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Miniaturized Total Analysis Systems: Integration of Electronics and Fluidics Using Low-Temperature Co-Fired Ceramics

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The advantages of microanalyzers, usually fabricated in silicon, glass, or polymers, are well-known. The design and construction of fluidic platforms are well-developed areas due to the perfectly established microfabrication technologies used. However, there is still the need to achieve devices that include not only the fluid management system but also the measurement electronics, so that real portable miniaturized analyzers can be obtained. Low-temperature co-fired ceramics technology permits the incorporation of actuators, such as micropumps and microvalves, controlled either magnetically, piezoelectrically, or thermally. Furthermore, electronic circuits can be also easily built exploiting the properties of these ceramics and the fact that they can be fabricated using a multilayer approach. In this work, taking advantage of the possibility of combining fluidics and electronics in a single substrate and using the same fabrication methodology, a chemical microanalyzer that integrates microfluidics, the detection system, and also the data acquisition and digital signal processing electronics is presented. To demonstrate the versatility of the technology, two alternative setups have been developed. In the first one, a modular configuration is proposed. In this case, the same electronic module can be used to determine different chemical parameters by simply exchanging the chemical module. In the second one, the monolithic integration of all the elements was accomplished, allowing the construction of compact and dedicated devices. Chloride ion microanalyzers have been constructed to demonstrate the operability of both device configurations. In all cases, the results obtained showed adequate analytical features.

The advantages regarding the miniaturization of total analysis systems (μ TAS) are well-known.¹ Most of the work found in the literature has focused on microfluidic devices, as they are the basic platform needed for μ TAS development. However, the scaling down of other key components of these TAS, such as the electronics needed to perform chemical measurements, has not

received the same attention. This probably responds to the difficulty involved in the integration of electronic circuitry using common microfabrication techniques and materials. Silicon technology permits the development of high precision electronic systems in the micro- and nanoscale. However, it results in a complex, expensive, and long-term fabrication process that involves the use of clean room facilities and specialized staff. On the other hand, the well-established printed circuit board technology permits one to obtain, by means of a faster and easier fabrication methodology, complex electronic circuits based on discrete components; however, it does not permit their conjugation with microfluidic platforms. The low-temperature co-fired ceramics (LTCC) technology has been widely used in electronics because it is suitable for high-volume and low-cost fabrication of multilayer printed circuit boards using surface mounting techniques and thick-film technology.^{2–4} The LTCC technology also combines the dielectric properties of ceramic layers with the high conductivity of embedded metal tracks to obtain multilayer and highly complex electronic circuit boards.^{5,6}

The advantages of the LTCC multilayer fabrication methodology have also been applied to design and construct miniaturized analytical systems with inner three-dimensional fluidic structures. These geometries enable the integration of several steps of an analytical procedure, such as detection systems (i.e., spectrophotometry, potentiometry, or amperometry), pretreatment steps (i.e., mixers, gas diffusion, and preconcentration chambers), and microactuators for flow control (micropumps, microvalves). When compared to conventional microfabrication techniques, such as those using glass, silicon, or polymers, LTCC technology shows some additional advantages including the following: (i) rapid prototyping, which allows a rapid modification of the design, (ii) low fabrication costs, (iii) no need of special fabrication conditions, such as clean rooms, and (iv) no need of sealing elements, such as epoxies, since the sintering fuses and seals the ceramic layers.

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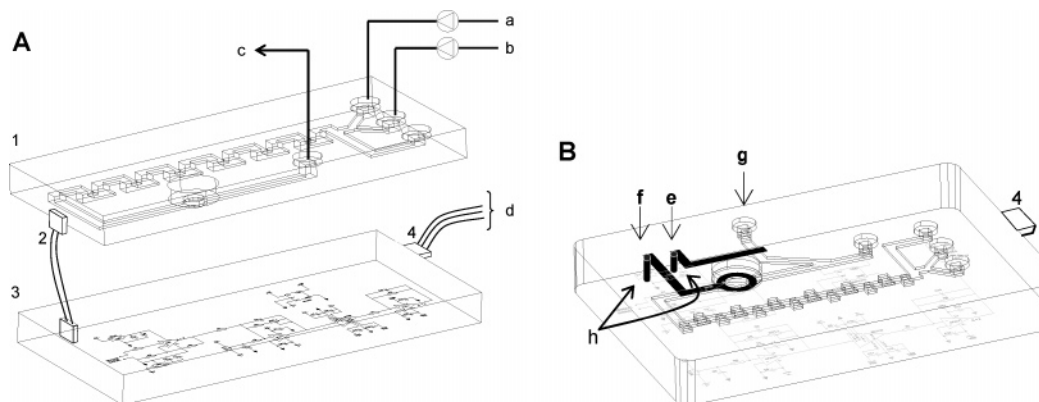


Figure 1. FIA experimental setup. (A) Modular configuration. (a) Sample/water inlet; (b) conditioning solution inlet; (c) waste outlet; (d) digital signal processing. 1, LTCC microanalyzer; 2, electrical signal connector; 3, LTCC electronic measurement system; 4, power supply and electrical output signal. (B) Monolithic configuration. (e) Reference electrode Ag track; (f) ISE track conductor; (g) reference electrode auxiliary channel; (h) electrical vias.

Information on chemical analyzers using LTCC is scarce in the literature.^{7–10} Some of the examples found include a mesoanalytical system for the detection of heavy metals in environmental fluids⁷ or the integration of a potentiometric detection system including PVC-based ion-selective membranes and an Ag/AgCl reference electrode.¹¹

The potential of this technology to easily integrate fluidics and electronics in a single system has already been demonstrated.¹² Martínez-Cisneros et al. fabricated a device that integrated monolithically the fluidics needed for determinations using enzyme reagents and a temperature control unit based in a sensor/actuator system to perform reactions at an optimal 37 °C.

To show the versatility of the LTCC fabrication methodology, two conceptual approaches are shown in this work. The first approach is that of a modular analyzer, where the electronics (a simple, inexpensive, portable, battery-operated, and programmable miniaturized potentiometer) are built apart from the chemical module that includes the microfluidic platform and the detection system. The chemical module, applied to the detection of chloride ions in water, has already been presented.¹³ In this case, the potentiometer could be attached to any other chemical module that integrated this type of detection system. The second approach takes the integration process further, integrating monolithically the electronics and the fluidics in a single substrate, allowing the construction of a compact and dedicated analyzer for specific applications.

EXPERIMENTAL SECTION

Modular Device. A modular configuration was developed so that the same electronic system could be used with different

chemical modules. Taking advantage of the rapid prototyping provided for the LTCC technology, there is no need to design general microfluidic platforms that accommodate a broad range of applications; thus, specific designs of microfluidic manifolds accurately adapted to each analytical problem can be made. In this way, a modular approach based on the use of a unique electronic module specifically designed for each type of detection technique (i.e., potentiometry, amperometry, colorimetry, etc.) and a variable personalized chemical module adapted to the sample requirements provide great advantages. Thus, different types of samples or analytes in the same sample could be determined by simply exchanging the microfluidic/detection platform. Additionally, sensors with short operational lifetime used as detectors into chemical modules could be used and easily replaced when needed. The modular approach, taking advantage of interchangeability, enhances the versatility of the proposed fabrication technology.

(a) Chemical Module. The miniaturized chemical module has been described in detail elsewhere.¹³ Figure 1A shows the modularity concept. The electronic and the fluidic platforms are attached by means of electrical connectors that would permit the use of different analytical microanalyzers. In Figure 1, the three-dimensional mixer used in both cases can also be observed, as well as the cavity especially designed to embed the ion-selective electrode (a Ag₂S/AgCl disk).

(b) Electronic Module. Dupont 951 green tapes were used as substrate for the electronic circuitry. They show a high thermal conductivity (3.3 W/mL·K), high isolation resistance ($>10^4 \Omega$), and a high dielectric constant (7.8). These features make it ideal for printing electronic tracks on it. Circuit design was made considering LTCC shrinkage, which is 12.7% in the x - y plane, according to the Dupont datasheets. Dupont 6146 Ag/Pd cofirable solderable conductor paste was employed to screen-print electronic paths on the green tapes. Dupont 6146 is compatible with Dupont 951, and it is ideally suited for applications that require soldering. Its fired resistivity is lower than 60 m Ω /sq. A 325 stainless steel screen mesh with 12- μ m emulsion was employed, as recommended for the resolution required for the printing of tracks and circuitry.

To produce a portable and user-friendly potentiometer, the design was divided in three stacked layers, which permitted the integration of all the components in the smallest area, without

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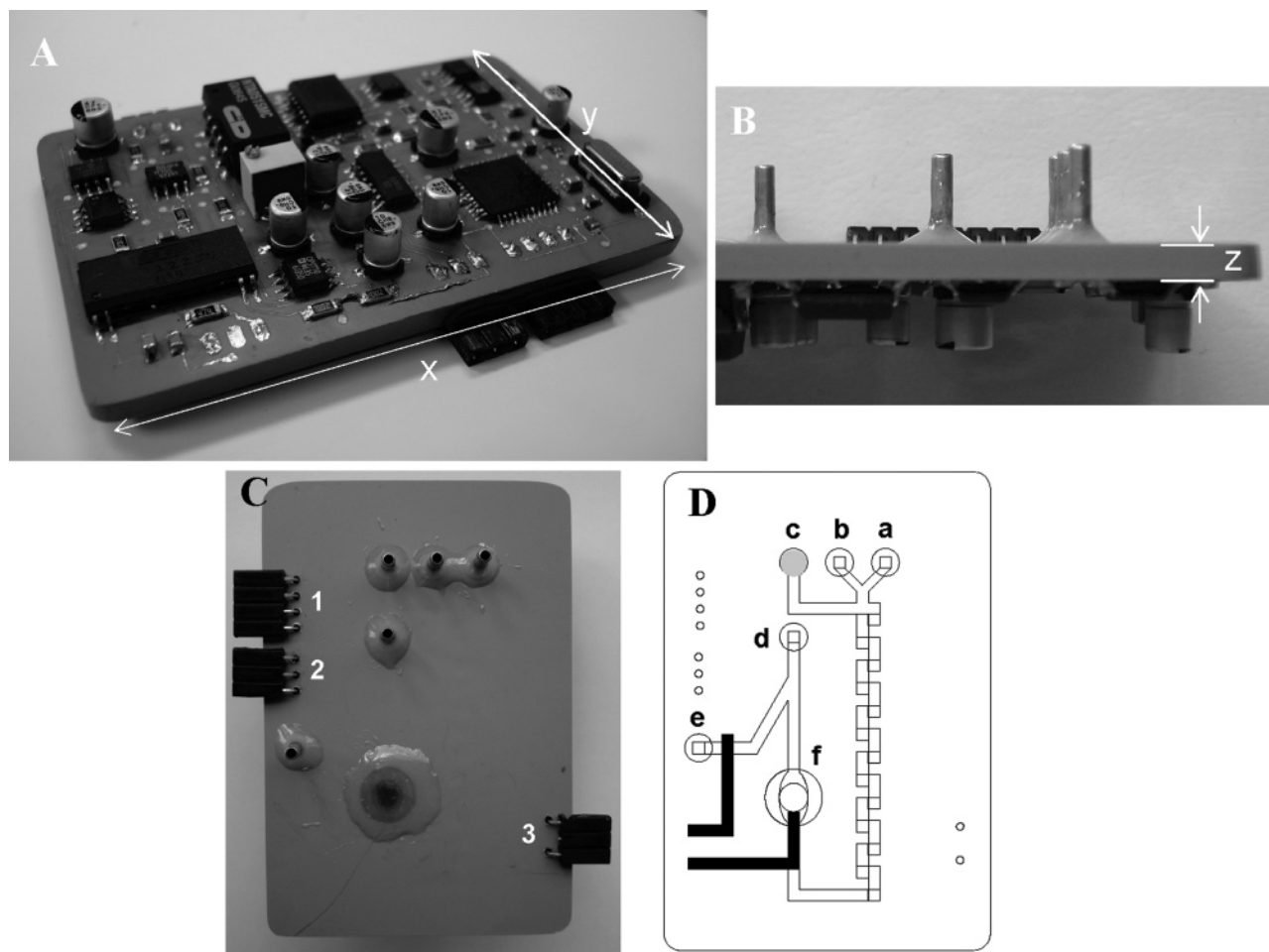


Figure 2. (A) Bottom view of the monolithic microanalyzer ($x = 7$ cm; $y = 4.9$ cm) with the electronics for data acquisition and digital signal processing. (B) Lateral view ($z = 0.3$ cm). (C) Top view of the monolithic microanalyzer. Fluidics and the detection system were integrated on this side. 1, Connector for the microprocessor programming; 2, serial communication; 3, power supply. (D) Fluidics and detection system distribution. (a) Conditioning solution inlet; (b) sample/water inlet; (c) closed channel; (d) waste outlet; (e) reference solution inlet; (f) ISE ($\text{Ag}_2\text{S}/\text{AgCl}$ disk).

losing robustness. Each layer was made of two Dupont 951 green tapes laminated at 3000 psi and 100 °C. Layers were placed at 120 °C for 25 min, as a preconditioning step, before printing the tracks. Conductor printing was done using a conventional thick-film screen printer. Vias for electrical connections between layers were formed using mechanical punching and Dupont 6141 Ag cofireable via fill (fired resistivity lower than 3 m Ω /sq).

Vias and conductors were dried using a box oven at 100 °C for 5 min. Once dried, layers were laminated (3000 psi at 100 °C) and sintered using the same temperature program previously presented.^{11,13} After sinterization, a hard surface ceramic-based board was obtained and discrete electronic elements could be mounted on it.

Monolithic Device. The intrinsic advantages of the LTCC technology permit one to integrate microfluidics, detection, and electronics, as all of them use the same substrate and the same fabrication methodology. Compact, robust, and portable microanalyzers with more autonomy can be produced following this approach. However, the fabrication of monolithic devices presents a limitation that needs to be considered: unlike the modular system, once the LTCC system has been built in a monolithic way, its analytical application in terms of analyte and type of sample to be measured is predetermined and it cannot be easily modified.

Therefore, the monolithic approach can be selected when microanalyzers for specific applications are needed. In this case, compactness and robustness would be preferred characteristics instead of versatility. Figure 1B shows the conceptual monolithic approach.

Microdevice Fabrication. The microsystem that integrates in the same substrate a miniaturized chloride ion analyzer and the electronics associated with potentiometric measurements is presented in Figure 2.

As illustrated in this figure, electronics were placed on one side of the device and microfluidics and the detection system on the other. Surface mounting elements were later encapsulated to avoid the risk of damage by liquid leakage and to enhance robustness. The design of the microfluidic and the detection subsystem was an improved version of the chemical module used in the modular configuration. In this case, as can be seen by comparing Figure 1A and Figure 2D, the fluidic platform included not only the cavity to integrate an ion-selective electrode (an $\text{Ag}_2\text{S}/\text{AgCl}$ disk) but also a pseudoreference electrode, previously evaluated in our research group. The reference electrode, consisting of a screen-printed silver track that was oxidized in presence of a chloride ion solution and it was placed in an auxiliary channel through which a constant KCl (0.1 M) solution flew constantly,

in order to main the reference potential at a constant value.¹¹ This way, the fluidic platform contained a complete potentiometric detection system.

As was the case in the modular electronic device, the electronics in the monolithic configuration are responsible for data acquisition and digital signal processing. Internal electrical connections between the electrodes and the electronic circuit were established using vias.

Electronic Module: Detection, Data Acquisition, and Signal Processing System. The electronic module system is composed of two main parts: (i) a first stage that amplifies the signal, corrects any offset present, and couples any impedance mismatch between the sensor and the measurement electronics; and (ii) a second stage for galvanic isolation and noise reduction that also includes signal conditioning circuitry, analog filtering, and digital processing with a microcontroller.

Potentiometric chemical sensors have high-output impedances, in the order of 100 M Ω , requiring readout circuitry with high-input impedance.¹⁴ The first stage of the circuit has a junction field effect transistor input providing the high-input impedance required. This stage also adjusts any offset present in the signal. Overall gain of this stage was set to 5. Galvanic isolation was implemented using an isolated operational amplifier (ISO122, Texas Instruments, Dallas TX) as well as a dc/dc converter (NMA1215, C&D Technologies, Blue Bell, PA). Since the selected design provides mutual isolation, more than one potentiometric sensor can be used. After the isolation stage, signals are analogically filtered using a 2-Hz low-pass Butterworth filter. Digital signal processing was performed using a microcontroller (PIC16F877, Microchip Technologies, Chandler AZ) that delivered the resulting signals to a personal computer through its serial port. The user interface was a virtual instrument. Additional digital filtering was performed by the microcontroller and also by the virtual instrument, producing noise-free signals. All integrated circuits were carefully chosen for optimal precision and noise reduction.

Chemicals and Experimental Setup. All reagents used were analytical grade when needed and obtained from Fluka. Stock solutions were prepared in MilliQ water every week and kept under refrigeration. Standards were prepared by dilution of the stock solutions.

A solution of 0.1 M KCl, flowing constantly through the auxiliary channel where the reference electrode channel was placed (marked as e in Figure 2D), allowed the production of a constant reference voltage. The electrical circuit was closed downstream from the indicator electrode in a free diffusion liquid junction, avoiding any contamination between the reference and the sample solutions.

The AgCl/Ag₂S sensor was prepared as previously described.¹⁵

The continuous flow system setup consisted of a peristaltic pump (Minipuls 3, Gilson, WI), a six-port distribution valve (Hamilton MVP, Reno, NV), 1.02-mm-internal diameter silicon tubing (Ismatec, Zürich, Switzerland), and 0.8-mm-internal diameter Teflon tubing (Scharlab, S.L., Cambridge, England).

RESULTS AND DISCUSSION

The developed microfluidic system was designed for the generation, acquisition, and processing of electrochemical signals in a continuous flow environment.

The electronic circuitry was built on a LTCC substrate using surface mount components. High-impedance input and high-precision operational amplifiers were selected for a better impedance coupling between electronics and the chemical sensor and for a precise signal amplification rate.

Surface mount integrated circuits are more sensitive to electromagnetic interference, causing additional noise. Therefore, isolation amplifiers were used to produce floating signals that permit several sensors with different reference electrodes to be connected in parallel with the same power supply without any cross-talk interference between them. A cleaner signal was obtained after the isolation stage. Additional digital noise reduction techniques were applied to the signal by analog and digital filtering.

The well-defined signals obtained showed little noise. Analog information acquired using the internal analog to digital converter of the microcontroller was processed by a digital filter (consisting of an arithmetic mean performed to a group of 200 data) to reduce noise in the system. Once data were digitally processed, they were sent to a personal computer using the RS232 communication protocol. Serial information sent from the microcontroller and acquired by the personal computer was shown on the screen using a virtual instrument interface. Finally, data were exported to an electronic data sheet where it was stored for further processing if required.

Modular Device. The modular design permits an easy way to exchange the chemical module allowing the analysis of different parameters or types of samples and to replace it entirely whenever malfunctions are observed.

Once the LTCC potentiometer was electronically tested, we combined it with the miniaturized chemical module to demonstrate the modular concept. Electrical and fluidic connections between the electronic module, the actuators handling the fluids, and the microfluidic module were established as shown in Figure 1A.

Key hydrodynamic parameters of the microfluidic system were selected on the basis of previous work.¹³ In this way, flow rate and sample injection volume were fixed at 1.55 mL/min and 300 μ L, respectively, using 0.1 M K₂SO₄ (pH 2.4 adjusted with H₂SO₄) as conditioning solution and water as carrier solution. KCl standards between 3.5 and 3550 ppm were prepared. The baseline signal was established by mixing water with the conditioning solution in the three-dimensional serpentine channel created in the LTCC microfluidic module. Simultaneously, the sample solution filled the injection loop. When the six-way valve was shifted, the sample was inserted in the main channel and propelled by water to the point where it met with the conditioning solution. When the sample reached the detector, a transient signal was obtained. Measurements were done by injecting standard solutions with different concentrations of chloride ion. The calibration plot obtained was $E = -25.9(\pm 5.3) + 52.6(\pm 3.4) - \log [\text{Cl}^-]$ ($n = 3$; 95% confidence; $r^2 > 0.999$). The detection limit found¹⁶ was 3.1-(± 0.5) ppm. The repeatability of the system, calculated as the

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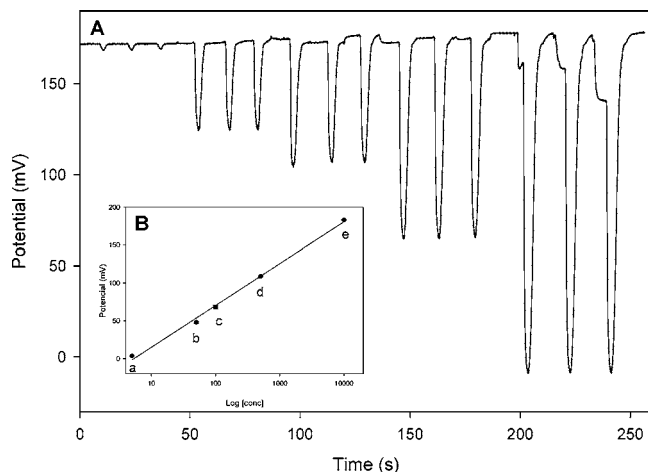


Figure 3. (A) System response to five different Cl^- concentrations: [a] = 5, [b] = 50, [c] = 100, [d] = 500, and [e] = 10000 ppm. (B) Calibration curve obtained.

relative standard deviation (RSD), was 2.05% ($n = 15$, 95% confidence) for an intermediate concentration (355 ppm).

Monolithic Device. The monolithic configuration allowed us to integrate electronics, fluidics, and the complete electrochemical detection system in a single substrate with a footprint smaller than a conventional credit card. Using this configuration, a complete portable microanalyzer for chloride ion determination was obtained.

The experimental setup and reagents used for the evaluation of the monolithic device were those previously used in the evaluation of the modular device. The same hydrodynamic parameters were used. In this case, standards between 5 and 10000 ppm were prepared and measured.

The calibration plot (see Figure 3) obtained was $E = -40.4 (\pm 0.5) + 55.3 (\pm 0.1) \cdot \log [\text{Cl}^-]$ ($n = 3$; 95% confidence; $r^2 > 0.995$). The detection limit found¹⁶ was $5.4 (\pm 0.1)$ ppm. The repeatability of the system was calculated as the RSD of replicate injections. For an intermediate concentration (100 ppm), the RSD obtained was 1.65% ($n = 15$, 95% confidence). The noise reduction

techniques applied to the electronics using both digital and analog filtering provided practically noise free signals.

CONCLUSIONS

The technology of LTCC, whose advantages as electronic substrate are well-known, has shown to be an excellent material to fabricate miniaturized analytical systems. These microanalyzers can include different unitary operations required by an analytical procedure. These include not only the microfluidics but also pretreatment steps, detection systems, signal conditioning, and data acquisition systems. Additionally, different kinds of micro-actuators and their control systems can be monolithically integrated, reducing the size of the complete system and therefore improving its functionality and enhancing its portability. In this work, we have presented two microanalyzer concepts that show the versatility and potentiality of the technology, one modular and the other monolithic, which integrates in a single substrate, with a footprint smaller than a credit card, the electronics, microfluidics, and the detection system. The results obtained have shown to be identical to those obtained by conventional measurement systems. The modular concept enables the possibility of combining the electronic module with other chemical modules based on potentiometric detection in an easy way. Meanwhile, constructing a monolithic device allows the production of portable and dedicated miniaturized total analysis systems integrating all the components needed using the same LTCC substrate.

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