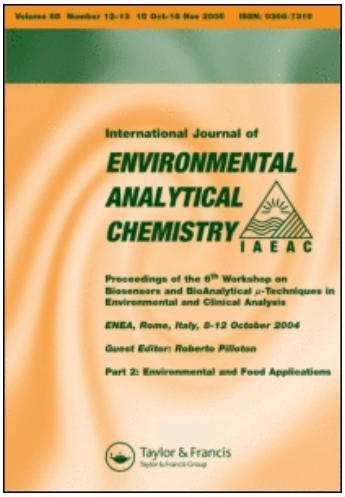

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Micro- and nanofluidic devices for environmental and biomedical applications

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MICRO- AND NANOFLUIDIC DEVICES FOR ENVIRONMENTAL AND BIOMEDICAL APPLICATIONS

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During the last decade, an increasing amount of pocket-size chemistry equipment based on the so-called "lab-on-a-chip" approach has become available. Besides the popular application in the analysis of biological macromolecules, such chips in combination with portable electronic equipment are applicable in, for example, "point-of-care" ion analysis of body fluids, forensics, identification of explosives, tracking of pollution in environmental or waste waters, monitoring nutrients in agricultural or horticultural water, controlling quality in food production or process control in chemical industry. This paper discusses the development of a number of demonstrator chips and microsystems with applications in some of these fields. In particular, an integrated microsystem for flow injection analysis of ammonia in surface waters, a hydrodynamic chromatography chip for the analysis of particles and polymer molecules and a chip for ion analysis in blood are discussed in detail. The last chip may also find applications in environmental analysis.

Keywords: Microfluidics; Nanofluidics; Silicon micromachining; Capillary ion analysis; Hydrodynamic chromatography; Flow injection analysis

INTRODUCTION

During the last decade, an increasing amount of pocket-size chemistry equipment based on the so-called "lab-on-a-chip" approach has become available. Well-known examples are the miniature DNA analyzers based on capillary electrophoresis, which speeded up the identification of the human genome. In a similar fashion they are now being used in other areas of the life sciences, like "proteomics" [1]. Besides these popular applications, such microfluidic chips, in combination with portable electronic equipment, are suitable for applications in many other field, including forensics [2], identification of explosives [3], tracking of pollution in environmental or waste waters [4], monitoring nutrients in agricultural or horticultural water, controlling quality in food production, general process control in chemical industry and point-of-care analysis of body fluids [5].

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This paper will discuss three different microfluidic systems developed in our institute, which can be considered representative of the current developments in the application fields mentioned above. We will start with the description of an integrated microsystem optimized for flow injection analysis of ammonia in surface waters. This system is based on the *in situ* mixing of chemicals to obtain a reagent system that gives a color change when ammonium ions are added, the change being measured optically.

The second demonstrator is a specialized chip for the analysis of particles and polymer molecules, based on a hydrodynamic principle. In this particular example, of interest to process industry but also for environmental analysis, the separation principle is based on the small dimensions that can be fabricated reliably with state-of-the-art silicon-based microtechnology.

The last demonstrator to be described is a chip that employs capillary electrophoresis for ion analysis. Conventional methods of ion analysis such as colorimetric or potentiometric titration, ion-selective electrodes and voltammetry, although well-developed for many different types of ions, have the drawback that they are generally only applicable for one specific ion, or a series of similar ions. Methods based on the separation of a mixture of ions, like ion chromatography, and subsequent non-specific detection of the ion fractions with optical or electrical techniques are therefore more widely applicable, but not easily miniaturized to a portable format, although first attempts in this direction are very promising, see the work of Murrihy and co-workers [6]. Capillary zone electrophoresis (CZE) on the other hand is a method that benefits from miniaturization, and in chip format has been under development since the mid-1990s. Here we present the first results from the use of CZE chips for alkali cation analysis.

MICRO AMMONIA FLOW INJECTION ANALYSIS SYSTEM

As an example of a micro total analysis system (μTAS), i.e., a system that incorporates all the necessary steps to perform a specified chemical analysis, including all sample treatments, transport, reactions and detection [7], the continuous measurement of the ammonia concentration in environmental water samples was chosen. Because photometric detection principles generally suffer less from the drawbacks of most (electro)chemical sensors (such as aging and fouling), the classical colorimetric method for ammonia determination based on Berthelot's reaction [8] was taken as a starting point for the development of a miniaturized flow injection analysis (FIA) system. Berthelot's reaction is highly selective for ammonia [9] and suitable for very low concentrations [10]. The actual ammonia concentration is related to the light absorption at the absorption maximum of indophenol blue at 590 nm. The reaction mechanism consists of two steps, a fast second-order reaction in which hypochlorite transforms all ammonia into monochloramine, followed by a slow reaction involving the addition of phenol to the intermediate monochloramine. The reaction is kept within a specified temperature range, to have sufficient conversion in a reasonable time-span while avoiding bubble formation (which occurs above 37°C) or decomposition of indophenol blue (above 45°C). The catalyst $Na_2Fe(CN)_5NO \cdot H_2O$ is added to reduce the reaction time. In practice all compounds needed for the Berthelot conversion of ammonia are pre-mixed in two reagents: a buffer solution with pH 11 containing hypochlorite, and a mixture of phenol and nitroprusside catalyst.

A reaction scheme in which several reagents have to be added sequentially in specified portions, as is the case here, can best be carried out in a flow injection format. Flow injection analysis, being a relatively simple and versatile method for the automation of wet chemical analysis, is based on the physical and chemical manipulation of a dispersed sample zone formed from the injection of the sample into a flowing carrier stream with detection downstream. In addition, FIA allows a fast throughput, consistent with demands in industrial process control or environmental monitoring; it is also easily miniaturized, thereby allowing the development of fast and portable systems. One particular fundamental advantage of implementation of channels with typical dimensions of 10 to 200 μm is that liquid flow in such channels is in the Aris–Taylor regime [11], where radial diffusion is fast compared with residence time, which results in reduced band broadening and detector signals that are symmetric (Gaussian) as a function of time, in contrast to detector signals in conventional FIA systems.

The layout of a system that implements Berthelot's reaction in a lab-on-a-chip version of a FIA system is shown in Fig. 1. The complete system, containing four peristaltic piezo-electrically driven micropumps [12] that are used to propel the liquid through the microchannel network, is integrated on a 10-cm diameter silicon plate. The analysis procedure is as follows (refer to Fig. 1): A sample plug is fed from a side branch into a main channel with a continuous carrier flow of demineralized water. While this sample plug travels through the system, the first reagent is added. To ensure complete reaction the sample and the reagent are mixed, and further down the main channel the second reagent is added and mixed. In the next 30 sec the mixture runs through a reactor channel controlled at 37°C (the governing system flow rate is $10\,\mu L\,min^{-1}$) before it passes a detection cell [13] in which light absorption at a wavelength of 590 nm is measured. From this absorption measurement, the original amount of ammonia is calculated.

For the given system layout several different fluidic components are required: a separate *pump* is needed for every fluid (carrier, sample, first and second reagent), a *mixer* after each addition of reagent, a *reaction chamber* to control the temperature and an *optical detection cell* to perform the actual measurement, and *fluidic channels* to connect all components. Several concepts for connecting microfluidic components are known in literature, e.g., vertical stacking of silicon chips [14] or hybrid integration of fluidic modules on a printed circuit board [15]. The system described here is based on

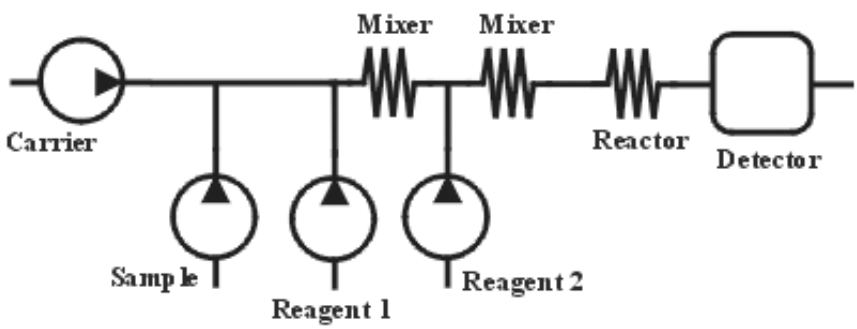

FIGURE 1 System layout of a miniaturized flow injection analysis system for the detection of ammonia. The system consists of four pumps, one for the sample to be analyzed, one for the carrier fluid, and one for each of the reagent mixtures. See text for detailed description of analysis procedure.

planar monolithic integration of components, which, similar to monolithic ultralarge-scale integration of microelectronic components, leads to the most advanced degree of miniaturization. The main advantage of this approach for fluidic circuits is that dead volumes and fluidic paths are reduced to the absolute minimum, which renders the system more accurate and faster. The most important drawback of monolithic integration is that failure of one component may render the complete system useless. To prevent this, either sufficient redundancy has to be contained in the monolithic system or the fabrication of the system has to be perfected to give high yields. The latter approach generally requires high market volumes that can compensate for the high costs of development.

To investigate the feasibility of the monolithic system, see Fig. 2, four samples of ammonia were fed to the system, two 10-mM samples of followed by two 20-mM samples. The readout of the detector (i.e., the current through the photodiode) is shown in Fig. 3. It can be seen that at the wavelength used a pure hypochlorite sample also gives some absorption of unknown origin (possibly due to an unwanted degradation product of the indophenol; this was not further investigated). Recent results using optimized chemistry did not show this hypochlorite peak [15]. Since hypochlorite is always added in excess of the ammonia present in the sample, and thus also in excess of the indophenol that will be formed, the extra absorbance should be taken as a baseline correction for the indophenol levels. If this is done, the peak levels for the two different ammonia concentrations indeed differ by a factor of 2.

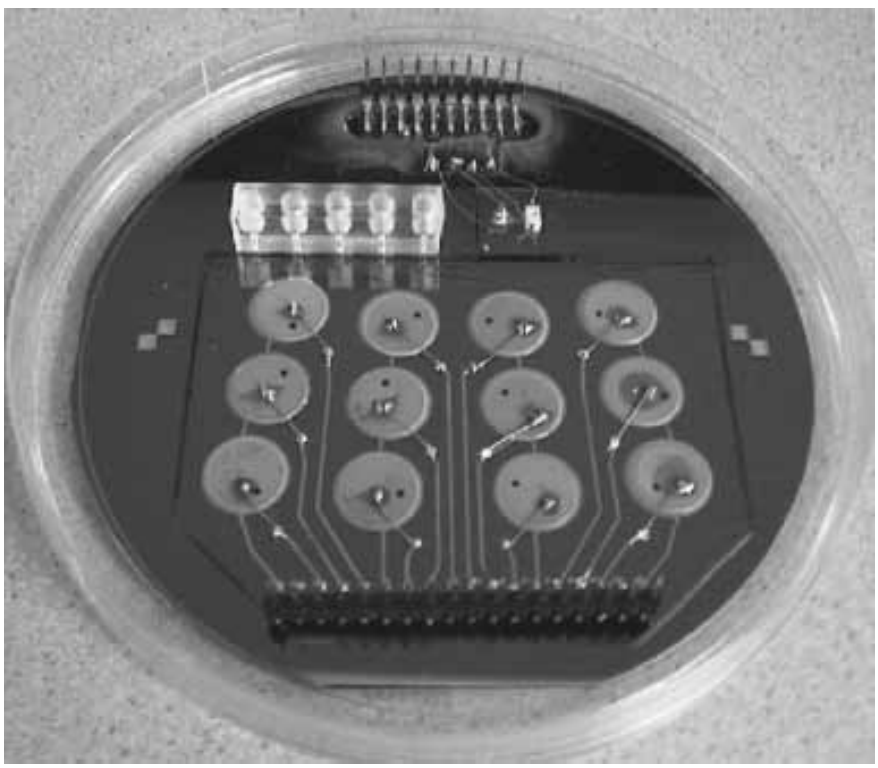

FIGURE 2 Photograph of a monolithic integrated flow injection analysis system with a diameter of 10 cm. The 12 gray circular elements are piezo-electric disks; three of such disks form one peristaltic micropump.

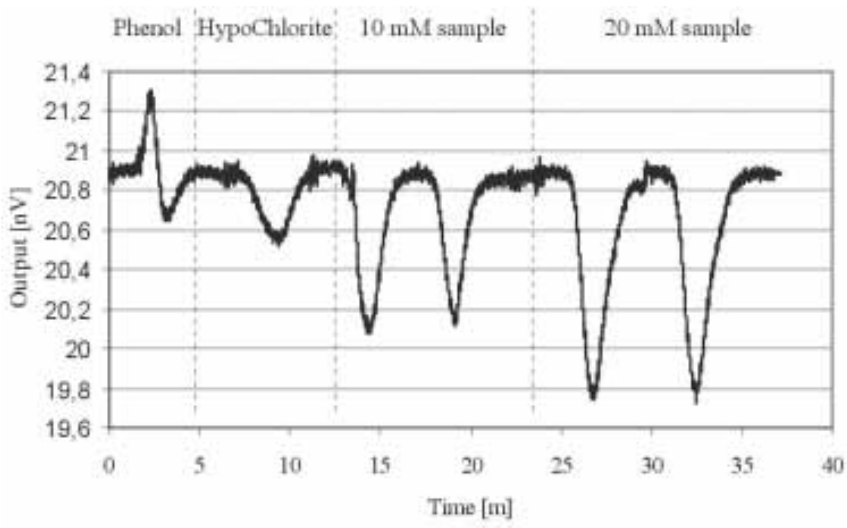

FIGURE 3 Response of the monolithic system to injected 10- and 20-mM ammonia samples, and to injected reagent plugs.

The noise level of the graph in Fig. 3 suggests a limit of detection of *ca.* 2 mM; the reproducibility of the measurements is also *ca.* 2 mM (obtained from a comparison of the duplex peaks in Fig. 3).

HYDRODYNAMIC CHROMATOGRAPHY ON A CHIP

Although silicon may generally not be the material of first choice for applications in the field of fluidics for (bio)chemistry and medicine, the extended toolbox of fabrication methods makes it a very attractive material for the demonstration of microfluidic principles for these fields. In particular, the monocrystalline nature of silicon substrates in combination with anisotropic etching processes (precise dry-etching techniques and sophisticated thin-film surface micromachining processes) can be used to create a large variety of innovative microstructures. An example of a device where very precise micromachining in silicon is essential for device functionality is the so-called hydrodynamic chromatography (HDC) chip.

In the device that we developed, essentially consisting of a 10 cm long, 1 mm wide and 1 μm high separation channel, small particles and large molecules are separated in a parabolic (pressure-driven) flow profile [16]. The method of hydrodynamic chromatography in such a micromachined channel is based on the principle that in narrow conduits (effective size $< 1\,\mu m$) with laminarly flowing liquid larger molecules or particles (sizes ranging from 0.002 to 0.2 of the conduit size) are transported faster than smaller ones, as they cannot fully access slow-flow regions near the conduit walls [16,17]. HDC is used for analytical separation in similar applications to traditional size-exclusion chromatography (SEC). Unlike the latter, HDC has no stationary phase and therefore is faster and more efficient. However, part of its performance is lost by imperfect instrumentation when performed classically in packed columns (in which the open spaces between the particles constitute flow channels

with dimensions of one or a few micrometers) [18] or open capillaries [16]. The former suffers from extra-column peak broadening, the latter from too low detection volumes.

An integrated on-chip HDC system (Fig. 4) should both preserve the efficiency and provide more material for detection by using a thin but wide separation channel. Other advantages are negligible solvent and sample consumption and easier temperature control, as a thin channel exchanges heat much more easily than robust columns.

The separation channel of the HDC chip in Fig. 4 was fabricated by etching a shallow (1-μm) depression in a silicon oxide layer on a silicon substrate, and subsequently bonding this substrate to a flat Pyrex plate. Furthermore, with a state-of-the-art deep reactive ion etching (RIE) method, before the bonding step, 10-μm slits were etched in the silicon substrate, which serve as an injector which ensures the introduction of a well-defined and narrow plug of analyte in the separation channel; full details of the injector design and the injection procedure can be found elsewhere [19]. Successful separation of a mixture of polystyrene particles of 26, 44 and 110–180 nm diameter was achieved in less than 3 min [20], see Fig. 5. The unexpectedly large

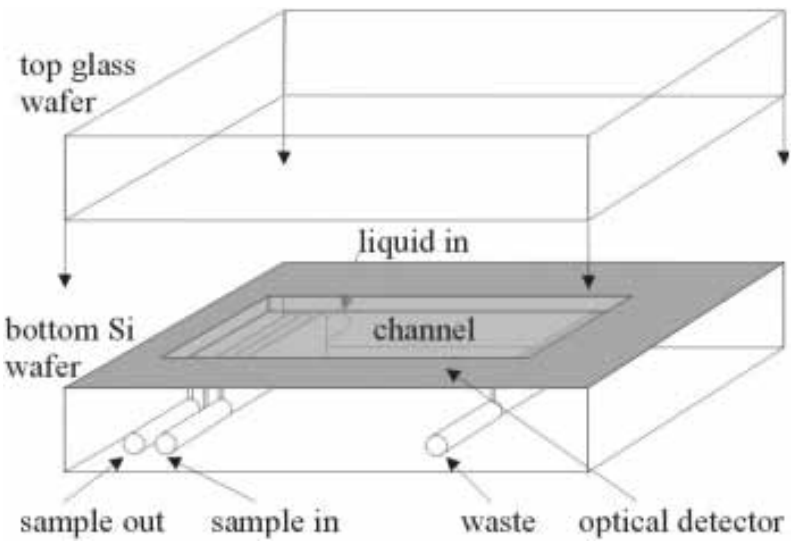

FIGURE 4 Design of a planar HDC chip – the injection slits are shown on the left. The optical detector in this case is a microscope focused on a point close to the end of the separation channel.

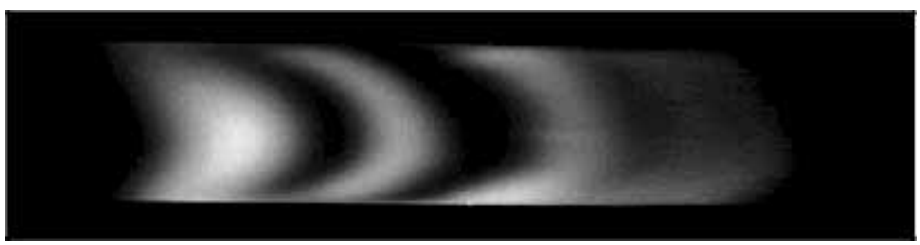

FIGURE 5 Separation of fluorescent polystyrene particles in a 1 mm wide and 1 μm high separation channel on an HDC chip. Fluorescent zones from left to right: fluorescently labeled anionic dextran (10 kDa) as a marker, 26-nm, 44-nm, and 110 + 180-nm fluorescent polystyrene particles, all in a concentration of 0.25–0.5 mg/mL in 10 mM phosphate buffer (pH 7.0); working pressure 4 bar, hydraulic pump. Flow is from left to right.

curvature of the zones in the figure is mainly caused by a non-uniform channel height: Although very precise etching techniques ensured that the depth variation of the depression was less than 0.5% over the width of the channel, thermal expansion differences between the Pyrex and silicon substrates during processing resulted in some minor bending of the substrate sandwich, which gives rise to the channel height variation responsible for the curvature of the separated zones.

ON-CHIP CAPILLARY ION ANALYSIS WITH INTEGRATED CONDUCTIVITY DETECTION

A very convenient method for ion separation, which actually benefits from miniaturization and has the additional advantage that it can be electronically controlled and therefore automated, is the already mentioned capillary electrophoresis (CE) technique. Basically a CE instrument consists of an injector, a separation channel and a non-selective detector. One of the benefits of performing CE on a chip is that these components can be integrated, so that dead volumes are reduced and the analysis will be improved, both in quality and in speed.

Separation of cation on a number of general purpose borofloat glass chips (Micronit Microfluidics B.V., a description of the fabrication of these chips was published elsewhere [5]) with typical micromachined geometries for on-chip capillary electrophoresis mixtures was performed. The chips had a metal electrode pattern, serving as a conductivity detector, deposited at the end of a 82 mm long separation channel. Figure 6 shows the chip layout. At the entrance side of this separation channel, either a "cross" or a "double-T" injector connected to at least three supply channels was present. This fluidic structure was grafted in a borofloat glass plate by etching in hydrofluoric acid. Round and square through-holes, serving as inlets or outlets for liquids or as access holes for electrical contacts, were powder-blasted in the same plate. Electrode patterns were deposited on a second glass plate and this plate was bonded to the first by a thermal process. Finally, the bonded pair of glass plates was diced into individual chips.

The chip was inserted in a specially designed home-made holder, which allows inspection of the liquid in the chip by optical microscopy and provides electrical connection

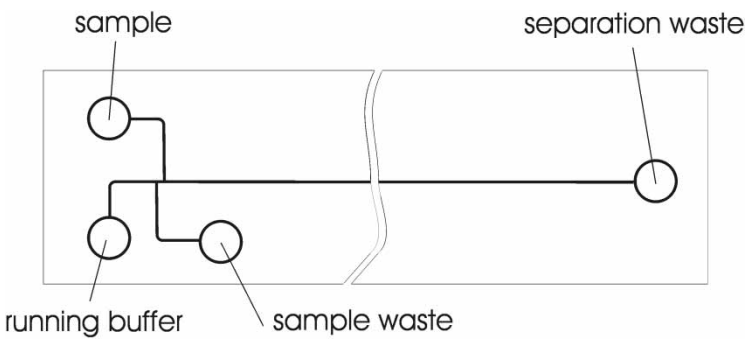

FIGURE 6 Schematic drawing of glass microchip with double-T injector. The chip used in this study had metal electrodes (not shown in the figure) used for conductivity detection at the end of the separation channel where the outlet hole is present. The total size of the chip is 90 mm × 18 mm × 2.2 mm.

from the chip to control and measurement electronics. In the experiments, two different high-voltage supplies were used, one with a maximum output of ±1 kV (Ibis Technologies B.V., The Netherlands) and one with a maximum output of +3 kV (Micronit Microfluidics B.V., The Netherlands). Both voltage supplies were controlled with dedicated software. The conductivity detector, operating with an AC voltage at 25 kHz, was connected via a home-made high-field decoupled electronic amplifier circuit to an oscilloscope (Agilent Technologies). Data analysis was performed with a demo-version of a commercially available software package (DAx, Van Mierlo Software Consultancy, The Netherlands).

Model samples containing K^+, Na^+ and Li^+ nitrates or chlorides dissolved in water or in a buffer mixture of histidine and 2-(*N*-morpholino)ethanesulfonic acid (MES), each in 20 mM concentration, were injected and separated by electrophoresis on the chips. The graph in Fig. 7 shows a typical electropherogram, for a sample 10 mM in the previously mentioned cations, using the buffer mixture described above and an electric field for separation of 120 V/cm. We want to stress that the data shown are the direct output of the detector, with no other data treatment than a gain and offset adjustment. They show a good signal-to-noise ratio and complete baseline separation. The total time of the measurement with the electric field used was *ca.* 4 min. More recent work has demonstrated similar separations within less than 10 sec, for shorter chips (*ca.* 20 mm) and higher electric fields [5].

Reproducibility in retention times was found to be within 16% from chip to chip for seven chips from two wafers of the same batch. Since this variation is unacceptable for routine use of the method, several procedures were investigated to reduce the variation, which was thought to be due to run-to-run variations in electro-osmotic flow caused by sample impurities. It was found that reproducibility could be improved to within 2% variation after a sequence of washing and conditioning steps, including a rinse with 0.1M sodium hydroxide solution, a procedure that may easily be automated. Similar procedures are routinely used in conventional electrophoresis on fused-silica capillaries [21]. Reproducibility of retention times is important for the implementation of

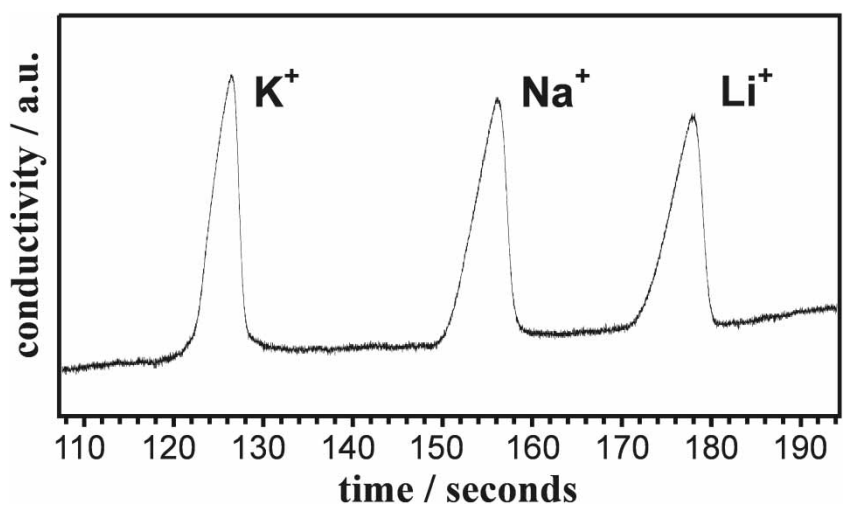

FIGURE 7 Typical CE separation result obtained on a chip with integrated conductivity detector (see text for details). In this particular case the K^+ peak appeared 126 sec after sample injection.

automated analyte identification, although a calibration method using an internal standard might be preferred for the most accurate performance.

Peak height variation from run to run and chip to chip was *ca.* 10%, but it has to be mentioned here that the injection procedure, which is believed to be the main cause of this variation and which in our work was found to be very sensitive to changes in electro-osmotic flow irregularities, was not optimized in these experiments. Peak area is related to the concentration of the analyte, so for accurate quantitative measurements this parameter should be reproducible. Results published by others show that conventional capillary electrophoresis in combination with conductivity detection, using special sample treatments and internal standards, can determine even low-ppb levels of ions [22]. This indicates that there is plenty of room for improvement for capillary ion analysis on a chip, and we are currently trying to improve the glass chips with conductivity detection to achieve similar detection limits.

FUTURE OUTLOOK: NANOFLUIDICS AND SINGLE CELL ANALYSIS

The introduction of the lab-on-a-chip may offer opportunities to advance the medical field, because of the ever shrinking size of the resulting devices, allowing minimally invasive methods and enabling the development of versatile portable equipment for ''point-of-care'' monitoring and treatment of patients. This trend may eventually lead to remote healthcare monitoring systems that allow medical specialists to track the patient's status on-line in his home environment. Additionally, handy equipment will give patients the choice to be more directly involved in monitoring their own health, thereby increasing the chances of improving their quality of life and reducing healthcare expenses.

We are currently conducting a research programme in which one particular problem in the medical field is tackled, i.e., the monitoring of a lithium-containing drug in the blood of patients with mood disorders. Preliminary results of experiments on whole blood, which were carried out on electrophoresis chips similar to those described in the previous section, but with a shorter separation channel (20 mm), have been published elsewhere [5].

Dimensions of fluidic channels continue to be scaled down, even to dimensions below 1 μm, entering the area of ''nanofluidics''. This is the domain where surface effects start to dominate liquid behavior, while ultimately a liquid can no longer be considered as a continuum but as an ensemble of individual molecules. Bulk properties of the liquid (such as viscosity and dielectric constant) and dissolved molecules and ions are no longer valid, and new phenomena that could be used for separating and detecting species appear. The field of nanofluidics may become important through this promise of the discovery of new phenomena rather than from the decrease in system size and weight, and the reduction in consumption of resources.

New microfabrication techniques will be needed to explore this field of nanofluidic phenomena, and many examples have already been published in recent literature. In our institute we have tried to enter the nano-area by the optimization of conventional fabrication techniques such as surface micromachining [23] and deep reactive ion etching, combined with conformal thin film deposition techniques [24]. Using these techniques, it has been possible to make channels with dimensions below 100 nm and to realize a pneumatically actuated, capillary pressure driven micropump capable of

delivering picoliter amounts of liquid in a controlled way [25], and to create flow channels with integrated micropipettes that can trap and hold beads to which DNA strands are attached [26]. Such technological achievements deliver the tools for single cell analysis, and perhaps also for "single cell therapy monitoring", an as yet unexplored field in which the changes in the content of a single (living) cell are followed after the introduction of a tiny amount of a pharmaceutical substance.

CONCLUSION

This paper has discussed a number of demonstrators with applications in the environmental, chemical engineering or biomedical field, fabricated with the aid of silicon and glass micromachining technology. Although silicon may not be the final material of choice for a commercial product, it certainly has its value for the proof-of-concept stage in a development process. In particular, for future scaling down of fluidic structures, silicon microtechnology at the moment is much more advanced than any technology to machine other materials, allowing channel structures with inner dimensions of 100 nm and less.

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