solid support.

The use of the MSFIA technique for the in-line SPE procedures for analyte isolation and preconcentration provides a reduction of the required amounts of solid sorbents and eluents. Some examples of SPE–MSFIA systems presented in the literature are: the preconcentration and fluorimetric determination of warfarin in waters using a packed column with a C₁₈ resin^[28]; the determination of arsenic in waters by HGAFS using a packed column with an anion exchange resin,^[29] the smart analyzer for the determination and speciation of iron in waters using chelating disks,^[30] the spectrophotometric determination of the total phenolic index based in the 4-aminoantipirine method using a packed column with Amberlite XAD-4 resin^[31]—in which LLE with chloroform is substituted by an in-line SPE procedure; or the spectrophotometric determination of nitro-substituted phenol isomers based on the use of sorbent disks made from co-polymeric poly(styrenedivinylbenzene) modified with benzenesulphonic groups.^[32]

Furthermore, if we are talking about efficiency in analytical methodologies, we have the requirement to talk about the MSFIA methods and its combination with multipumping flow systems (MPFS),^[33] implemented for the sample pretreatment of radioactive species. The required pretreatment for matrix isolation is accomplished in a completely automated fashion, saving reagents and time per determination. Once the sample pretreatment has been completed, the target analytes are determined off-line with a low background proportional counter. In the recent literature appear two MSFIA systems for the pretreatment of the determination in waters of radioactive strontium^[34] and radioactive yttrium.^[35] Furthermore can be found two hybrid MSFIA—MPFS systems for

the pretreatment of the determination of radium^[36] in waters and for the separation and preconcentration of americium and plutonium in waters^[37] using a transuranide (TRU) resin.

Finally, a relevant fact in the contribution of SPE–MSFIA procedures in the sample pretreatment prior to spectroscopic measurements is the accomplishment of reflectometric measurements based on optical fiber flow-through optical sensors (optrodes).^[38] By this way is attained a considerable reduction in the consumption of reagents in comparison with reflectometric batch or classic FIA systems. Some examples of this are: the flow-through optical fiber sensor for sulphide determination based on the in-line generation of the methylene blue dye and its subsequent preconcentration in octadecyl-chemically modified (C₁₈) disks^[39]; or the flow-through solid-phase reflectometric method for the simultaneous multiresidues determination of nitrophenol derivatives, which is based on the in-line anion exchange sorptive preconcentration of the target species followed by direct detection onto the sorbent material by means of chemometric deconvolution of the overlapped spectra.^[40]

Reagent Immobilization

The versatility of the MSFIA technique can be exploited for the development of analytical methodologies using immobilized reagents. Reagents are packed in a flow-through mini-column allowing an increased efficiency of the procedure from the point of view of GAC.

Soto et al.^[41] developed a MSFIA system with spectroscopic UV detection for the determination of hypochlorite in commercial products. This system is based on the selective decomposition of hypochlorite by means of an immobilized cobalt oxide

catalyst. The resultant analytical methodology is almost an ideal Green Analytical Method.

Other MSFIA approaches based on reagent immobilization are: the inclusion of a flow-through solid-phase chemiluminescent sensor with immobilized 3-aminophthalhydrazide (luminol), for the chemiluminometric determination of orthophosphate in waters^[42]; or the use of a glucose-oxidase packed-bed reactor for the conversion of the substrate followed by post-column chemiluminescent detection of the generated oxidizing species after reaction with luminol.^[43]

MSFIA Hyphenation with Separation Techniques Prior to UV-vis Spectrophotometric Detection

Two of the most recent applications of MSFIA technique are based on its hyphenation with separation techniques. Concretely, two new hyphenated flow techniques have been recently developed, named multisyringe chromatography (MSC) and multisyringe flow injection analysis-capillary electrophoresis (MSFIA-CE).

The MSC technique was developed by González-San Miguel et al.,^[44] reporting a low pressure completely automated alternative to liquid chromatographic separations, following an alternative quick and smart way. This technique is based on the use of short monolithic columns allowing the accomplishment of liquid chromatographic separations at lower pressures than in HPLC classic systems. With the miniaturization of the chromatographic system the amount of the required reagents and solvents is also minimized, allowing us to work in a more environmentally friendly way. The MSC technique has been applied in the determination of β -lactamic antibiotics in pharmaceuticals,^[45] or in the determination of B₁, B₆, and B₁₂ vitamins also in pharmaceuticals.^[46] The MSC technique was also combined with in-line SPE for the determination of losartan potassium and hydrochlorothiazide in waters.^[47] The general trend of the MSC systems, which is shown in Table 3 for the case of the determination of B₁, B₆, and B₁₂ vitamins, is the reduction of reagent consumption in comparison to conventional HPLC systems and concomitantly achieving higher injection throughputs. So, the MSC technique

TABLE 3 Comparison of the Analytical Features of the MSC System for the Determination of Vitamins B₁, B₆, and B₁₂ in Pharmaceuticals with Those of Earlier HPLC Methods for the Same Purpose

Parameter	MSC	HPLC ^a
Chromatographic separation time (min)	8	13–26
Flow rate (mL min ⁻¹)	0.5	0.8–1.5
Mobile phase consumption (mL analysis ⁻¹)	4.0	13.6–20.8
Sample throughput (h ⁻¹)	7	2–4
Stationary phase	C ₁₈	C ₁₈
Mean particle size (μm)	Monolith	3–10
Length × i.d. (mm)	25 × 4.6	150–300 × 3.9–4.6
Elution mode	Isocratic	Isocratic or Gradient
Pressure	Low	High

^aResults obtained from references [50–55].

can be defined as a low cost, quick, versatile, and greener alternative way to perform liquid chromatographic separations.

The MSFIA-CE technique was initially characterized as a SIA-CE^[48] technique for the direct determination of mono-substituted nitrophenolic isomers. It was followed by the incorporation of two additional syringes, developing the first hyphenated MSFIA-CE^[49] system. This novel system took profit of the increased versatility allowed by the two additional syringes, carrying out the efficient and miniaturized in-line SPE of mono-substituted nitrophenolic isomers, followed by their subsequent separation and spectrophotometric detection at a wavelength of 401 nm. The automation and miniaturization of the required pretreatments prior to the CE separation can be accomplished effectively in an in-line perspective by means of MSFIA technique, increasing the efficiency of the analytical method from the point of view of GAC.

CONCLUSIONS

In this article has been carried out a revision of the recent literature about the newest applications of the MSFIA technique. It has been focused to the minimization of the consumption of reagents and other different strategies inherent to MSFIA technique and their contribution to the Green Analytical Chemistry field.

Finally, we would like to propose the use of the MSFIA technique combined with spectroscopic detectors as an efficient tool for the automation of sample pretreatment, becoming analytical methodologies in a cleaner way.

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