Green Analytical Chemistry

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We discuss the origins and the fundamentals of Green Analytical Chemistry (GAC), based on the literature published about clean, environmentally-friendly or GAC methods. We pay special attention to the strategies and the tools available to make sample-pretreatment and analytical methods greener. We consider that the main principles are to replace toxic reagents, to miniaturize and to automate methods, making it possible to reduce dramatically the amounts of reagents consumed and wastes generated, so reducing or avoiding side effects of analytical methods. We also consider on-line decontamination or passivation of wastes to be of special interest in making analytical chemistry sustainable.

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1. Introduction

For analytical methodologies, development and validation include optimization of some critical analytical parameters (e.g., accuracy, sensitivity, reproducibility, simplicity, cost effectiveness, flexibility and speed). However, other aspects concerning operator safety and environmental impact of analytical methods are not commonly considered. Because of that, a paradoxical situation emerged during the 1990s, due to the side effects of analytical methodologies developed to analyze different kinds of sample, including environmental samples that generate a large amount of chemical waste, resulting in a great environmental and human impact. In some circumstances, the chemicals employed for analysis were even more toxic than the species being determined.

Taking into account current public concern on environmental matters, environmental analytical studies and the consequent use of toxic reagents and solvents have increased to a point at which they became unsustainable to continue without an environmentally friendly perspective.

The need for carefully checking of the side effects of chemistry in general and analytical chemistry in particular has moved laboratories to control wastes and to collect residues to avoid contamination of water and discharge with urban wastes. However, there is evidence of a real problem – the great quantity of toxic residues – which creates difficulties in their management.

With this background, Green Analytical Chemistry (GAC) started as a search for practical alternatives to the off-line treatment of wastes and residues in order to replace polluting methodologies with clean ones.

In this review, we provide a picture of the origin, the state-of-the-art and the future prospects of GAC based on the most relevant, representative scientific references found in the Chemical Abstracts Service (CAS), the US National Library of Medicine and the Science Citation Index (SCI) database of the Institute for Scientific Information (ISI), Philadelphia, PA, USA.

2. Origin of the concept

In 1987 in Paris during *Euroanalysis VI*, Malissa presented his ideas about changes in paradigms in analytical chemistry [1]. The dissertation based on the different steps covered by the chemistry in history, included the concept of the ecological paradigm being imposed at the end of the twentieth century. These ideas were in good agreement with the conclusions of the Pimentel report, published in the USA in 1985 [2], about the impact of chemistry on the health of the Earth. Ten years later, *The Analyst* journal of the Royal Society of Chemistry in the UK proposed the topic of Environmental Analytical Chemistry as a model of analytical practices in an integrated approach to analytical chemistry that also consider the environmental side effects of analytical practices [3].

"Green Chemistry is the use of chemistry techniques and methodologies that reduce or eliminate the use or generation of feedstocks, products, by-products,

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solvents, reagents, etc. that are hazardous to human health or the environment'' [4]. In short, it is the use of chemistry for pollution prevention. The same philosophy and ideas on Green Chemistry are those previously developed in analytical laboratories (GAC).

Although the analytical community has been environmentally sensitive for a long time and the idea of improving analytical methods by reducing consumption of solvents and reagents pre-dates the theoretical developments, the first descriptions of GAC methods (or clean analytical methods) appeared in 1995 [3,5,6]. However, in the light of these new ideas, previous developments in both sample pretreatment and measurement methods were incorporated into the new integrated approach to analytical chemistry [7].

The scientific references found in the CAS and SCI database, relating to GAC (also called clean analytical chemistry or environmentally-friendly analytical methods) have been growing significantly in recent years. Fig. 1 shows that the literature on this topic has grown exponentially since the 1990s and two clear changes can be identified in the rate of scientific literature production at the end of the twentieth century and in this new century – with 4 papers per year published before 2000, 11 papers a year from 2000 to 2005, and 22 papers a year since 2005. This change in the rate of publication on GAC methods is related to the increasing concern of the scientific community about the environmental impact of their activity.

3. Milestones in Green Analytical Chemistry

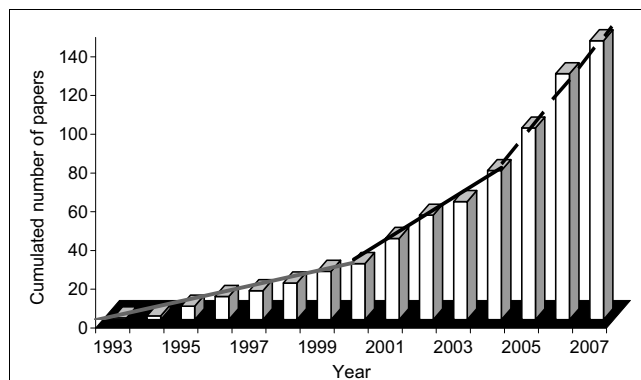The adverse environmental impact of analytical methodologies has been reduced in three different ways:

Figure 1. Evolution of the scientific literature about Green Analytical Methods (obtained from the Chemical Abstracts Service (CAS), the US National Library of Medicine and the Science Citation Index (SCI) database of the Institute for Scientific Information (ISI), Philadelphia, PA, USA), using the subjects Green Analytical Chemistry, clean analytical chemistry or environmentally-friendly analytical methods.

i) reduction of the amount of solvents required in sample pre-treatment;
ii) reduction in the amount and the toxicity of solvents and reagents employed in the measurement step, especially by automation and miniaturization; and,
iii) development of alternative direct analytical methodologies not requiring solvents or reagents.

Fig. 2 shows GAC milestones in the period 1970–2007. There is a difference between the conceptual milestones and the tools suitable for making methods greener. In this sense, it is interesting to note that the concepts of GAC and Green Chemistry were established in the 1990s but the tools arose from developments in the 1970s, indicating that experimental advances pre-dated theoretical ones.

To reduce the amount of solvent required for sample pretreatment, the application of microwave energy for sample digestion was first proposed in 1975 in the pioneering study of Abu-Samra et al. [8]. However, organic analytes were isolated from diverse sample matrices in the mid-1980s. Compared to traditional convective heating sample-preparation methods, microwave-assisted extraction (MAE) saves solvent, and is rapid and efficient from the point of view of energy use.

An alternative to MAE is supercritical fluid extraction (SFE), based on extracting analytes by a fluid in supercritical conditions. SFE emerged in the mid-1980s to overcome difficulties of solid-sample extraction and the use of supercritical CO_2 avoided the side effects of organic solvents. However, despite the promising features of SFE, it has not fulfilled the expectations of researchers in chemical analysis [9].

Pressurized fluid extraction (PFE) is similar to Soxhlet extraction, except that the solvents are used near their supercritical region, where high temperatures produce high solubility and high diffusion rates of solutes in the solvent, while the high pressure, in keeping the solvent below its boiling point, enables high penetration of the solvent in the sample. PFE provides high extraction efficiency with low solvent volumes (15–40 ml) and a short extraction time (15–20 min). PFE is also known as accelerated solvent extraction (ASE), which was first developed by Dionex in 1996 [10] and validated on a commercially-available, automated extraction system.

Solid-phase extraction (SPE) is an important methodology to avoid the use of large amounts of organic solvents in preconcentration and extraction steps. It has been used mainly for trace enrichment of water samples with many advantages over liquid-liquid extraction (LLE), such as:
i) reduction in the amounts of solvents used;
ii) extractions unhindered by emulsion formation;
iii) high extraction efficiency; and,
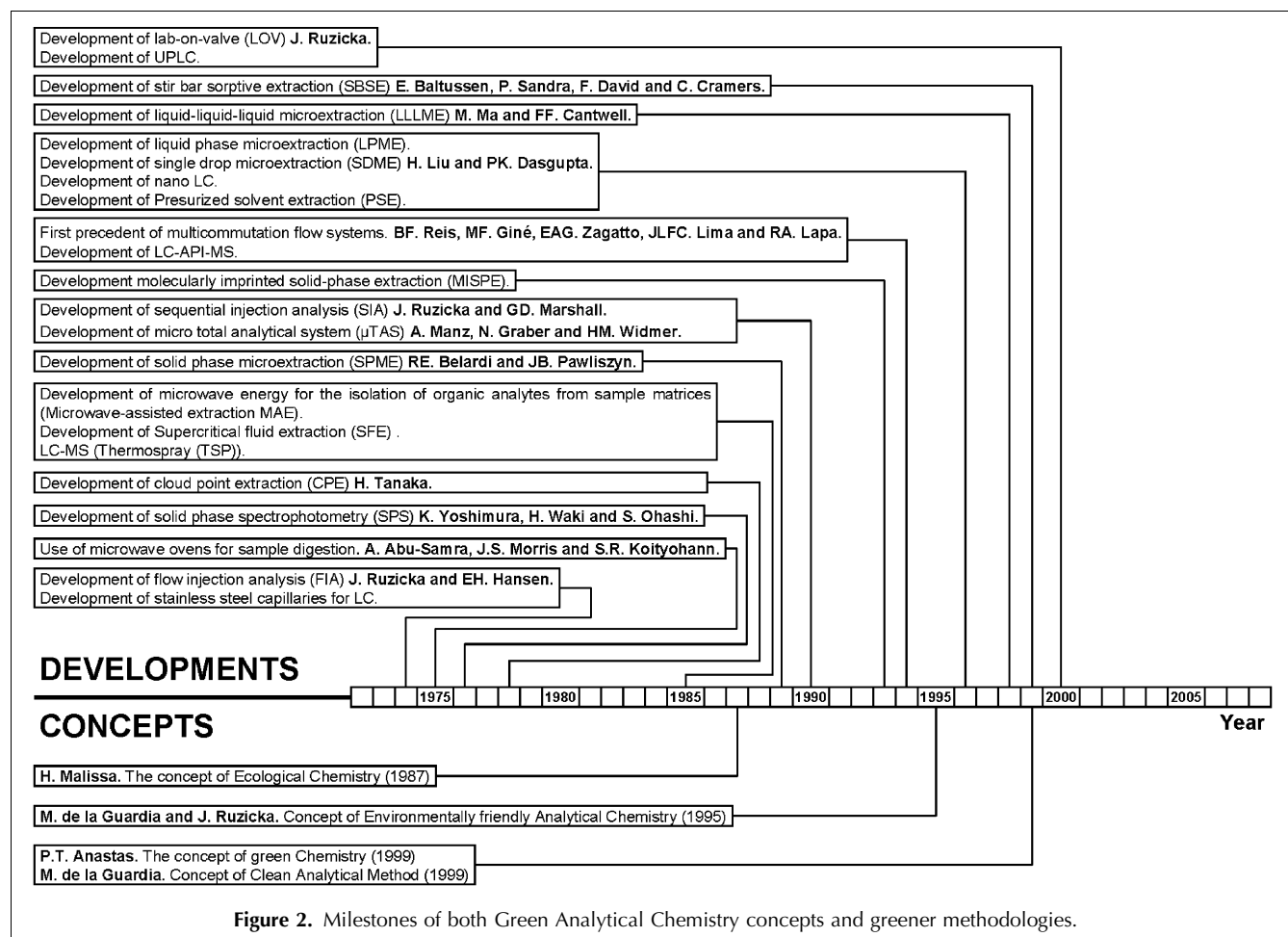iv) ease of automation.

Figure 2. Milestones of both Green Analytical Chemistry concepts and greener methodologies.

The development of solid-phase microextraction (SPME) by Belardi and Pawliszyn in 1989 [11] was also of great importance in greening analytical sample preparation. It is based on the sorption of analytes directly from the samples or in headspace vials by a thin film of an extracting phase immobilized over the surface of a fused-silica fiber. The extracts can be desorbed thermally or using solvents.

Another solid-phase alternative to using organic solvents is stir-bar sorptive extraction (SBSE), which is based on the interaction of analytes with a coating of polydimethylsiloxane (PDMS) deposited on a magnetic rod. It was developed in 1999 by Baltussen et al. [12]. The stir bar can be desorbed with a small volume of a suitable solvent, but, for volatile and semi-volatile compounds, on-line thermal desorption provides a very sensitive approach that avoids using organic solvents. SBSE uses a thicker polymeric layer than that employed in SPME, resulting in a high enrichment factor.

Liquid-phase microextraction (LPME) is an emerging technique that employs a small volume of solvent. The two main methodologies that have evolved from solvent microextraction in recent years have been single-drop microextraction (SDME) and liquid-liquid-liquid micro-extraction (LLLME). SDME was developed in 1996 by Liu and Dasgupta [13] and is based on the suspension of a microdrop of a water-immiscible organic solvent in an aqueous donor solution. LLLME, which is based on liquid-liquid extraction and a back-extraction, was first developed by Ma and Cantwell in 1998 [14].

Cloud-point extraction (CPE) provides another alternative for greener sample pretreatments. It is based on cloud-point and phase-separation phenomena observed in surfactant aqueous solutions, which favor miscibility and separation of surfactant micelles and water as a function of temperature. The CPE technique was introduced by Watanabe and Tanaka to preconcentrate metal ions from aqueous samples [15]. Subsequently, the scope of CPE has been extended to extraction of proteins, enzymes and organic environmental pollutants.

The development of modified surfaces to be used as SPE units is also of interest in GAC. Molecularly-imprinted polymers (MIPs) are capable of recognizing specific molecules with a sorption capacity dependent on the properties and the template concentration of the surrounding medium. MIPs have been exploited in a

number of applications, including separation of materials, antibody mimics and recognition elements in biosensors. Molecularly-imprinted SPE (MISPE), based on surface modifications by immobilizing the chelating agents on the appropriate support, has been employed for metal-ion preconcentration.

Concerning the measurement step, greener analytical procedures are inherent to automated flow-based methodologies, due to their capability of reducing reagent and solvent consumption and also to the possibility of incorporating decontamination of wastes on-line [7]. From the first paper published by Ruzicka and Hansen on flow-injection analysis (FIA) in 1974 [16], the development of flow-analysis-based techniques seems a search to minimize reagent consumption.

The evolution of flow systems comprises the use of solid-phase reagents, and especially immobilized reagents in solid-phase spectrophotometry (SPS), which Yoshimura et al. introduced in 1976 [17]. In SPS, the solid support is placed inside the flow cell and analyte retention, preconcentration and detection are performed simultaneously, increasing the sensitivity and the selectivity of the analytical procedures and reducing the reagents consumed.

Sequential-injection analysis (SIA) is a robust alternative to classical flow injection (FI) that allows implementation of different flow methodologies without modification of the manifold [18]. The main advantages of SIA over FIA are the dramatic reduction in the amounts of solvent and reagents consumed, simplicity and reduction of wastes.

One of the recent approaches in flow systems is multicommutation. This technique involves use of discrete commutation devices (e.g., three-way solenoid valves or minipumps) to build up dynamic manifolds that can be reconfigured by software [19]. This approach increases the versatility of FIA systems because each analytical step can be implemented independently. Usually, one commutation device is employed to manage each solution, so only the reagent volume required is introduced into the system for sample processing.

All current procedures could become environmentally friendly by reducing the amounts of reagents consumed and it can easily be achieved by downscaling the manifold components and arranging them in a single device. This concept is known as the micro-total analytical system (μ-TAS), which involves arranging all steps of sample processing in a single device of a few square centimeters [20].

Micro FIA (μ-FIA) systems, which exploit micro-electronic techniques to integrate pumps, mixing and reaction chambers as well as detectors in a single chip provide the so-called lab-on-valve (LOV) concept, proposed by Ruzicka [21].

Classical techniques (e.g., liquid chromatography (LC) and capillary electrophoresis (CE)) have been down-scaled by reducing the size of the chromatographic column (capillary high-performance LC, HPLC), the particle size of the stationary phase (ultra performance liquid chromatography, UPLC) or integrating the whole system on a chip.

The ability of mass spectrometry (MS) to extract chemical fingerprints from trace levels of analyte is invaluable and its combination with GC, LC and inductively coupled plasma (ICP) have provided routine tools to enable simultaneous detection and characterization of a wide range of analytes in very complex matrices.

The evolution of the available instrumentation and mathematical data treatments (chemometrics) has allowed the development of solvent-free methodologies based on direct measurements on solid or liquid samples without any chemical sample pre-treatment. Examples of methodologies based on direct measurement and chemometric data treatment are applications of vibrational spectrometric-based techniques (near infrared (NIR), mid-infrared (mid-IR) or Raman spectrometry), fluorescence, UV-Vis spectroscopy and nuclear magnetic resonance (NMR). The main advantage of these methods is to avoid sample pre-treatment, thus reducing the use of solvents and reagents, and also the time of analysis.

4. Greener sample pretreatments

The public concern over protecting the environment has induced chemists to look for new sample-preparation techniques that could reduce the adverse environmental impact of organic solvents [22].

Table 1 summarizes the characteristics of the main sample-treatment methods developed to avoid or to reduce use of organic solvents, as selected from papers identified in the literature as describing clean, green or environmentally friendly methods.

Microwave-assisted extraction (MAE) has been applied to the extraction of organic compounds from very different types of matrix. It employs less organic solvent and a shorter extraction time than traditional extraction methods. In a comparative study by Pastor et al. [36], it was evident that MAE reduced extraction time by a factor of 20 and organic solvent consumtion by a factor of 10, as compared with the Soxhlet extraction, and reduced solvent consumtion by a factor of 15 and extraction time by a factor of 3, compared with ultrasound-assisted extraction (UAE).

MAE has been proposed for GAC extraction of atrazine, simazine and prometryne from synthetic-soil samples, using water and some organic solvents [23]. Triazines could be efficiently extracted with 30-ml water as they provide a cheap, safe, environmentally-friendly alternative to organic solvents.

MAE can be used together with a micellar system to extract organic compounds from soils. This method was

Table 1. Some green alternatives, obtained from papers in which one of the objectives was to make analytical methods greener

Extraction method	Analyte	Matrix	Solvent	Amount solvent per sample	Ref.
MAE	Triazines	Soils	Water	30 mL	[23]
	Phenols	Soil	POLE:water (5:95)	8 mL	[24]
SFE	Pesticide residues	Plants	CO_2 // n-hexane	1 mL	[25]
	Pesticide residues	Strawberries	CO_2// acetone	10 mL	[26]
ASE	Estrogens	Soils	Acetone	n.c.	[27]
	Carotenoids	Food	Methanol/ethyl acetate/light petroleum	n.c.	[28]
SPME	Phenols	Water	Acetonitrile:water (70:30)	70 μL	[29]
	VOC	Snow	Thermal desorption	–	[30]
SBSE	Pesticide residues	Juice	Thermal desorption	–	[31]
SDME	Aniline derivatives	Water	Extrc. benzyl alcohol–ethyl acetate, 80:20 Retroextrc.: HCl (pH2)	Extrc.: 150 μL Retroextrc.:1 μL	[32]
LLLME	Phenoxy herbicides	Bovine milk	DS: sample + HCl (0.5 M) OS: 1-octanol AS: 0.1 M NaOH	AS: 7 μL	[33]
	Aniline derivatives	Water	DS: sample + NaOH (pH13) OS: benzyl alcohol–ethyl acetate, 80:20 AS: HCl (pH2)	AS: 3 μL	[32]
MASE	Pesticide residues	Juice	DS: sample + NaCl (saturated) AS: cyclohexane	AS:800 μL	[31]
Micelle mediated extraction	Trichlorfon	Cabbage	SDS 0.01 M	200 mL	[34]
Modifications of surfaces	Cu	Water	HCl 0.1N	10 mL	[35]

MAE, Microwave-assisted extraction; SFE, Supercritical fluid extraction; SPME, Solid-phase microextraction; SBSE, Stir-bar sorptive extraction; SDME, Single-drop microextraction; LLLME, Liquid-liquid-liquid microextraction; MASE, Membrane-assisted solvent extraction; PHB, Poly(3-hydroxy)butyrate; VOC, Volatile organic compounds; POLE, Polyoxyethylene 10 lauryl ether; DS, Donor solvent; OS, Organic solvent; AS, Acceptor solvent; SDS, Sodium dodecyl sulfate.

used for the analysis of phenols in soils and provided a viable, greener alternative by replacing organics with surfactants [24].

The main advantages of MAE are:
i) short extraction time;
ii) reduction in the amount of sample required;
iii) high sample throughput;
iv) reduced cost; and,
v) great safety, since it does not require the use of hazardous materials and can be contained in closed reactors.

SFE also offers an attractive alternative to overcome the unfavourable effect of non-polar organic solvents employed in extracting non-polar compounds. The main advantages of SFE are:
i) it can achieve high concentrations;
ii) it is quantitative;
iii) it is fast;
iv) it is simple; and,
v) it is selective.

SFE is also an environmentally-friendly analytical methodology that can be automated easily and com-

pletely. SFE has been employed in extraction of pesticide residues from plants [25] and fruits [26].

In the same way, accelerated solvent extraction (ASE), also known as pressurized solvent extraction (PSE), pressurized fluid extraction (PFE), pressurized liquid extraction (PLE) and solvolytic extraction, is a solid–liquid extraction process performed at high temperatures (50–200 °C) and high pressures (10–15 MPa). ASE is a form of PSE similar to SFE, although, in ASE, the extraction is carried out under pressure to maintain the solvent in its liquid state at high temperature, but always below its critical condition. Although the solvent used in ASE is usually organic, pressurized hot water can also be used. Nowadays, ASE is considered a potentially, attractive, alternative technique for extracting organic compounds from environmental or biological matrices [27] and for food applications [28], its main advantages over traditional extraction methods being dramatic decreases in the amount of solvent used and the extraction time.

In SPME, sorbent-coated silica fibers are used to extract analytes from aqueous or gaseous samples. After extraction, the fibers can be desorbed by using small

amounts of organic solvents or transferring thermally the fiber directly into the injection port of a GC. Based on the first approach, seven phenols were extracted from water using oxidized multi-walled carbon nanotubes for extraction and 70 μL of acetonitrile:water (70:30) for elution [29]. However, SPME with thermal desorption has been used for the analysis of snow samples by GC [30], avoiding completely the use of organic solvents.

SBSE is not as popular a technique as SPME, but it has been used as a green alternative for extracting pesticide residues in sugarcane [31].

LPME is essentially miniaturised liquid–liquid extraction, in which the analyte moves between the bulk aqueous phase and a very small volume of organic solvent. Recent developments use a single droplet of solvent, suspended at the tip of a needle and exposed to the sample solution (SDME), and they have been employed for extracting aniline derivatives from water samples in a two-step procedure [32].

By using membrane-based devices, different ideas have been developed to extract and preconcentrate different tipes of analytes, avoiding or reducing the amount of organic solvents.

In LLLME, a thin film of organic solvent is immobilized in the pores of a polypropylene hollow fiber placed on the exterior of the hollow fiber carrying the donor aqueous phase. The pH of sample is adjusted to neutralize the target compound and the internal channel of the fiber acts as the acceptor aqueous phase, with a pH adjusted to ionize the target compounds. With stirring, neutral compounds in the donor phase are extracted into the organic film on the fiber and then back extracted into the acceptor phase inside the fiber. This technique has been used in extracting herbicides from milk [33] and aniline derivatives from water samples [32].

Another membrane-based approach is called supported-liquid-membrane extraction (SLME) or membrane-assisted solvent extraction (MASE). In this case, separation occurs when compounds are transported to a greater extent than others from a donor phase through the membrane into an acceptor phase. For non-porous membranes, the efficiency of the transport of compounds depends to a large extent on the partition coefficient between the different parts of the extraction system, so good selectivity can be achieved by choosing appropriate membrane material and organic acceptor phases. This technique has been used for green extraction of pesticide residues from juice [31] using only 800 μl of organic solvent.

CPE offers advantages:
i) it is inexpensive;
ii) good concentration efficiency;
iii) low environmental toxicity; and,
iv) safety.

Surfactants can dissolve organic compounds entrapped in the micellar phase. Complete separation of the micellar phase and the original water phase is achieved as a function of temperature and the presence of some salts. The use of surfactants to increase the solubility of organic compounds in water has been succesfully combined with SPE to extract pesticides from vegetables [34].

Beyond sample-preparation methods previously commented upon, derivatization of surface molecules is a valuable tool in making sample treatment greener. Molecular imprinting has become a powerful method for preparing robust materials that can recognize specific chemical species. However, applications as real alternatives or complements to biomolecules are limited to some extent by inherent shortcomings (e.g., non-specificity and low affinity of binding sites [37]).

However, chelating solid phases can be made by immobilizing chelating agents on appropriate supports. This methodology has been succesfully applied to extracting trace-metal ions from water samples [35].

5. Green analytical methodologies

Investigation of GAC methodologies encompasses a number of strategies to minimize or to eliminate the use of toxic substances and the generation of wastes. The main focus has been the development of new routes to minimize the amounts of side products and to replace toxic solvents [38].

5.1. Screening methodologies
It is clear that one of the aims of the GAC is to reduce the number of samples to be analyzed by classical, non-environmentally friendly methodologies and also to reduce the waste generated as a result. However, this reduction in the number of samples for analysis should be done in a safe, controlled way. It can be achieved by using the so-called ''screening methods'' that involve procedures to indicate whether target analytes are present above or below a threshold but also comprise those that provide fast acquisition of semi-quantitative data about all components of a sample.

In general, screening methods tend to to be qualitative, involving little or no sample treatment, and the response is used for immediate decision-making, with confirmation requiring a conventional alternative. Put plainly, a screening method is a simple measurement that provides a ''yes/no'' response, avoiding the need to process a large number of samples so as to limit complex sample treatments of conventional techniques to those samples with positive responses.

It is important to note the great efforts made by the scientific community in this direction in recent years. In this respect, it is interesting to mention immunoassays (IAs), which were first developed for monitoring insulin in blood in 1960 [39] and are now usually employed in clinical chemistry to determine hormones, drugs and

viruses in biological samples [40,41]. Enzyme-linked immunosorbent assay (ELISA) is the most common IA technique employed. The main advantages of those biology-based analytical-screening techniques is the complete replacement of organic solvents by aqueous media and the consequent reduction of toxic wastes.

As well as so-called rapid colorimetric tests employed to determine the presence of some inorganic compounds, we should mention the different analytical techniques commonly employed for rapid analysis of elemental composition of samples:

- X-ray fluorescence, which provides excellent qualitative or semi-quantitative data without any pre-treatment;
- inductively coupled plasma atomic emission spectrometry (ICP-AES) and inductively coupled plasma mass spectrometry (ICP-MS), which are the most sensitive, selective techniques for multi-elemental determination of several components in the same sample;
- mass spectrometry (MS), which offers good advantages for selective determination of compounds and sensitive determination of organic pollutants, providing fast sequential information on multiple compounds with high level of sensitivity; and,
- ion-mobility spectrometry (IMS), which is usually used for screening explosives at airports and detection of compounds from pyrolysis, detecting chemicals for the military industry, including warfare agents, and monitoring stack-gas emissions in industry [42].

5.2. Replacement of toxic reagents
As can be seen in Table 2, the use of flow-based procedures has contributed to achieving greener analytical methods, by automation and miniaturization, but also by replacing toxic reagents by non-contaminating reagents (see Fig. 3a)).

Guava leaf extract has been used as an alternative natural reagent for the FI determination of Fe [43] without the need for further purification.

The use of SPE in combination with FIA systems has been proposed as a way of replacing toxic reagents. A time-based, multi-syringe FI (MSFI) approach was developed for automating disk-based sorbent extraction of nitro-substituted phenol isomers followed by on-line simultaneous determination of individual species by diode-array spectrophotometry [44]. The method involved on-line enrichment of target analytes and removal of potentially-interfering matrix components. The nitrophenol isomers were eluted with an alkaline solution and the UV-vis spectra were recorded. Deconvolution of strongly-overlapping spectra was done using multivariate regression models.

A GAC procedure was developed for nitrate determination in natural waters based on direct spectrophotometric measurements [45], using an FIA system with an anion-exchange column. The proposed method em-

ployed only one reagent ($HClO_4$) and avoided interferences of humic acid, NO_2^-, PO_4^{3-}, Cl^-, SO_4^{2-} and Fe^{3+}. The same principle was applied in the SIA determination of phosphate in urine [46]. The interferences of Ca, due to the crystallisation of calcium phosphate, were avoided using a cation-exchange resin.

As can be seen in Table 2, there is great interest in replacing organic solvents as the mobile phase in HPLC. Solvent-free HPLC methods have been proposed for the determination of dyes in foods [47]. In this case, organic solvents were substituted by surfactants as mobile phase.

Acified water, without organic solvent, was employed as the mobile phase in separation and quantification of UV filters in cosmetics by using cyclodextrins as organic modifiers [48], and for separation of steroids, amino acids and proteins using thermo-responsive copolymers as the stationary phase [49].

Chlorophyl, extracted from pea leaves, has been proposed as a natural fluorometric reagent for the determination of Hg, based on quenching fluorescence in the presence of Hg^{2+} [50].

Replacement of Hg-based electrodes has been a hot topic in GAC method development of stripping voltammetry. Table 2 shows the different electrode materials proposed.

Bismuth thin films, deposited in situ on a copper substrate, have been proposed for monitoring Cd, Pb, Co, Ni [51]. Moreover differential pulse voltammetry (DPV) and adsorptive stripping voltammetry (AdSV) at a modified silver solid amalgam electrode (m-AgSAE) have been employed for the determination of trace amounts of genotoxic substances [52].

The use of vapour-phase generation with Fourier transform infrared (FT-IR) spectroscopy provided a green alternative for ethanol determination in mouthwashes [53]. Without pre-treatment, 2 μL of samples were injected inside a reactor heated at 70 °C, and the vapour phase generated was transported to the FTIR spectrometer using carrier flow of nitrogen. The proposed procedure is a simple, fast, environmentally-friendly alternative, which avoids using reagents and chlorinated organic solvents commonly used for this determination.

5.3. Minimization of wastes
The substitution of all toxic reagents employed in chemical analysis is not easy, so reduction of the amounts employed should be also considered (see Fig. 3b)). In this sense, multicommutation has the advantages of minimizing both reagent consumption and waste generation. In this approach, micro-volumes of samples and reagents are sequentially inserted into the reaction coil of a single line manifold, providing a simple system, suitable mixing conditions, and easy optimization of the sample/reagent ratio, and avoiding excessive use of reagents. Multicommuted flow systems can be designed with solenoid micro-pumps that can

Table 2. Some green analytical methods proposed in the literature

Green strategy	Flow method	Analyte	Reagent	Green aspects	Ref.
Replacement of toxic reagents	FIA - UV	Fe	Guava leaf extract	Use of Guava extract as colorimetric reagent	[43]
	Multi-syringe FIA - UV	Nitro-substituted phenols	-	Flow-through disk-based system – organic solvent extraction	[44]
	FIA - UV	Nitrate	$HClO_4$	Use of SPE – to avoid interferences	[45]
	SIA - UV	Phosphate		Use of SPE to avoid interferences	[46]
	HPLC	Colorants	Triton X-100	Use Triton X-100 as mobile phase and to modify the C18 column	[47]
	HPLC	UV filters	EthOH-water-acetic acid – hydroxypropyl-β-cyclodextrin	Use cyclodextrin as mobile phase modifier	[48]
	HPLC	Steroids, amino acids and proteins	Aqueous mobile phase	Use of thermo-responsive copolymers as stationary phases	[49]
	Fluorimetry	Hg(II)	Clorophylla	Use of Chlorophyll as reagent	[50]
	Anodic and Cathodic stripping voltammetry	Cd, Pb, Co, Ni	Bismuth film electrode	Replacement of Mercury-based electrodes	[51]
	Adsorptive stripping voltammetry	3-nitrofluoranthene	Silver Solid Amalgam Electrodes	Replacement of Mercury-based electrodes	[52]
	VP-FTIR	Ethanol	–	VP-FTIR avoids the use of chlorinated solvents	[53]
Minimization of reagents and wastes	Multicomm. - UV	Cyclamate	$NaNO_2$/KI	Solenoid micropumps	[54]
	Multicomm. - UV	Carbaryl	PAP	Solenoid valves	[55]
	Multicomm.-HG-AFS	Hg		Solenoid valves	[56]
	Multicomm. - FTIR	Benzene	$CHCl_3$	Solenoid valves	[57]
	FIA-FTIR	Malathion	$CHCl_3$	Closed FIA manifold	[58]
	FIA-UV	Chloride	$Hg(SCN)_2$/Fe(III)	$Hg(SCN)_2$ immobilized in epoxy resin	[59]
	FIA-Chemiluminescence	Chlorpyrifos	Luminol or periodate	Controled reagents release from a solid phase	[60]
	Double line SIA-UV	Cu, Fe, Mn, Zn	1,10-phenanthroline/ formaldoxime / zincon		[61]
	FIA-SPS	Fe(II)	Acid and reducing agent	SPS - reduce reagent consumption	[62]
	μFA - vis	Cu(II)	2-carboxy-2-hydroxy-5-sulfoformazyl benzene	Micro fluidic manifold	[63]
	μ UV assay	Malondialdehyde	Thiobarbituric acid and ethyl acetate	Micro extraction - UV	[64]
	Capillary HPLC	Flavonoids	Acetonitrile	Reduction of the organic solvent volume to less than 1 mL per run	[65]
	UPLC	Lovastatin	Acetonitrile	Reduction of the organic solvent volume to less than 1.5 mL per run	[66]
	LC-MS	Drugs	Acetonitrile	Multicomponent (7) determination in only 8 min. and 4 mL per run	[67]
	LC-MS	Pesticides	Methanol	Multicomponent (10) determination in only 10 min. and 3 mL per run	[68]
	μ CE-MS	Drugs	Acetonitrile/methanol	Multicomponent (4) determination in only 1 min.	[69]
	μ CE	Phenolic compounds		Micromachined capillary electrophoresis (CE) chip with a thick-film amperometric detector	[70]
	NIR	Pesticides	Acetonitrile		[71]

Category	Technique	Analyte	Reagent	Notes	Ref.
Recovery of reagents	Cyclic FIA – UV/vis	Lead	Arsenazo III	Cation exchange column to regenerate the reagent and retain toxic ions.	[72]
	FIA-FTIR	Propyphenazone and caffeine	–	Distillation unit - on-line recycling of the CHCl$_3$	[73]
On-line decontamination of wastes; Detoxification TiO$_2$ and UV radiation	FIA-UV/vis	Formetanate	PAP/ KIO$_4$		[74]
Multicomm.-HG-AFS	Hg		Deactivation heavy metals - matrix of Fe(OH)$_3$		[56]
Reagent-free methodologies	FT-Raman	Iprodione	–	Direct measurement in glass vials	[75]
	FT-Raman	Sweeteners	–	Direct measurement in glass vials	[76]
	NIR	Pesticides	–	Direct measurement in glass vials	[77]
	NIR	Peroxide value	–	Direct measurement oil	[78]
	PAS	Mancozeb	–	Direct measurement solid pesticide	[79]
	Sample matrix-assisted PI-CVG-AFS	Hg	UV radiation	Sample matrix reduce Hg ions to Hg(0).	[80]

FIA: Flow injection analysis; UV: Ultraviolet; SPE: Solid phase extraction; SIA: Sequential injection analysis; µFA: micro Flow analysis; HG-AFS: Hydride generation-Atomic fluorescence spectrometry; PAP: p-aminophenol; MB: Methylene blue; FTIR: Fourier transform infrared; HIFU: High-intensity focused ultrasound; SPS: Solid phase spectrometry; NIR: Near infrared; PAS: Photoacoustic spectroscopy; PI-CVG-AFS: Photo induced-cold vapor generation–Atomic fluorescence spectrometry.

reproduce the micro-volumes of solutions dispensed, thus dowscaling the methods automated.

As can be seen in Table 2, multicommutation has been employed in combination with spectrophotometry for fast, clean determination of cyclamate [54]. The procedure exploits the reaction of cyclamate with nitrite in acidic medium and the spectrophotometric determination of the excess of nitrite by iodometry. The method consumes only 3 mg KI and 1.3 µg NaNO$_2$, generating 2.0 mL of effluent waste per determination.

Multicommutation has been applied for Hg determination in milk by hydride generation atomic fluorescence spectrometry (HG-AFS) [55]. The method dramatically reduces reagent consumption (by a factor of 4) and effluent generation, and it also improves laboratory productivity by increasing sample throughput.

An FT-IR multicommutation method was developed to determine benzene in motor fuels [56]. The method permitted direct determination of benzene without any pre-treatment of samples. Advantages of the method were a solvent consumption of 1.2 ml per determination and an analytical throughput of 81 samples per hour.

Analytical characteristics of multicommutation have been compared with those obtained by classical FIA and SIA, in improving the automated spectrophotometric determination of carbaryl with p-aminophenol (PAP) [57]. Multicommutation provided a limit of detection (LOD) comparable to that obtained using FIA and lower than that found by SIA, but generating a total waste volume per sample of 1.7 ml, which was comparable to that found in SIA and 6 times lower than that obtained by classical FIA. This comparative study showed that SIA is the best strategy for reducing reagent consumption but multicommutation provides a faster, more sensitive alternative to SIA.

A closed FIA system was developed to extract malathion from pesticide formulations with 2 ml CHCl$_3$ prior to the determination of the pesticide by FTIR [58].

The retention of reagents in solid supports was proposed for the determination of chloride in natural waters by reaction with Hg(SCN)$_2$ immobilized in an epoxy-resin bead [59] and for the chemiluminescence determination of chlorpyrifos in fruit based on immobilizing luminol or periodate on an anion-exchange column [60].

SIA permits great reduction in the volumes of waste, and several metal ions were determined in waters using a double-line sequential injection spectrophotometric system [61]. The proposed configuration added sample and chromogenic reagents as merging zones. The methodology was applied to the spectrophotometric determination of copper, iron, manganese, and zinc in samples of diverse origin.

SPS simultaneously reduces the volumes of reagents used and improves analytical selectivity and sensitivity. It concentrates the analyte in situ due to its accumulation in
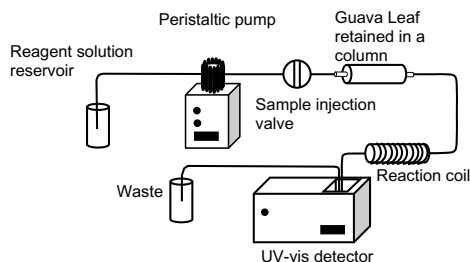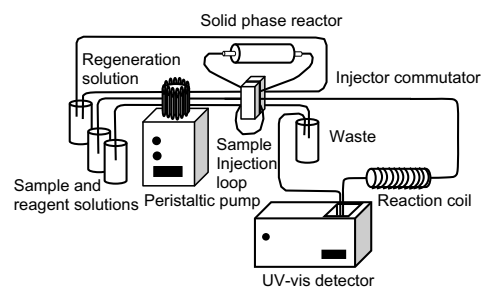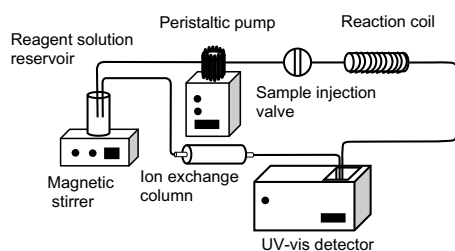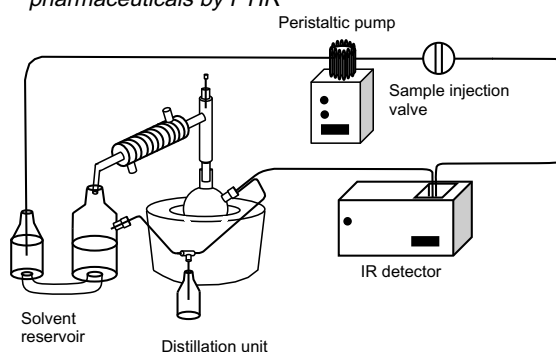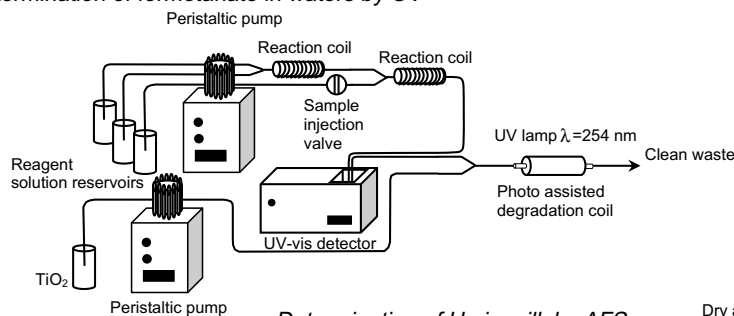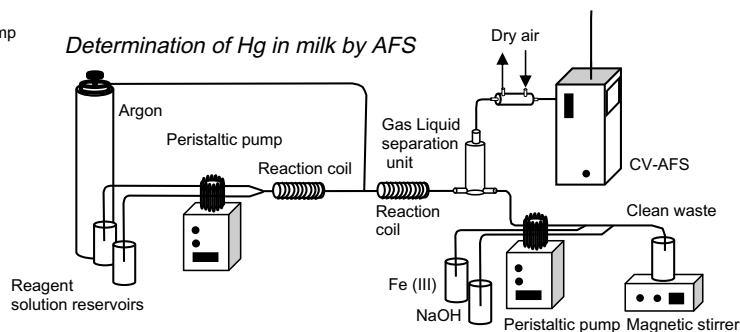
Figure 3. Basic components of characteristic manifolds designed to: (a) replace toxic reagents, (b) minimize wastes, (c) recover reagents, and (d) decontaminate wastes on-line.

a small volume of the solid support, thus resulting in better sensitivity and lower LODs in comparison with measurements made in solution.

FI-SPS was proposed for iron determination [62]. Iron(II) is reversibly retained on 1-(2-thiazolylazo)-2-naphthol immobilized on C18-bonded silica, yielding

a brown complex. The metal ion is eluted as iron(II) with a small volume of a dilute-acid solution without removing the immobilized reagent, which can be used for at least 100 determinations. The proposed procedure reduced effluent generation (3.6 mL per determination) and consumed micro amounts of reagents.

Waste generation can also be minimized by reducing the size of manifolds developed. A clear example was the micro-flow system comprising a planar glass chip with a PDMS top plate fitted with a fiber-optic probe, employed as optical sensor, for monitoring Cu(II) [63].

By miniaturizing the manifold, a micro-extraction-spectrophotometric assay developed for the determination of malonaldehyde (MDA) in blood after formation of MDA-thiobarbituric acid (TBA) adduct [64] reduced the volumes of sample and waste. In this case, the volume of serum sample required was 20 µL and the total volume of aqueous phase was 420 µL.

Fast-response miniaturized systems with negligible waste production are particularly promising for meeting the requirements of GAC, so the concept of miniaturizing separation and detection systems has an important role to play.

Capillary HPLC is based on decreasing the size of packed HPLC columns in the capillary range, where column ID is 100–500 µm and flow rates are 0.4–100 µL/min, It improves the speed and the mass sensitivity of a separation.

Improvement in mass sensitivity achieved with capillary HPLC is perhaps the most understandable advantage of the technique – for the same size of injection, a 300-µm capillary format offers sensitivity 235 times greater than a column with an ID of 4.6 mm.

Three major additional advantages of capillary HPLC over traditional HPLC are faster column equilibration, smaller solvent volumes and lower back-pressures (e.g., using a 0.3×50-mm capillary column, a run for a small-molecule separation will take 5 min at 10 µL/min, using 60 µL of solvent with a pre-wash and a post-wash [65]).

Similarly, by using a small particle size in the stationary phase of an HPLC system, speed and peak capacity (number of peaks resolved per unit time in gradient separations) can be improved significantly (i.e. ultra-performance LC (UPLC)). Technical improvements – in stationary-phase particles (<2 µm) and instrument technology (capable of resisting the high pressure generated and with a detection system providing an appropriate sampling rate) – have allowed columns to be shortened in line with particle size without loss of resolution. In addition, the increase in sensitivity with UPLC should be 2–3 times greater than with HPLC, depending on the detection technique [66]. A typical conversion of a method from HPLC to UPLC could reduce analysis time from several minutes to 30 s, and also reduce the amounts of solvent consumed and waste generated.

Furthermore, the use of MS detectors in combination with chromatography is of paramount importance in new applications, as they improve detection sensitivity by 10–1000 times and so reduce the amount of sample needed [81]. As a direct consequence, the decrease in mobile phases used has greatly reduced the amounts of waste produced. One of the major breakthroughs has been the development of new MS interfaces, especially atmospheric pressure ionization (API) sources, such as electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI), which have simplified the compatibility between the separation step working in the liquid phase and the MS detector working in the gas phase.

Moreover, in many cases, MS detectors have replaced the classical detectors, reducing the number of systems required for a single analysis and at the same time avoiding some of the chromatographic ''toxic'' gases typically used.

Another advantage of combining HPLC or GC with MS is simultaneous screening, identification, confirmation and quantitative multi-component determinations in a single run, in this way, reducing the time of analysis and the waste generated. This shows the great potential for HPLC-tandem MS (HPLC-MS^2) methods, where direct injection of samples or sample extracts is often feasible, removing sample treatment and solvent consumption.

HPLC-MS has led to major breakthroughs in quantitative bioanalysis since the 1990s, due to its inherent specificity, sensitivity, and speed. In the past few years, increased use of LC-MS in various analytical fields, including forensic [67] and clinical toxicology [68], has been spectacular, so it is now competing with GC-MS for the status of being the Number One analytical technique in toxicology. This is due not only to its technological advantages but also to its reduced cost.

However, samples from biological matrices are not usually directly compatible with LC-MS^2 analyses, as they require pre-treatment, so we need to mention the on-line combination of SPE and chromatography [82], in which the solid phase is packed in columns that are normally much shorter than analytical columns. In these SPE systems, the analyte is retained, pre-concentrated and separated from impurities and weakly retained compounds in the SPE column, to be later eluted inside the chromatographic column by switching a valve. Sometimes, the ''flush-back'' technique is also used; that involves changing the direction of flow through the SPE column to minimize band broadening.

By using SPE coupled to HPLC, sample handling is reduced and sample treatment is completely automated. The major advantage of on-line SPE over off-line extraction is that the sample-preparation step is embedded in the chromatographic separation so eliminating most of the sample-preparation time traditionally performed at the bench.

Coming back to the concept of miniaturized separation and detection systems, at present, on-chip separations are dominated by CE and other electrophoretic methods. However, as μ-TAS, develops, there is growing demand for additional modes of separation, especially chromatographic, in order to improve handling of increasingly complex samples [83].

For CE microchips injecting small sample volumes, highly-efficient separations can be achieved within just one-tenth of the time required for capillary-based electrophoresis, while also reducing the volumes of residues generated. However, the low sample capacity of the CE microchips requires sensitive detectors, so, currently, most CE microchips are coupled to MS [69].

An example of this kind of analytical system was employed for separating and detecting toxic phenolic compounds, based on coupling of a micromachined CE chip with a thick-film amperometric detector [70]. The integrated microsystem offered rapid (4 min) simultaneous measurement of seven priority chlorophenolic pollutants.

A promising alternative to CE is electrochromatography (EC), a technique that includes features of both electrophoresis and LC, so there are in the literature several excellent reviews covering the broad area of separations in μ-TAS [84] and also specific discussions on chip EC [85].

However, NIR can be used for pesticide determinations, reducing the volumes of waste generated [71]. The methodologies described above were based on pesticide extraction with acetonitrile and subsequent measurement of transmittance. Reagent consumption was clearly reduced (1 ml acetonitrile) and samples can be stored in the glass vials for later analysis.

Other analytical techniques that could be considered GAC methods, due to their simultaneous screening, identification, confirmation and quantitative multi-component determinations in a single run with little or no sample preparation, are ICP-AES and ICP-MS.

5.4. Recovery of reagents

The recovery of reagents provides a satisfactory way to cut down on the side effects of analytical methods, as it is an important step towards achieving zero emissions in research.

Laboratory wastes are not dscarded directly into the environment but are treated off-line. However, this practice increases the running costs of analytical laboratories and creates a problem through the accumulation of toxic residues. A green alternative to waste storage is therefore on-line recovery of solvents and toxic or expensive reagents. Fig. 3 shows the basic components of ways described in the literature to reduce consumption of reagents by using solid reagents (Fig. 3B) and to recover solvents on-line (Fig. 3C).

A useful way of recovering reagents on-line is to incorporate a cation exchange mini-column after a flow-through cell. In this way, the main reagent can be regenerated on-line and heavy-metal ions can be removed from the waste, thus reducing both reagent consumption and waste generation [72]. The method involves spectrophotometric determination of Pb with chromogenic reagent arsenazo (III), accumulation of Pb onto the cationic exchanger, and subsequent regeneration of the arsenazo (III), which makes the system reversible and the reagent reusable.

In FT-IR determination of propyphenazone and caffeine in pharmaceuticals, incorporating a distillation unit after the measurement cell provides on-line recycling of $CHCl_3$, which is used as carrier and solvent, thus reducing both cost and side effects of laboratory waste [73]. The system developed permits a dramatic reduction of reagent consumption, and makes sampling and cleaning of the measurement cell easy and fast.

5.5. On-line decontamination of wastes

As described above in the context of GAC, special emphasis should be placed on assessing the environmental impact of new methods in addition to traditional goals (e.g., accuracy, precision, sensitivity, and LODs). In 1994, different flow methods proposed involved an additional effort to detoxify wastes generated. Basically, on-line treatment of waste involves adding a decontamination step after analytical measurement to obtain clean waste (Fig. 3d).

In 1999, to detoxify wastes on-line, it was suggested using:

  i) thermal degradation;
 ii) oxidative detoxification;
iii) photodegradation; and,
 iv) biodegradation [7].

Some of these strategies have yet to be applied to specific methods.

A detoxification step based on in-line TiO_2-catalyzed photodegradation reduces the toxicity of wastes. It has been applied for the determination of formetanate in waters [74] using their reaction with p-aminophenol (PAP). After the measurement step, the analytical waste was merged with a TiO_2 (anatase)-catalyst slurry and then detoxified by on-line UV irradiation. After that, the catalyst can be recovered through flocculation and reused.

Metal ions are non-degradable pollutants, so it is impossible to decontaminate metal wastes. However, it is possible to passivate wastes containing heavy metals and to reduce greatly the volume of waste (e.g., in the determination of Hg in milk by AFS [56]). The analytical waste was merged with NaOH and that solution was mixed with a solution of Fe(III), which precipitates $Fe(OH)_3$ and co-precipitates Hg, thus contributing to deactivation of traces of Hg and other heavy metals

present in samples and standards, reducing the toxic wastes from several liters to less than 1 g of an hydroxide mixture with a high content of Fe.

5.6. Reagent-free methodologies

Methods based on direct measurements of untreated samples can be the best options to make analytical determinations greener.

FT-Raman spectrometry has been used as a reagent-free methodology. The quantitative determination of different analytes performed directly on the sample, solid or liquid, using standard glass vials as sample cells, eliminates reagent consumption and avoids waste generation, also reducing the need for sample handling and the contact of the operator with potentially toxic substances. This technique has been used for the determination of iprodione in solid-pesticide formulations [75] and for the analysis of sweetener formulations [76].

The evolution of chemometrics has supported development of solvent-free methodologies based on mathematical treatment of signals obtained by direct measurements on untreated solid or liquid samples. Partial least squares NIR (PLS-NIR) provides a direct procedure for pesticide determination in formulations [77]. NIR spectroscopy using transmittance measurements, in combination with chemometrics, has proved to be a powerful tool for the determination of the peroxide index in edible oil using PLS calibration without the need to use solvents or derivatization reagents [78].

Another example of solvent-free methodology is based on photoacoustic-Fourier-transform infrared-spectroscopy (PAS-FT-IR), which was applied to determine Mancozeb in agrochemicals [79]. The method involved direct measurement of the transmittance spectra of solid samples

Other reagent-free methodologies proposed in the literature include photo-induced mercury cold/chemical vapor generation (PI-CVG), which uses sample matrix as a reductant. It was proposed for atomic fluorescence detection of trace mercury in wine or liquor samples [80]. The new method is based on the reduction of mercury by wine ethanol irradiated with UV light. The standard-addition method was used for real sample analysis to achieve the reagent-free goal.

Direct measurement of the elemental composition of samples through energy dispersion X-ray fluorescence (ED-XRF) is not called a green methodology. However, it is clear that these measurements involve no sample treatment and can be done without creating wastes.

6. Conclusions

The use of GAC methods has proved to be a smart strategy to provide both environmental and economic benefits, so we would like to propose for these methods the term ''Sustainable Analytical Procedures'' (SAPs).

The growth and evolution of chemometrics has shown that spectroscopic methods could be the best way towards GAC. However, the development of new methods of sample preparation, which reduces dramatically the amounts of reagent and organic solvents, also improves the characteristics of other methodologies, which cannot be applied directly to the samples as electrochemical and chromatographic methoids can.

The progress of flow methodologies has contributed to GAC, but we are convinced that their potential has not yet been exploited fully.

Multipumping flow systems have proved to be a cost-effective, valuable alternative to fully automated analytical methods for pharmaceutical, food, environmental, agroindustrial and large-scale routine clinical analysis. Moreover, they are fast, precise and accurate, and require less operator intervention or maintenance than classical FIA.

Miniaturization is one way to avoid side effects of analytical methods, and has been the subject of a significant number of research efforts. In this respect, combination of modern analytical techniques with breakthroughs in microelectronics and miniaturization allows development of powerful analytical devices for effective control of processes and pollution. Combining miniaturization in analytical systems with advances in chemometrics is very important. Of course, development and improvement of new components for instrumentation is critical in GAC.

Using examples, we have illustrated the power and the versatility of modern analytical systems and their potential for minimizing the consumption of hazardous substances and the amounts of waste generated during assays.

Commercialization, together with acceptance by quality-control laboratories and industrial plants, should gear up GAC methods to the large scale needed for environmental and industrial applications. This transformation is also required in the context of education in chemistry. Replacement of old experimental practices by attractive procedures exploiting available instrumentation will result in the immediate reduction of wastes as well as developing the environmental conscience essential for our students in the future.

Our final conclusion deals with the principles and philosophical fundamentals of the search for green methods. Many of the methodologies that have contributed to GAC were developed before the introduction of concepts such as ecological paradigms (1987), environmentally-friendly analytical chemistry (1994) and Green Chemistry (1999). But, it has been in the light of these ideas that laboratories have taken into consideration practical aspects (e.g., the toxicity of reagents employed, the amounts of reagents consumed, the

volumes of waste generated, and the responsibility of the analyst faced with both the results and the side effects of the methodologies they have employed). Because of that, we can expect in the years ahead tremendous advances in the development of new methodologies and in the regulatory norms that control laboratory activities.

Acknowledgements

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