Thermochimica Acta 603 (2015) 172–183

Contents lists available at ScienceDirect

Thermochimica Acta

journal homepage: www.elsevier.com/locate/tca

Toward high-throughput chip calorimetry by use of segmented-flow technology

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ARTICLE INFO

Article history:
Available online 24 October 2014

Keywords:
Chip calorimetry
Segmented-flow technology
Biofouling
Hair follicles
Spheroids

ABSTRACT

The adaptation of segmented-flow technology to flow-through calorimetry was demonstrated by different kinds of newly designed chip calorimeters useful for liquids and suspensions as well as for solid samples. In segmented-flow technology, sample material is suspended in aqueous segments of nano- or microliter volume and transported by a water-immiscible carrier liquid. The analysis of the signal dynamics given by segmented samples in flow led to optimal settings of flow rate and sample volume for maximal throughput. For 12 μL sample segments, a cycle time of 4 min could be achieved. The protection of the measuring chamber of the calorimeters against biofouling caused by the water-immiscible carrier liquid was verified for segmented bacterial samples. The unique possibility to measure solid and aggregated samples in flow-through was demonstrated by the investigation of human hair follicles and fibroblast spheroids.

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1. Introduction

Calorimetry enables the quantification of the metabolic activity of living matter with high signal-to-noise ratio and high resolution. To perform measurements in real-time and non-invasively is a significant advantage. In comparison to the very specific information achievable by molecular biological methods like the determination of the gene expression level of the genes of the interesting enzymes, the information on the studied metabolism based on calorimetric measurements represent a general summary of the metabolic activity of the cell. The non-specificity of calorimetric signals can be advantageous since it is more likely to discover unknown phenomena [1]. Unfortunately, calorimetry suffers from high sample need and low throughput. Miniaturization in form of chip calorimeters brought essential progress. To achieve high sample throughput, two different methods were applied. The use of chip arrays allows a high degree of parallelization. However, such devices [2–4] are quite expensive, difficult to clean and require sophisticated sampling facilities. The construction of flow-through systems [5–10] is simpler but measurements have to be performed serially which reduces the sample throughput. Furthermore, the dimensions of microfluidic channels lead to laminar flow at low Reynolds numbers <30 [11]. The parabolic flow profile provokes sample dispersion in the direction of flow [12]. Due to the high surface-to-volume ratio, contamination of the microfluidic channels like biofouling plays a more important role [13,14] with the consequence of an increased effort for cleaning operations.

These bottlenecks of state-of-the-art flow-through chip calorimeters can be overcome by the adaptation of the segmented-flow technology (SFT). Primarily, the SFT was developed to handle samples of pico- to nanoliters in microfluidic systems [15]. Samples suspended in aqueous droplets are transported through the fluidic channels by a carrier liquid that is immiscible with water. Due to the interface tension, plug flow characteristic is achieved. Usually, the carrier liquid completely wets the channel walls. As an effect of the viscous entrainment of the carrier liquid and the capillary pressure inside the droplets, a thin lubricant film

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http://dx.doi.org/10.1016/j.tca.2014.10.021
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is present between the droplets and the walls. It can be assumed that the thin film protects against contamination of the walls by the sample (e.g., biofouling, see Section 3.2) and cross-talking between the samples [16]. Although the thermal conductivity of the used carrier liquid, perfluoromethyldecaline, is ten times higher than that of water, the thermal behavior of the chip calorimeter remains unaffected because the film thickness ranges only between 1% and 5% of the channel's half height [17].

The design of calorimeter components including measuring chambers, heat exchangers, injection ports, and transport channels is a challenge if they should meet the requirements for the SFT, which mainly means that all components of the fluidics must be highly hydrophobic to prevent attachment of the aqueous sample to the channel walls. Moreover, only moderate changes in the cross-sections of the fluid pathway can be tolerated to avoid fragmentation of the droplets [15,18,19].

The adaptation of SFT should constitute a major step toward improving the performance of chip calorimetry. Expected benefits are (i) an increased sample frequency due to plug flow characteristics [12], (ii) the suppression of biofouling in microbiological applications which reduces the cleaning effort, and (iii) the possibility to transport aggregated and solid samples through the calorimeter.

In the presented work, we demonstrate how SFT can be adapted to chip calorimetry. We summarize essential features of two different types of segmented-flow calorimeters which we developed. One of them was optimized for measurements of liquid samples and suspensions (SFL calorimeter) and the other one for operations with solid and aggregated samples (SFS calorimeter). Details of the SFS calorimeter and results of two applications have already been given in a recently published paper [20]. Here, a new feature of this calorimeter is described which enables the automatic treatment of aggregated samples by active pharmaceutical ingredients (API) immediately before heat detection.

Three different classes of experiments were performed. Device characterization experiments (i) provided information about the dynamics of the signal generation in continuous segmented flow. The signal dynamics was analyzed to obtain optimal operation parameter settings for a maximum sample throughput. Furthermore, specific experiments were performed to verify the suppression of biofouling due to a thin film of the sample transporting carrier liquid. The proper work of the SFL calorimeter was demonstrated by two continuous segmented-flow application experiments (ii), the growth monitoring of *Pseudomonas putida* and *Saccharomyces cerevisiae*. Two new application experiments using the SFS calorimeter (iii) emphasize the considerably extended application range of flow-through chip calorimeters working with SFT. To our best knowledge, calorimetric measurements on human hair follicles (HF) and cellular spheroids were performed in flow-through for the first time.

2. Materials and methods

2.1. Segmented-flow chip calorimeters

Based on a prototype chip calorimeter [5,6,21], two new calorimetric devices useful for sample management by means of segmented-flow technology were developed. One of them is optimized for measurements of liquid samples and suspensions (SFL calorimeter) and the other one for operations with solid and aggregated samples (SFS calorimeter). The prototype chip calorimeter has been successfully applied for investigations of biological and microbiological materials for several years. The heat power detector used is a chip module which consists of a thermopile chip with four independently readable thermopiles (TP1–TP4) and which is enclosed in a small high precision thermostat.

Essential innovations of the new devices are a monolithic, Teflon made flow channel, a measuring chamber with an encased Teflon flow channel, and, in case of the SFL calorimeter, a newly developed highly efficient heat exchanger. The flow channel is made of a Teflon tube with an inner diameter of 1.7 mm and a wall thickness of 80 μm (Polytetra, Mönchengladbach, Germany). The material of the tube ensures stable hydrophobic conditions over a long experiment duration which is a precondition for operations in the segmented-flow mode. Furthermore, the small tube wall thickness and the high oxygen permeability of Teflon (diffusion coefficient $D = 3.6 \times 10^{-17}\,m^2\,s^{-1}\,Pa^{-1}$) supports the maintenance of aerobic metabolism which is advantageous in case of biological applications. In the thermopile area, the flow channel is encased by a poly(methyl methacrylate) (PMMA) mold forming the measuring chamber (Fig. 1A and B). Appropriate dimensions of the mold with respect to an optimal thermal contact between Teflon tube and thermopile chip were found by numerical simulations [20]. The size of a volume segment in front of a thermopile is 12 μL. By thermally shrinking of selected parts of the Teflon tube, the design of a monolithic flow channel is possible, comprising of measuring chamber, heat exchanger and sample transport channel. The

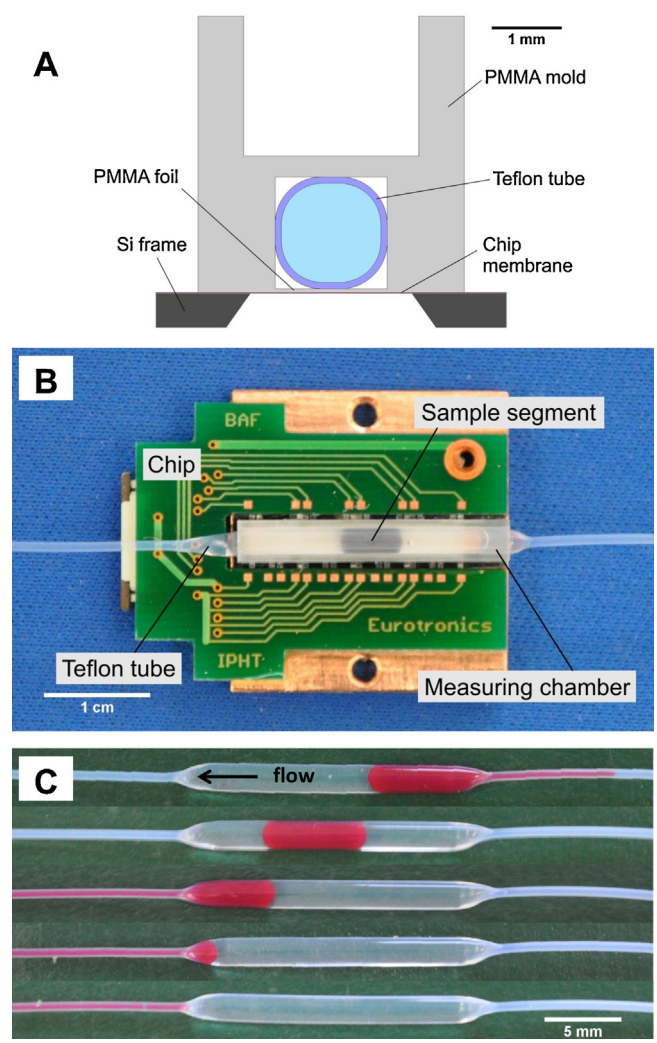

Fig. 1. Flow channel attached to the heat power detector. (A) Cross section of the thermopile chip and the measuring chamber with encased Teflon flow channel. (B) Photograph of the thermopile chip module with measuring chamber atop. (C) Teflon flow channel outside of the measuring chamber with different positions of a passing sample segment (porcine blood).

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