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Modern qualitative analysis by miniaturized and microfluidic systems

Ángel Ríos [a,b,*], Mohammed Zougagh [b,c]

[a] Department of Analytical Chemistry and Food Technology, University of Castilla-La Manch, Ciudad Real E-13004, Spain
[b] Regional Institute for Applied Chemistry Research, IRICA, Ciudad Real E-13004, Spain
[c] Castilla-La Mancha Science and Technology Park, Albacete E-02006, Spain

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ABSTRACT

The evolution toward miniaturization has affected many facets in our life and similarly is also a clear trend in modern analytical science and laboratories, resulting in miniaturized devices and measurement processes with interesting, advantageous practical implications. This article presents a general view of miniaturized analytical systems, covering devices giving qualitative information. Qualitative information is more than the simple identification of compounds in samples, as the modern concept of qualitative analysis also includes the analytical information not represented by numbers (as is characteristic of quantitative analysis). Thus, classification of samples by screening methods, or the definition of an analytical profile of analytes in a sample, as diagnostic tests provide, must be viewed as a type of qualitative analysis. Following this concept of qualitative analysis, different miniaturized analytical approaches are described, as are future trends, pointing out advantages, disadvantages and challenges.

Contents

1. Introduction

Analytical science is the scientific discipline dealing with the production of information (qualitative, quantitative and structural) about materials or target systems, in general. This information is mainly addressed to satisfy client information needs according to specific requirements ("fitness for purpose"). It is generated through the implementation of the analytical process. Simplification, automation and miniaturization are clear trends for laboratories, characterizing new analytical processes that are more efficient and have greater potential to provide information. These trends in laboratories are possible because of technological developments in the past few years, in parallel with an evolution towards simplification and the miniaturization affecting many other facets of our life (e.g., computers and telephones). Simplification, automation and miniaturization have produced a revolution in laboratories in every field of application.

Miniaturization is rapidly growing with novel ideas in recent years [1]. As in other fields, analytical systems have been affected by this tendency. Concretely, the capacity to carry out laboratory operations on a small scale using miniaturized devices is very appealing. Thus, *micro-total analysis systems* (μTAS), also called lab-on-a-chip (LOC), have renewed interest in the scaling laws of 20–25 years ago [2]. To this end, small scale reduces the required time to synthesize and to analyze a product, as greater control of molecular interactions is achieved at the microscale level. In addition, reagent cost and the amount of chemical waste can be very much reduced. Now, at the beginning of this century, it is clear that lab-on-a-chip approach is starting to be considered as a potential analytical tool

* Corresponding author. Tel.: +34 926 295 232; Fax: +34 926 295 318.
E-mail address: angel.rios@uclm.es (Á. Ríos).

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in many application fields. However, some miniaturized analytical systems, such as capillary gas chromatography (CGC), microliquid chromatography (μGC) and micro-capillary electrophoresis (μCE), which can be considered as intermediate level of miniaturization (partial miniaturization), have been consolidated in routine laboratories for the analysis of complex samples. Miniaturized analytical systems really do constitute powerful tools in modern chemical analysis, although facing existing challenges [3].

One primary, important part of chemical analysis is qualitative analysis. As previously reported by the Valcárcel group, qualitative analysis cannot be considered a declining branch of analytical science [4]. Instrumental analysis and other recent "at home" alternatives, such as kit or spot tests (e.g., the popular pregnancy test), reinforce the role of qualitative analysis viewed in a modern way {i.e., not only for identification of compounds in the sample [5], but also classification of samples following screening strategies [6]}.

This modern view of qualitative analysis connects very well with the present needs of laboratories. This new view received practical support on the publication, in Europe, of the Decision of the European Commission 2002/657/EC about the analytical requirements of screening methods applied to the analysis of residues of organic pollutants for food-safety-control purposes. In this way, the support of the EC for the clear establishment of the principles of metrology in qualitative chemical analysis through the G6MA-CT-2000-01012 project (MEQUALAN) [7,8], allowed reporting the implementation of quality principles in qualitative analysis.

From this background, the convergence of qualitative analysis and miniaturization opens up new approaches and opportunities to solve a good number of real-world analytical problems. This goal is the objective of this article.

2. Miniaturized analytical systems

Miniaturization means "small or very small scale", and is therefore associated with the size of the systems. From this point of view, we can distinguish three different levels:

- mini-scale (several mm or μL);
- micro-scale (a few mm to 50 μm and processing samples between a few μL and 10 nL); and,
- nano-scale (below 50 μm – even 1 μm in some cases, and with sample size below 10 nL, or even at the pL or fL level).

But, in any case, the association with the reduction of size can be somewhat confusing, and it does not always involve a small scale (depending on what is understood by the "normal scale"). Moving this concept to analytical science, miniaturization can be viewed as making on a small scale a part or the whole of the analytical process, or reducing the size of the different devices involved in the analytical process or the analytical technique itself. Thus, the corresponding three levels of miniaturization can be associated with the following.

(i) Analytical mini-systems or mini-techniques, involving some specific devices, such as mini-reactors, mini-columns, or the application of mini techniques, for which commonly the prefix mini- has been replaced by micro- (although inappropriately, according to the general classification). This is the case for microgravimetry or for microtitration. Other longer scale equipment (chromatographic instruments, mainly) have been named as micro-GC, micro-/nano-HPLC, not due to the size of the "miniaturized" equipment, but because of the use of minidevices (such as pumps, valves or capillary columns) for handling micro or nano volumes and introducing separation advantages over the normal-sized equipment. From this point of view, commercially available CE equipment (fabricated at large-scale size) could be associated with micro-/nano-CE. Just in this case, the term μCE is correctly used when the electrophoretic separation is performed in micro-chips. This characteristic is not so frequently used for GC and LC in micro-chips.

(ii) Analytical microsystems are microstructured devices, integrated as analytical structures in the μm range, produced by using microfabrication techniques. They include microdevices (microreactors, micropumps, microvalves, capillary columns, microsensors and microactuators, and array microsystems), micro-techniques (μFIA, lab-on-a-chip valve, μCE), and the complete analytical process (μTAS).

(iii) Analytical nano-systems are systems at the nm size, built with atomic precision, by using nanotechnology facilities. Nanotechnology is a multidisciplinary field of applied science and technology working at ~1–100 nm, and dealing with the fabrication of devices at this size. Useful materials, devices and systems at this size range may be obtained by two different approaches. In the "bottom-up" approach, materials and devices are built from molecular components that assemble themselves chemically by the principles of molecular recognition. In the "top-down" approach, nano-objects are constructed from larger entities without atomic-level control. Examples of analytical nano-systems are nano-electromechanical systems, and nano-electrodes.

It is well known that (bio)chemical analysis is performed through the so-called analytical process, which integrates a group of steps and sub-steps connecting the sample with the corresponding results. Miniaturization, at the different levels and categories defined above, can affect a single step/sub-step, various integrated steps/sub-steps, or the entire process. Fig. 1 illustrates these possibilities, taking the analytical process as the central part, and considering it as the topic "analytical black box", which can be the basic view for integrated analytical (micro)systems; or the specific sequence of the three main steps: preliminary operations, signal measurement and transduction, and data acquisition and processing. Hence, the upper part of Fig. 1 represents a (micro)system performing the whole process, whereas the lower part includes the different analytical standard operations involved in the process. This view allows the miniaturization in the analytical process to be described as:

- the partial miniaturization of step(s), devices or equipment; or,
- the integrated (micro)systems for performing the entire analytical process, whose miniaturization should be viewed in combination with automation and simplification of the process.

Thus, considering the upper part of Fig. 1, simplification-automation-integration has resulted in a TAS of portable equipment, whereas the trends to the miniaturization of TAS produced μTAS, and *in-vivo* measurement devices as a result of the miniaturization of portable equipment. μTAS is the maximum extension of miniaturization and integration of the whole analytical process on a chip, with corresponding challenges in many cases so far [3,10]. These microsystems work as a sample-in/answer-out systems, where one of the main challenges is integration of sample treatment [9].

Probably, the term LOC (although synonymous with μTAS) gives a more appropriate idea of the laboratory on a chip, as these miniaturized systems are used for not only analysis of the samples, but also synthesis of compounds and biochemical studies of cells and microorganisms. In some cases, interesting developments have even been reported as integrating chemical synthesis and analysis on a chip [11]. These microchips use microfluidic systems to automate standard laboratory processes and to conduct chemical and biochemical processes in a miniaturized format.