A PREFILLED, READY-TO-USE, ELECTROPHORESIS-BASED LAB-ON-A-CHIP DEVICE FOR MONITORING IONS IN BLOOD AND URINE
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ABSTRACT
We present the Medimate Multireader®, the first point-of-care Lab-on-a-Chip device based on Capillary Electrophoresis. We show that it is possible to analyze lithium in whole blood and sodium in urine, using a commercially viable Multireader that is suitable for self testing. In addition, we demonstrate the ability to detect creatinine using the same platform.

KEYWORDS: Lab-on-a-Chip, Point-of-Care, Capillary Electrophoresis, Conductivity Detection, In Vitro Diagnostics, lithium, sodium, creatinine

INTRODUCTION
At present, most diagnostics in the clinical laboratory are carried out on large clinical devices, only to be used by trained personnel. It was expected that microfluidics would change the laboratory setting, because of the miniaturization possibilities of the lab-on-a-chips. Until now the iStat has shown to be viable as a commercial product, but operation is still limited to professionals. Research at the University of Twente, including commercialization, has now resulted in the first Microchip Capillary Electrophoresis (MCE) platform suitable for analysis of electrolytes. Most importantly, it can be used by lay persons in their home environment.

Research at the Mesa Institute for Nanotechnology, performed from 2000 to 2005, proved the possibility to measure lithium in a whole blood sample.1,2,3 Between 2005 and 2010, further development by Medimate resulted in a commercially viable in vitro diagnostic device for lithium measurements that is suitable for self testing, the Medimate Multireader®. The system consists of a disposable µCE chip and the Multireader, see Figure 1.

Figure 1. Electrolyte measurement: a) shipped blister including the prefilled µCE chip, assembled in a plastic disposable for ease of handling and sample application b) application of a single blood droplet from finger stick c) disposable inserted into the Multireader, including high voltage power supply and conductivity detection unit. The measurement is completed typically within 1 to 5 minutes.

During the commercialization phase, many challenges had to be overcome. For instance, lithium, the first analyte that was targeted, is one of the most difficult electrolytes to be analyzed. Lithium is used as a drug for patients with Manic Depressive Illness, also known as Bipolar Disorder. It is therapeutic in the range of 0.4 – 1.2 mmol/l. The technological challenge with lithium is the low concentration range, compared to other electrolytes, like potassium, calcium, magnesium and particularly sodium. The detection limit of lithium is determined to be 0.2 mmol/l with an accuracy of 0.1 mmol/l or 10%. This detection limit is 700 fold lower than the normal sodium concentration. To be able to measure the lithium accurately, a very high resolution and a very high signal to noise ratio had to be realized. This was achieved by many chemical, electrical and electrochemical innovations. Amongst others, it was chosen to use a novel single entrance solution, combined with a furthermore closed embodiment to perform the MCE process.

In addition, the shelf life was addressed. To prevent leaking of the closed embodiment, which is designed as a commercially viable prefilled disposable with a sufficient shelf life, the pressure gradients that are caused by expansion/shrinkage of the fluid due to temperature changes had to be solved. For this specific problem Medimate has incorporated a gas filled expansion chamber inside the µCE chip. Here we describe the progress of the Medimate Multireader® as an in vitro diagnostic device to test lithium, sodium and creatinine.
THEORY
To perform a measurement the sample is applied at the entrance of the channel system. The electrolytes from the sample are injected in the background electrolyte by moving boundary electrophoresis after applying an electrical voltage across the sample and channel system. In the double-T an injection plug is formed. Changing the high voltage potential results in the injection of this plug into the separation channel by capillary zone electrophoresis. At the end of the channel the contact conductivity detection electrodes measure the change in conductivity. The time at which the different species pass the conductivity electrode is an indication for their identity and the change in conductivity is a measure for their concentration.

EXPERIMENTAL
In Figure 2 a picture and schematic representation of the µCE chip are shown. To finalize the product the chip is pre-filled with the background electrolyte and assembled in the housing prior to blistering. Combined with the Multireader different serum, whole blood and urine samples can be measured.

RESULTS AND DISCUSSION
At present the Medimate Multireader® has been validated for lithium tests in serum and whole blood and received a CE 0344 certificate for self testing. This validation is founded on the results of serum measurements and whole blood measurements, as are shown in Figure 3. The results are within the medical relevance region. Currently market tests are being performed.

Recent tests have also proven the possibility to measure sodium in urine. Figure 4 shows the results of a comparison of internal tests with the Flame Photometer. At this moment validation tests are performed at the Medisch Spectrum Twente Hospital in Enschede, the Netherlands. A specific challenge with the measurement of sodium in urine is the high dynamic range of species within the sample. To handle different stacking effects an internal standard is used, which is added to the urine sample prior to measurement.
Preliminary tests have demonstrated the possibility to detect creatinine at 1 mmol/l in serum. Future research is focused on improvements on the detection limit of creatinine and the reproducibility of the measurements.

Figure 4. Left: Comparison of sodium in urine measurements using the Medimate Multireader® and the flame photometer IL943. Right: Indicative creatinine measurement. The serum sample was spiked with 1 mM creatinine, which can be observed in the electropherogram.

CONCLUSION
The Medimate Multireader® with the µCE is a capillary electrophoresis platform capable of measuring electrolytes in a commercially viable manner. Validation results show the possibility to detect lithium in serum and whole blood in the therapeutic and toxic range of the medication. Furthermore, first results are shown for the measurement of sodium in urine and the possibility of detection of creatinine using the same platform.

FUTURE DEVELOPMENTS
Medimate will extend the lithium analysis tests in the market and start rolling out the system in Europe. Furthermore the CE platform will be adapted for the detection of more species, starting with sodium and creatinine. Medimate will also continue the development of a smaller design of the Multireader, as is shown in figure 5.

Figure 5: Smaller model of the Medimate Multireader®, expected 2011.

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