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Measuring human blood serum with chip based fast liquid differential scanning calorimetry

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ABSTRACT

This paper describes how two different chip-based liquid sensors have been used for experimental Fast DSC measurements on human serum. The paper starts with describing the first chip-based liquid sensor, based on the XI-400 chip. Repeatability (measurements with the same chip) and reproducibility (measurements with different chips) measurements are described when a linear or a second-degree polynomial baseline is subtracted from the raw data. Human serum with deviating Immunoglobulin levels was measured. The second half of the paper describes the second generation chip based-liquid sensor, based on the XI-468B chip. The new more sensitive chip is described and used for measurements with ten serum samples from healthy individuals and five serum samples from patients diagnosed with CCRCC kidney cancer. Differences are found between the serum from healthy individuals and the serum from the CCRCC kidney cancer patients.

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1. Introduction

With standard Differential Scanning Calorimetry (DSC) it is possible to detect several kinds of cancers and diseases by measuring blood plasma [1–6]. In such measurements with DSC is blood plasma heated up and the energy required for melting the proteins (denaturation) in the blood plasma is recorded as a function of temperature. In the case that both the sample and reference liquid are the same, the result of the DSC measurement would be a flat horizontal line. When as sample blood plasma and as reference a matched liquid to the blood plasma is used then the measurement result would be a curve build up from the three main proteins in blood plasma. The three main proteins in blood plasma are Albumin, Globulins and Fibrinogen. In DSC these proteins can be separated in the DSC thermogram because each protein has its own specific melting temperature. The amount of protein can be determined by looking at the enthalpy of the peak (area under the peak), the higher the enthalpy the higher the protein concentration.

It is possible to detect cancer by comparing DSC thermograms of blood plasma from healthy individuals with DSC thermograms of blood plasma from cancer patients [1–6]. The amount of protein in blood plasma however varies from person to person, and thus also the DSC thermogram varies from person to person [1]. By creating a DSC thermogram which is built up from multiple DSC measurements of blood plasma from healthy individuals which shows the deviation between the different curves, one can directly compare a newly measured curve with the set of healthy curves [1–3].

To our best knowledge DSC with standard temperature scan rates was used in all the publications related to DSC and cancer detection to this date. Standard DSC works with relatively slow temperature scan rates of about 1 °C/min. Using a temperature scan rate of 1 °C/min and a temperature range of 30 °C–100 °C means that a single measurement takes 70 min. In previous work we presented a chip based Fast Liquid DSC (FLDSC) sensor which can measure protein denaturation in bovine serum at a temperature scan rate of 400 °C/s. Using a temperature scan rate of 400 °C/s means that the time necessary for a single measurement can be reduced from 70 min with standard DSC to 0.2 s with chip based FLDSC. This may lead to a lower costs of diagnosis.

This paper presents measurements with human serum performed with FLDSC sensors based on the XI-400 chip and the XI-468B chip. The XI-468B chip was especially designed for the FLDSC sensor and has an improved sensitivity. and the FLDSC sensor based on the XI-468B chip is used for measurements with serum

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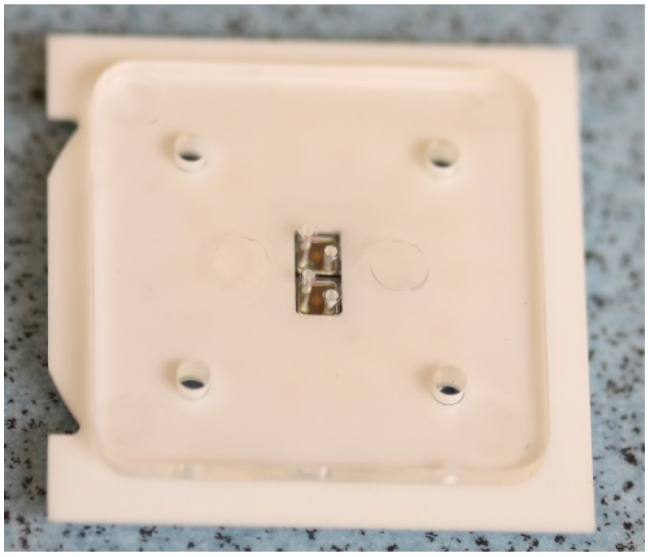

Fig. 1. FLDSC chip with ceramic baseplate (24 × 24 mm) and plastic cover (20 × 20 mm).

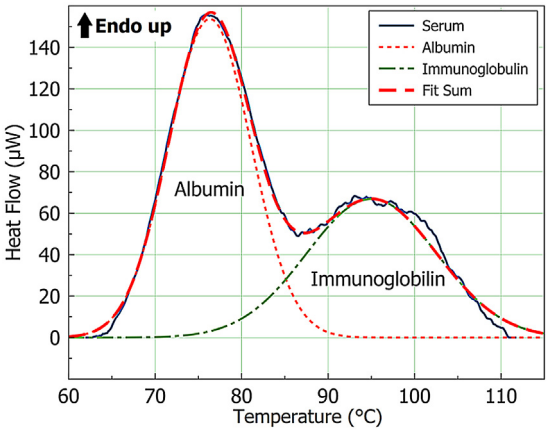

Fig. 3. Curve fitting of an FLDSC measurement of human serum at 400 °C/s with two Gaussian curves. The first large peak mainly originates from the Albumin and the second smaller peak mainly originates from the Immunoglobulin in the human serum.

from healthy individuals and serum from kidney cancer patients. The results of these measurements show that differences exists between the FLDSC thermograms of serum from healthy individuals and kidney cancer patients.

2. Device description

We started the measurements of human serum with the in 2013 introduced FLDSC sensor based on the XI-400 chip, see Fig. 1. The FLDSC sensor based on the XI-400 is extensively described in [7] and is a modification of the standard sensor for the Flash DSC1 from Mettler Toledo [8]. The standard sensor for the Flash DSC1 is not able to measure liquids because the liquid sample would evaporate during a measurement, due to its open structure. To prevent evaporation of the liquid sample a plastic cover is glued on top of the standard sensor in such a way that two liquid chambers are created. In the plastic cover are 2 cone-shaped holes for each liquid chamber which are used as in- and out-lets. The evaporation problem has been solved because the cover covers the part of the liquid which is heated up by the heater in the membrane. The heated liquid is surrounded by cool liquid, and only cool liquid can evaporate in the in/outlet holes. The thermal effect of that does not reach the sample liquid above the heater. The sample liquid, which is entirely surrounded by cover and cool liquid, can even be heated up to above the boiling point. Fig. 2 shows a cross section of the FLDSC sensor.

3. Materials and methods

To prevent aggregation of the serum during the measurements 3-(1-pyridinio)-1-propanesulfonate (NDSB) (SIGMA lot #BCBG9978V) was added to the serum to a final concentration of 1M NDSB [9]. Human serum which was measured with the FLDSC sensor based on the XI-400 chip was concentrated with a Speedvac until 50% of the liquid was evaporated. Next the concentrated serum was diluted with a 3M NDSB solution to a final concentration of 1M NDSB. All specimens were handled in a coded fashion as prescribed by the Dutch national guidelines for secondary use of specimens ("code goed gebruik: http://www.federa.org/code-goed-gebruik-van-lichaamsmateriaal-2011")

The human serum which was measured with the FLDSC sensor based on the XI-468B chip was diluted with a 3M NDSB solution to a final concentration of 1M NDSB. As reference for all the measurements water was used, mixed with NDSB to a 1M final concentration. Ethical approval was obtained for this research.

4. Results and discussion

Blood plasma contains thousands of different proteins, but only few of them are visible in the DSC thermogram. Garbett et al. measured with DSC the 16 most abundant proteins in human blood plasma in the concentration they are normally found in blood plasma [1,2]. In the measured DSC thermogram two large endothermic peaks, which mainly originate from the albumin and immunoglobulin proteins and a smaller endothermic peak which originates from the protein fibrinogen are seen. We started our research by measuring ethylenediaminetetraacetic acid (EDTA) plasma, heparin plasma and serum to determine which kind of plasma or serum gives the best result with FLDSC. Heparin plasma

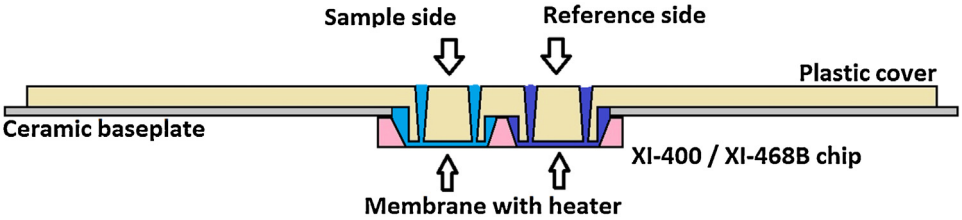

Fig. 2. FLDSC sensor cross-section (not to scale). The FLDSC sensor consists of the ceramic baseplate with either the XI-400 or the XI-468B chip, and with on top a plastic cover. In light blue is shown the sample side liquid chamber and in purple the reference side liquid chamber. Only the liquid just on top of the heater is heated up, while the rest of the liquid remains at room temperature (for interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

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