Microelectronic Engineering 158 (2016) 107–117

Contents lists available at ScienceDirect

Microelectronic Engineering

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

Review article

Microcalorimeter: Design considerations, materials and examples

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ARTICLE INFO

Article history:
Received 23 October 2015
Received in revised form 22 March 2016
Accepted 23 March 2016
Available online 9 April 2016

Keywords:
Calorimeter
Microcalorimeter
Thermal sensor
Enthalpy array
Biosensor

ABSTRACT

This review paper first discusses the design considerations that are being applied in the development of a highly sensitive, miniaturised and high throughput assay microcalorimeter. Major factors include reaction chamber, thermal insulation, fluid handling, mixing techniques and temperature sensing. Miniaturisation is the key to handle smaller sample volume within the nanoliter to picoliter regions, which is made possible by advancement in materials and fabrication technologies. Materials under review include silicon, silicon nitride, parylene-C, PMMA, PDMS, SU-8 and polyimide. The materials are compared in terms of size, cost, biocompatibility, chemical resistance and thermal properties. Finally, we compile the list of works across the globe and their contributions that demonstrated microcalorimeter prototypes with high thermal insulation, precise microfluidic handling capabilities, rapid mixing of fluids and high throughputs. This review offers broad perspectives and insights for those working on microcalorimeter, enthalpy arrays, microfluidic biosensor, thermal sensor and micromixer.

Contents

1. Introduction

Calorimetry is an analytical science for determining the changes in heat of a system with its surroundings. Calorimeter devices measure the quantity of heat transferred to or from an object. It is an essential tool to characterize the thermodynamics of chemical reactions of a sample. A microcalorimeter is a miniaturised calorimeter, which makes possible the detection of the temperature changes of a small sample volume in the order of nanoliters (nL) down to picoliters (pL) regions. In order to take advantage of this capability, researchers normally employ an array of microcalorimeters, which consists of a number of parallel microcalorimeters. This system promises benefits such as high-throughput measurement, portability and low power consumption [1,2].

One potential usage will be in the pharmaceutical industry, where an array of microcalorimeters can be used in the early stages of the small molecule drug discovery process, also known as the fragment-based drug discovery (FBDD). The detailed thermodynamic characterization is needed to screen drug candidates [2]. A microcalorimeter can

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http://dx.doi.org/10.1016/j.mee.2016.03.050
0167-9317/

determine whether the process heat from the binding interactions between the small molecule (drug candidate) and the target proteins (disease) corresponds with assumed metabolic pathways. Detection of unknown reactions is also possible. Such system is sometimes referred to as an enthalpy array. It has potential to test tens of thousands of chemical compounds, while significantly shorten the screening time. Another advantage is in term of cost. Biological samples could be very expensive and are often not available or reproducible in large quantities [1,2]. One prototype of an enthalpy array is presented in section four of this review.

Calorimetric measurement can be categorised in term of temperature change (adiabatic or isoperibol), power compensation (isothermal) and heat conduction. The temperature-change microcalorimeter is the most direct way of measuring heat. The temperature sensor records the heat released (or absorbed) by the chemical reaction of the samples in the reaction chamber. The recorded calorimetric signal is the temperature of the reaction chamber as a function of time. With an appropriate electrical or chemical calibration, the energy equivalent to the reaction chamber can be determined. The measured temperature change is converted to a heat change by multiplying the energy equivalent of the microcalorimeter (in cal/K) with the measured temperature change (in K) [3].

In a power compensation microcalorimeter, a heater controller keeps the temperature of the reaction chamber constant at all times. When a chemical reaction occurs in the microcalorimeter, the heater controller senses the temperature difference and applies power to regulate the chamber back to the initial temperature. The recorded power change (μcal/s) is stored as a function of time. The heat change is calculated by integrating the power change of the heater over the time of measurement [3].

In a heat conduction microcalorimeter, a controlled heat sink keeps the reaction chamber at a constant temperature. The heat sink is coupled to the heat flow sensors. When the temperature changes due to a chemical reaction, the heat flow sensors will generate a voltage that is proportional to the temperature change [3].

This review paper focusses on the evolution and state-of-the-art designs, materials and technology of miniaturised and high-throughput microcalorimeters. The design considerations are discussed in section two. Some challenges and concerns are addressed. Several mixing and merging methods are also reviewed. The third section highlights the materials that are utilised in the microcalorimeter's design. These include silicon (Si), silicon nitride (Si_3N_4), parylene-C, polymethyl methacrylate (PMMA), polydimethylsiloxane (PDMS), SU-8 and polyimide. Comparison of materials in terms of mechanical stability, biocompatibility with the biochemical samples, chemical resistance and thermal properties of material are also discussed. Section four compiles the list of microcalorimeter prototypes and highlights several examples that produce an excellent thermal insulation, an efficient microfluidic handling capabilities, a rapid mixing of fluids and a high throughput.

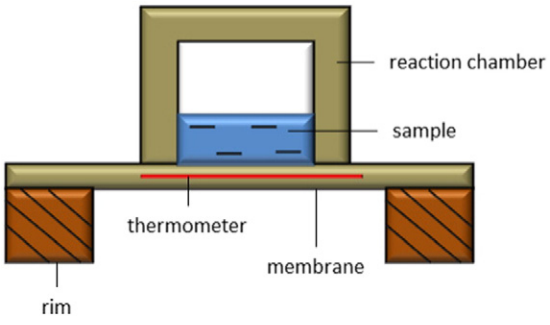

Fig. 1. An illustration of a generic microcalorimeter [4].

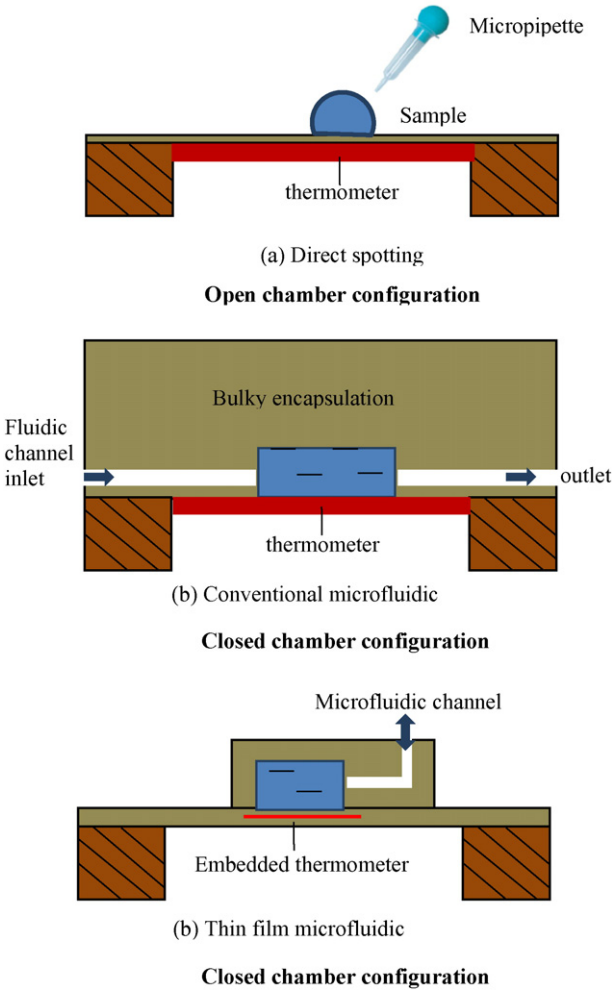

Fig. 2. Two types of reaction chamber; open and closed [2].

2. Design considerations

Five major components should be considered for the design of a microcalorimeter: reaction chamber, thermal insulation, fluid handling including mixing techniques, and temperature sensing. These components can be integrated in a single prototype.

2.1. Reaction chamber

A microcalorimeter is built on a membrane as the main structural and thermally insulating component (Fig. 1). The choice of material for the membrane is often a thin film with low heat capacitance. A silicon or stainless steel rim supports the membrane. For temperature sensing, the thermometer is embedded within the membrane and is placed beneath the reaction chamber. The samples are delivered and mixed in the reaction chamber.

The reaction chamber can be classified into two categories; open chamber [5–10] and closed chamber [11–17] as shown in Fig. 2. The key difference is the method of fluid transfer. In the open chamber configuration, droplets of sample are directly delivered into the chamber via a micropipette or inkjet. In the closed chamber configuration, microfluidic channels are built-in to deliver the fluid sample [2]. Conventional microfluidic channels are often bulky and are used to encapsulate the reaction chamber. Polymer thin film microfluidic channels are micromachined with the reaction chamber, giving an edge to miniaturisation and better thermal isolation.