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PRE-CONCENTRATORS: TRENDS AND FUTURE NEEDS

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ABSTRACT

This review addresses the trends in the production of small dimension pre-concentrators for its use in miniaturized total chemical analysis system – μTAS.
Pre-concentrators are defined as any device used to enhance the analyte concentration, through its preconcentration and quick release prior to its analysis, in order to guarantee a better detection limit.
It is possible to observe that there are few pre-concentrators in the market. Besides showing small dimensions, these devices also present reliability, reproducibility and relatively good cost. The driving forces to these developments were mainly security issues and environmental matters.
Practically any chemical analysis might benefit from the manufacturing of miniaturized pre-concentrators. However, some of them would especially benefit. Small amount analyte, generally around ppm or sub-ppm range, and analysis that demand quick response or must occur in situ are the main target to this device development. Therefore, great advance in analyses of medical, biological, environmental and safety areas are expected, besides the development of new materials and theoretical models. Then, new materials, mainly the nanostructured materials, and new models, particularly for adsorption/desorption in miniaturized devices, are to be obtained in the near future and great effort can really be seen. Finally, better detectors aiming better fitting to the device are also in vogue. These detectors can range from small sensors device to complex analytical equipment and most of times miniaturized as well.
Not only will the creation of these devices allow cost minimization and quicker analysis time that enables continuous monitoring, but will impact other science and technology areas such as the analytical equipment development.
A new approach for preconcentration and/or retention is proposed.

1. INTRODUCTION

In the chemical engineering and mechatronics the miniaturization and/or system automation led the development of MEMS (*Microelectromechanical Systems*) structures, where actuators and electronics systems were simultaneously produced and integrated [1] These structures allowed smaller control equipment, such as valves, that allied to the computational development in the last decades led the obtaining of more efficient devices, such as reactors.
In Chemistry it is possible to observe a notable evolution because the miniaturization might be useful not only in preparative but also in analytical area once it permits the obtaining or manipulation of small volume samples. In analytical chemistry, the idea of miniaturized total chemical analysis system - μTAS - is researched by many authors [2].
Miniaturized systems (μTAS) allow, or will allow in the near future, short time analysis making use of few resources. Therefore, the development of systems that permit analysis using microliters cooperate to the development of cleaner technologies once it uses less reactant and produces less wastes, devices that require less resources and do not represent discharge problems.
On the other hand, the obtaining of such devices will require the approach in a lot of steps and an important one is the sample pre-treatment. The samples for chemical analysis, especially in the environmental or biological area, show extreme complexity that might impede its total determination quickly and efficiently in a few steps. Thus, some sample pre-treatment is required.
Among the various issues to be taken into consideration in the sample pre-treatment step, the detection limit is one of the most relevant. Many times simple and inexpensive sensors cannot be used due to the low detection limit required, generally around ppm or sub-ppm range. Small amount sample or analyte and analysis that demand quick response or must occur *in situ* are another examples where detection limit is a concern. Therefore, these are examples that might benefit from preconcentration and pre-concentrators development.
A recent review in the sample pre-treatment process [3] suggests a general diagram where the preconcentration has a special attention. An adaptation to the diagram with special emphasis to the preconcentration and concentration enhancement factor is shown in Table A.
The preconcentration is not perfectly developed even for simpler systems, such as gaseous emission. Lichtenberg [3] observes that there are few miniaturized systems for gaseous sample preconcentration and only the use of microfilters for particle removal is more common. According to Lichtenberg, the first case for gaseous sample preconcentration was presented by Sandia National Labs in 2000 and used heating for adsorbed material removal.

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This review will consider pre-concentrators as any device used to enhance the analyte concentration, through its preconcentration and quick release prior to its analysis, in order to guarantee a better detection limit. The emphasis of this work relies on constructed devices and less to the techniques that were very described by Lichtenberg formerly.
First, a quick description of two already available pre-concentrators in the market will be given. Then, the liquid and gaseous phase preconcentration devices found in the literature will be shown. Therefore, the aim of this review is to evaluate the development of new pre-concentrator structures to show the real need of new pre-concentrators.

Table A - Classification of techniques used in the sample pre-treatment and detection limit or concentration enhancement factor obtained (adapted from [3]).

Sample pre-treatment		**Some detection limits**
Derivatization		0.55 fmol for arginine and 0.83 fmol for glycine using 1-nl reaction chamber
Separation of the sample from sample matrix		---
Biochemical sample pretreatment		DNA concentrations of 27 ngμl^{-1}
Sample preconcentration	**Techniques**	**Concentration enhancement factor**
	Stacking of neutrals analytes	20
	Field amplified injection	10-20
	Field-amplification stacking	10-100
	Surface affinity reactions	Up to 30
	Solid phase extraction	80-500
	Porous membrane structure	Up to 100

2. AVALIABLE DEVICES

A small analysis equipment has recently been presented by the Sandia Labs (USA). The equipment technical description [4,5] shows four different steps to the analysis: sample colection/concentration; separation; chemically selective detection; gas flow control. The first one corresponds to the pre-concentrator unit. The analyte collection is done by a film deposited on a silicon nitride membrane. The film choice allows different analyte concentration once the adsorption ability depends on the film surface chemistry and the film porosity. The silicon nitride membrane where the film was deposited can be quickly heated and the analyte is the desorbed. For gas samples, the second step (separation) corresponds to a gas chromatography column and the detection is done by an array of Surface Acoustic Wave (SAW) sensors. These sensors are covered by a sorbent film to improve the analysis sensibility. To the liquid analyses [6] the chromatography and the electrophoresis techniques are used for separation and the detection is done by laser-induced fluorescence [7].
On this system, sarin and mustard gas can be preconcentrated and the result is not affected by humidity. The pre-concentrator can also remove bacteria by pyrolysis followed by volatilizing. The costs can also be minimized if organic polymers are used instead of silicon for pre-concentrator manufacturing.
Chemiresistor and SAW sensors were recently tested for the monitoring of volatile organic compounds (VOC's) in soil and groundwater [8]. The results were adequate for m-xylene but for TCE (trichloroethylene) the detection limit was still high, which suggests the preconcentration. Another advantage of preconcentration prior to the detection is the minimization of chemical interferents and other phenomena that affect the results. The sensors and their test were also described in others references [9-12].
After the addition of a pre-concentrator to a chemiresistor sensor, the variation on the obtained signal as a function of the distance between pre-concentrator and sensor was evaluated for methyl salicylate vapor detection. It was possible to observe a value four times lower when the sensor and the pre-concentrator are moved away from 1.6 mm to 5 mm [13], which indicates the use of a maximum proximity between them. However, although the pre-concentrator was heated to 200ºC, no chemiresistor sensor array problems were seen when the pre-concentrator and sensors were near.
Tests for a system that concentrates and removes water particles have been developed in the same laboratory [14]. The phenomenon applied corresponds to dielectrophoresis (iDEP) where non-uniform electric fields are applied, for example, for microorganism separation, such as *Escherichia coli*, from the aqueous matrix. It was possible to notice distinct behavior between the alive and dead cells in the prototype [15]. Another interesting prototype for the explosive detection was also manufactured [16]. The project suggests the use of a pre-concentrator due to size miniaturization of the whole device and the lower power consumption operation required. The pre-concentrator uses metal felt as absorber and the desorption cycle is obtained by heating. The pre-concentrator was added to a hand-held trace detector of Ion Track Instruments [17]. The prototype was tested with TNT (2,4,6-trinitrotoluene) and RDX (cyclotrimethylenetrinitramine) and it was obtained a preconcentration efficiency of 72% for 1 nanogram of TNT. It was considered extremely important to test the same pre-concentrator for ilicit drugs and to verify the efficiency using other detectors, such as mass spectrometer systems or ion mobility spectrometers. In fact, the combination of pre-concentrator and an ion mobility spectrometer system allowed the detection of one microgram of methamphetamine, cocaine, heroin, and tetrahydrocannabinol (THC) [18].
The same way security matters were the driving force for the construction of these devices, the announcement by Sandia of manufacturing a pre-concentrator provoked great repercussion in the military area, due to the possibility of using it anywhere once its dimensions are relatively small. It could be used in fan systems, besides working continuously, which cannot be done by trained animals [19]. Therefore,

the miniaturization allowed the obtention of “portable, fast, sensitive, easy to use, low cost sensors with low false alarm rates” [20].

Also, one of the great interests in the pre-concentrators manufacturing is the combination to chromatographs in order to obtain portable equipment. The combination of chromatography systems and pre-concentrators, not only allows low detection limit but also guarantee more reliability in the determination of the material to be analyzed. Once chromatographs analyze liquid and gas samples, a large amount of samples can be analyzed, “running from toxic industrial materials through chemical agents, through bio toxins, to pathogens” [21]. This year one portable equipment [22] using a “MEMS-based column” and “integrated micro-sample pre-concentrator, capable of processing analyses en less than 1 minute and sensitivity in the parts per billion” will be available.

Finally, as Alonso-Amigo [23] remembers, there is a series of miniaturized devices have been applied to the genomics and proteomics. However, such devices show almost no integration. Weigl [24] also reports that nowadays a series of companies have developed microfluidic technologies to highly predictable and homogeneous samples that are common in the drug discovery process. Many of those devices uses sample preconcentration.

3. DEVICES DESCRIBED IN THE LITERATURE RECENTLY

A lot of pre-concentrator devices were recently described in the literature, even though many of them are not micromachined. Some of these possibilities will be shown below.

3.1 PRECONCENTRATION IN GAS PHASE

Preconcentration is common in many analytical techniques, such as gas chromatography, and many of them use conventional pre-concentrators. The conventional-type pre-concentrator is essentially a stainless steel pipe, several centimeters in length and full of an adsorbing product. The adsorbing products used are similar to the stationary phases used in the chromatographic columns. Therefore, products range from active carbon to porous organic polymers.

VOC’s analysis has taken so much attention due to their harmful environmental effect. VOC´s are normally detected by gas chromatography and can make use of pre-concentrators [25]. Small sorbent trap, known as microtap, has already been reported [26-28] to preconcentration and some have been miniaturized [29]. The device, named microconcentrator, was produced on a silicon surface and makes use of a thin film polymeric layer, normally used as a stationary phase in gas chromatography, to promote adsorption. The device can also be used as injector for gas chromatography. A possible variation to semi-volatile organic compounds analysis in aqueous matrix is the membrane extraction [30] combined with liquid chromatography analysis. For volatile sulfur compounds (VSCs) preconcentration can be used active carbon [31]. Besides improving analysis sensibility, it also minimized humidity influence, which can also be useful for halitosis determination, for example.

For the conventional-type pre-concentrator, Nakamoto [32] found out a lot of analysis difficulties when the pre-concentrator accumulation time should be varied. The difficult are a consequence of desorption delay time. Desorption delay is due to the big sized device that imposes difficulties for quick heating and cooling cycles. Also pre-concentrator with variable temperatures is needed [33], for example to enhance the discrimination capability of odor discrimination systems. Therefore, a new lay out considering planar distribution of adsorbent, was proposed. This lay out is more similar to the expected one for micromachined systems.

Zellers et al. [34]proposed the construction of a micro gas chromatograph (μCG) to determine from “30-50 complex vapor mixtures at ppb – parts per billion - levels in the environment” in less than 20 minutes. One of the system components is a pre-concentrator also used to insert the sample in the chromatography column, called multistage micro-pre-concentrator/focuser (μPCF). The first prototype [35] used capillaries 7.5 cm in length and 1-20 mg adsorbents: Carbopack^{TM}, Carbotrap^{TM} and Carboxen^{TM}. 100 ppb volatile and semi-volatile organic compounds samples were tested. The preconcentration obtained was enough to analysis of indoor air quality. This way, the miniaturized device can use only 5 mg adsorbent and present preconcentration factors as high as 5600. The adsorbent consists in “roughly spherical granules, similar to 200μm in diameter, of a high surface-area, graphitized carbon” and is quickly heated by micro-heaters [36-39]. The set presents low dead volume, detects “low concentration compound at 25 ppb-l and narrow desorption peak widths” [40].

Therefore, up to now the development of gas phase pre-concentrator is principally related to the analytical equipment miniaturization, especially gas chromatography.

3.2 PRECONCENTRATION IN LIQUID PHASE

Preconcentration in liquid phase does not make use of specific device. It normally occurs simultaneously with detection using electro kinetic separation and aqueous solution, due to the facility for ion movement on these conditions. However, the use of adsorption processes is also possible and is actually applied in solid-phase extraction techniques. Recently, Lichtenberg [3] reviewed such techniques and therefore only some new comments will be shown here.

The adsorption is useful to evaluate ions in aqueous solution [41] and a miniaturized analyzer to trace analysis has been developed [42]. Another pre-concentrator was developed based on the increase in the silicon surface area. A high-surface area [43] was obtained through the etching of a reticulated structure on a silicon wafer. The device was tested and allowed copper ion preconcentration on aqueous solution. The silicon surface can be modified with organic silicon compounds to allow other compounds adsorption. The adsorption in a nanometer-thick polymer film was recently

used to preconcentrate and separate proteins in a microfluidic device [44].
Due to the importance of capillary electrophoresis to sample preconcentration, some comments are added, although recent reviews might be found [45,46]. The trend to the use of capillary electrophoresis and related methods [47] is the small amount of sample needed to the process and the good concentration enhancement factor that can be achieved. Therefore, on-line analyte preconcentration and capillary electrophoresis is important to biological and environmental researches. Thus, great development is to happen in the near future, specially in the drugs discovery and clinical diagnosis area. An example of microchannels manufacturing to capillary electrophoresis through cheap methods is the use of a laser printer and a polyester film. It corresponds to a largely accessible technology that makes use of organic and flexible substrates [48]. The process, which was considered as an interesting alternative to the capillary electrophoresis device prototype, was also tested for preconcentration, due to the existence of small iron particles inside the microchannels [49].

4. RELEVANT CONCEPTS TO THE DEFINITION OF PRE-CONCENTRATORS

Adsorption and desorption models in gas phase miniaturized systems make use of gas chromatography concepts, but a series of parameters still needed to be determined. Some examples of these needs are found in [30,35,50]. The same way, the sensors used in equipment where pre-concentrators are installed need to be modeled. Recently, computational models were presented to describe gas adsorption and desorption in conducting polymer micro sensors [51], SAW sensors have also been studied [52,53].
Liquid systems, in general, make use of electro kinetic separation and the reviews mentioned before present the important models and concepts [3,24,45,46,47].

5. TRENDS: MATERIALS/TECHNIQUES TO BE APPLIED

5.1 MATERIALS

Preconcentration requires the production of high-surface area adsorbent materials. High-surface area can be obtained through some different ways, one of them includes the porous silicon fabrication [54]. This substrate is got by silicon-wet etching and presents porous size ranging from nanometer to micrometer. Besides the high superficial area, porous silicon has a very reactive surface, which disturbs reproducibility when it is used for sensor fabrication. A way to minimize reactivity is favoring oxidation immediately after fabrication [55]. High superficial area was also obtained by anodic etching of aluminum films [56,57] to latter modification aiming VOC´s adsorption.
Another fabrication high superficial area method includes the nanofibers and they are commonly applied to sensor fabrication. A possible technique is the electrospinning [58-60]. A simple process, which uses PAN (polyacrilonitrile), was developed for the addition of many different particles inside the fiber or for nanofibers superficial modification [61]. Conducting polymers also allowed the fabrication of oriented nanowires used in the detection of H_2O_2 [62]. Sorptive polymers [63] are important because can provide a fast adsorption and desorption cycle.
Because these materials are intended to be in a very small region, new materials, specially nanomaterials and/or nanocomposites must be developed and it is possible to find some review about nanomaterials in the literature [64-70]. Nanoporous materials, organic or inorganic, are equally important [71-73]. Among all possibilities, organic polymers present many advantages due to the huge variety of chemical functions that can be got [74-76]. Printing technologies are also important and some of them have already been developed [77].
Nowadays an interesting example of commercialized material is the Nanopowder™ [78]. It has been tested to [79] separate proteins and remove bacteria, for military uses. The advantage is that the removal depends on electrostatics forces, which minimize the pressure difference during the process, for instance when it is used in filters.

5.2 ANALYTICAL TECHNIQUES

As mentioned before, among the equipment developed considering the preconcentration idea, the chromatographs are the most promising techniques for integration with pre-concentrators and/or miniaturization. The analysis speed, in many cases, is fundamental, and some interesting new approach for equipment manufacturing was presented in the last few years [80-82]. The preconcentration is sometimes required and must happen quickly, even when micromachined pre-concentrators are not used. The same way, the detector needs to be quick and usually a SAW detector is applied. Tests of gas chromatographs/SAW (GC/SAW) have already been processed for VOC's, explosives in the air, water and ground, which can be very useful in the environmental area. Staples emphasizes [80] that "GC/SAW technology is able to satisfy and follow accepted EPA testing methodology in the field".
A recent review about gas chromatographs miniaturization [83] classifies them into some categories: compact devices field devices, on chip micro chromatographs and special micro chromatographs. The compact chromatographs are used in mobile laboratories whereas field devices are portable gas chromatographs for on-site analysis. On chip micro chromatographs present a series of advantages, such as fast resolution for simple analytical problems, but has restricted analytical capabilities. Special micro chromatographs are designed for space investigations and need to stand on severe conditions. For dangerous pollutants in unknown mixtures, such as explosives, Yashin [83] suggests the use of portable gas chromatograph-mass spectrometer systems. Finally, the

review concludes that there are two trends for chromatography: quick analysis and miniaturization. However, in order to analyze in seconds, "stringent requirements on injection systems, temperature programming units and detectors, specially for field chromatographs" are imposed. The most important application of portable high-speed chromatographs is in environmental problems solutions such as pesticides, PCBs (polychlorobiphenyls), freons, VOC's, odors, indoor pollutants, etc.

Mass spectrometer [24,84]and ion mobility spectrometer [85] should also be miniaturized. The same way, the interface between these equipment and sample inlet systems should be miniaturization target as well. A good example is the use of adsorption of proteins on a membrane followed by mass spectrometer analysis [86].

6. FUTURE NEEDS

The next important technological development is related to obtaining inexpensive structures in high production level. Therefore, the use of plastic material [23,87] and continuous production line, know as *Roll-to-Roll* [88] in the microelectronics area, may increase in the next years. Rolltronics™ is an example of the use of continuous flow. This company got patents for the production of transistors using such technology. The great advantage is that devices are manufactured on flexible substrates, using wet process, which increases residue formation, though. Therefore, in the near future, organic and/or flexible substrates and continuous production will take place, probably using other processes. As mentioned before, printing technologies, which present less residue formation, are also important. Another possibility is adsorbent plasma thin film deposition.

Some new approaches would be considered on this field. On macroscopic systems, as the one used in chemical plants, capillarity phenomena can favor retention of aerosols or even small particles [89-91]. On these systems constrictions are normally used in a large tube to enhance the capillarity phenomena. These constrictions create large turbulence in the main flow and favor condensation. These effects might improve capillarity phenomena efficiency in small dimensions, especially for gas preconcentration. The design of pre-concentrators has not considered the use of these effects so far. However, preliminary results from the use of constrictions inside a microchannel showed the possibility of VOC's retention and/or preconcentration [92].

According with the idea of scalar miniaturization of macroscopic structures commonly used in chemical plants, seven of them were manufactured and tested [92-97]. These structures, manufactured in acrylic, can be easily disassembled and were used with gas and liquid flow. The main functions assigned to these structures were: catalysis and adsorption tests, removal of particles from liquid and gaseous flow, mixer for liquids and chromatography microcolumn.

Moreover, preconcentration relies on different phenomena but one of them is quite important: adsorption. Therefore, new adsorbent films must be obtained. These adsorbent layers preferentially must be thin films in order to decrease secondary phenomena that hinder preconcentration, such as permeation. Consequently, plasma deposited thin films must be considered. Several adsorbent thin films were obtained by plasma deposition [98-105] or electroless plating [17]. Therefore, the hydrophilicity and/or hydrophobicity of microstructure surfaces can be modified. It is also possible to produce a nanochanneled thin film [106] useful as a chromatographic stationary phase or a reactive and nanostructured metal surface [107] for catalysis.

Finally, in order to teach this new field and train undergraduate students, new equipment is required, preferentially low-cost systems. A low cost system, around US$ 7,000 [108], that allows training and research as well was proposed; therefore, in a near future it would be possible, due to the small size of the instrument, to provide it to the professor not the school. In this scenario, the researcher can move from one institution to other without losing his research work.

7. CONCLUSIONS

It is possible to observe that there are few pre-concentrators in the market. Besides having small dimensions, these devices also show reliability, reproducibility and good cost. The driving force for such development were mainly environmental and security issues such as drugs and terrorism. Indeed, any analysis would benefit from pre-concentrator manufacturing. However, some areas take special advantages. Analyte that are present in small quantities, (ppm or sub-ppm range) and analysis that demand quick response and should occur in situ are the main target to this device development. Therefore, not only great advances in the medical, biological, environmental and security analysis are expected but also the development of new material and concepts. This way, new materials, mainly the nanostructured materials, new concepts and models are going to be obtained in the near future. Indeed, great effort has been seen at the moment. Finally, better detectors are also research targets. These detectors can vary from small sensor devices to complex analytical equipment, most of the time also miniaturized.

Not only will the creation of these small devices contribute to the minimization of costs and better analysis time, which will allow continuous and real time monitoring, but also impact other science and technology areas such the manufacturing of analysis equipment.

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