DISPOSABLE POLYMER *"SMART"* LAB-ON-A-CHIP FOR POINT-OF-CARE TESTING (POCT) IN CLINICAL DIAGNOSTICS

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ABSTRACT

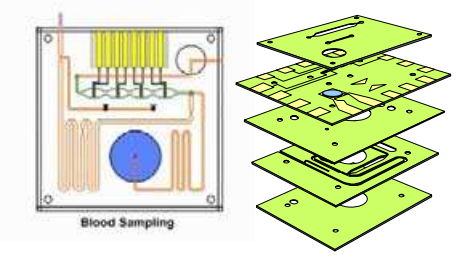
The recent development of an innovative disposable polymer smart lab-on-a-chip, which includes smart passive microfluidics, embedded on-chip power sources, and integrated biosensor array, has opened a new era for the point-of-care testing in clinical diagnostics. Several challenging issues in the development of the disposable polymer smart lab-on-a-chip have been explored and addressed in this work. A new disposable polymer *"smart"* lab-on-a-chip developed for measuring metabolic parameters from whole blood is presented in this paper.

Keywords: Disposable smart lab-on-a-chip, smart polymer microfluidics, POCT, clinical diagnostics.

INTRODUCTION

There has been a large demand for the development of disposable and smart lab-on-a-chips for clinical diagnostics in a platform of point-of-care testing (POCT) [1]. The smaller, faster and cheaper approaches, which worked so well for the IC chips of computer, have become a powerful tool for the development of biochips as well. Applications of small and inexpensive biochips, or lab-on-a-chips, are moving the highly complex analytical process from hospital laboratory to the point-of-care testing, where the complicated sequences of clinical tests can be performed quickly on a biochip by even un-skilled personnel. Thus, many efforts have been given over the development of various types of lab-on-a-chips for the POCT clinical diagnostics, including the analysis of metabolic parameters, proteins, DNAs, toxins, or infectious diseases from human blood or body fluids.

For decades, the microfabrication technologies on silicon or glass substrates have been well established along with the fast growth of semiconductor industries. However, the relatively high cost of conventional glass or silicon substrates has restrained their application for disposable biochips or lab-on-a-chips, which favor the usage of single-use platforms so that the risk of cross-contamination can be minimized. Recently, rapid prototyping techniques on polymer materials have been well developed, which allows the mass-production of disposable polymer lab-on-a-chips [2-3]. Such disposable lab-on-a-chips possess many advantages, including low sample/reagent volume, extremely short analysis time, cost effectiveness and ease-of-operation.



(a) (b)

Figure 1. Smart lab-on-a-chip: (a) schematic sketch and (b) multi-stacked polymer chips.

Along with the explosive growth of clinical diagnostics in emergency, there has been a large demand of POCT to conveniently measure the human metabolic parameters and provide the results in short time. The biochemical changes in the patient's blood can signal organ damage or dysfunction prior to observable microscopic cellular damages or other symptoms. For the realization of POCT in clinical diagnostics, the author's group in the University of Cincinnati (UC) has proposed and realized an innovative disposable polymer smart lab-on-a-chip as described in Figure 1.

DESIGN AND FABRICATION

In the realization of the smart lab-on-a-chip, numerous challenging issues related to the desired functions for being so-called *"smart"* will be discussed and specified, and then new approaches to address the issues have been proposed and developed, considering the design, fabrication and characterization of core components of the smart lab-on-a-chips. The discussion will be focused on the polymer microfabrication, the smart microfluidics, the disposable on-chip pressure generator, the biosensor array, and the hand-held or wristwatch analyzer.

Polymer Microfabrication

As for disposable usage, the cost of the raw substrate material and the associated fabrication

processes become a significant factor and prompt the first consideration in biochip design. Polymer materials have already been well accepted as a promising solution for mass-manufacturable disposable biochips. Microstructures on polymer substrate have been constructed and assembled by using simple technologies such as injection molding, hot embossing, thermal bonding and UV-adhesive bonding, etc. The biocompatibility of polymer materials is another advantage in case of biochip applications. Indeed, according to all the above advantages, the disposable polymer lab-on-a-chips have become the fastest growing platform in the realm of POCT in clinical diagnostics.

(a) (b)

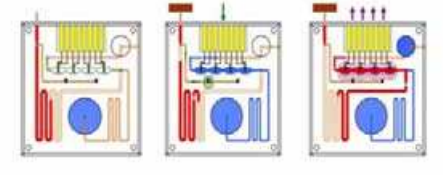
Figure 2. Micro injected polymer chips: (a) replicated polymer wafer and (b) passive valve.

A wide range in physical and chemical properties of polymers can be observed from material to material, which indicates a variety of fabrication methods are needed based on application purposes. Due to the high extension of elastomers and brittle structure of thermosets, thermalplastics are the best option for a polymer disposable biochip. As for the lab-on-a-chip fabricated at UC, all the components are constructed by using a polymer material such as cyclic olefin copolymer (COC). Figure 2 shows the microfabricated polymer chips using COC.

Smart Passive Microfluidics

The control of microfluidics in a μTAS device has been one of the most challenging issues. Among all kinds of body fluidics, the blood, which delivers the beneficial ingredients to individual organs and carries away the by-products, contains abundant health-related information and hence becomes the most interested target in clinical diagnostic applications. Despite its rich contents, the human blood has diverse components and experiences various difficulties in simulating and controlling its performance in microfluidic channels. Different from macro-scale fluidics, the micro-scale fluidic has many unique characters and requires novel methods for handling [4]. Various researches have been concentrating on active control devices such as microvalves and micropumps for fluidic flow regulation. However, disadvantages in high cost, complex structure, difficulty in fabrication, and complicated signal control. As a consequence, the trends of microfluidic control are shifting towards passive regulating microfluidic structures. Simple and effective but *"smart"* passive microfluidic mechanisms are very desirable for regulating the sample or buffer liquids in performing an assay.

Structurally programmable microfluidic systems (sPROMS), a new concept for microfluidic regulation, is then established and can be described as "sPROMs is a passive microfluidic control technique where a set of microfluidic manipulations are carried out in a pre-programmed sequence." The microfluidic operations and their sequence are determined primarily by the structural arrangement of the system without the need for an external control signal. sPROMs is analogous to the programmable read-only memory (PROM) of a computer where a specified set of instructions is hard-wired into the PROM chip. The basic principle of sPROMs is to control fluidic sequence by usage of a series of passive valves at pre-programmed locations [5, 7, 9]. Figure 3 presents the operation sequence of the biochip using sPROMs concept.



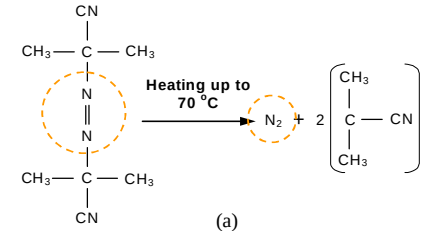
(a) (b) (c)

Figure 3. Schematic sketch showing an operation sequence of the biochip: (a) blood sampling; (b) calibration; and (c) detection.

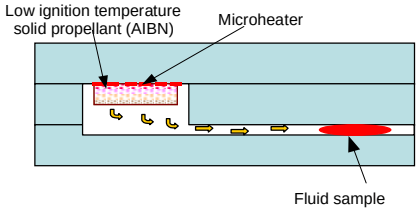
Disposable Pressure Generator/Power

Micropumps are the most popular devices as a pressure source for microfluidic systems and have been reported for different driving principles. However, micropumps/valves make the microfluidic systems complicated and sometimes are unsuitable for disposable biochips or lab-on-a-chips due to its complexity in structure/assembly and reliability problems. The complexities of active micropumps/valves make their integration into disposable microfluidic biochips or lab-on-a-chip devices difficult and costly. So, a new alternative pressure source with the advantages of low cost, easy fabrication, easy integration, high reliability, and compact size is desirable for disposable biochips or lab-on-a-chip devices, combining passive-type microfluidic components. In order to drive the sample traveling through the microchannels, an on-chip pressure generator is

functional pressure generator consists of a solid chemical propellant positioned on a microheater as described in Figure 4.



(a)



(b)

Figure 4. Chemical propellant for generating Nitrogen gas: (a) AIBN's composition and (b) schematic for generating nitrogen [8].

Azobis-isobutyronitrile (AIBN), the chemical propellant material, decomposes at 70 °C and releases Nitrogen gas as by-product. The output pressure of nitrogen gas, generated from the solid chemical propellant, is adjusted to a desired value by controlling the input power of the heater. Using this chemical energy source, the generated pressure depends on the deposited amount of the solid chemical propellant and the temperature of the microheater.

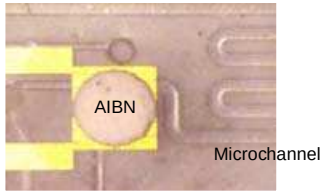
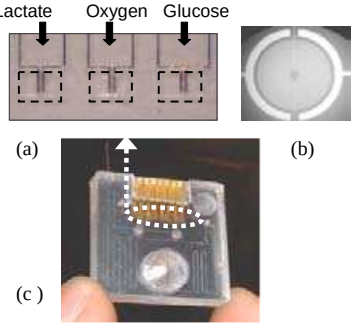


Figure 5. Screen printed AIBN on a microheater generation [8].

Due to its compact size, easy fabrication, easy integration, high reliability, biologically inert gas output, and functionality of gas generation, this pressure generator serves as an excellent driving mechanism for the biochip application. Figure 5 shows the characteristics of the functional on-chip pressure generator using AIBN as solid propellant [8]. We believe this disposable on-chip gas smart POCT.

Biosensor Array and Nanobiosesnors

As the size of biochip are miniaturizing towards on-site analysis, the electrochemical analyzing method presents most satisfying properties due to its low power consumption as well as it can be miniaturized without compromising its capabilities [6, 10]. Similar to many other bio-electrochemical sensors, the basic principle of the on-chip biosensor array is based on amperometric measurements. In the device, the most fundamental sensor design is the oxygen sensor, which is the basic sensing structure for plenty of other metabolic products such as glucose and lactate. After the diffusion profile for oxygen from the sample to electrode surface is saturated, a constant oxygen gradient profile is generated, which suggests a constant current generation. Under these circumstances the detection current is only determined by oxygen concentration in the sample solution. The glucose and lactate sensors are constructed by adding two layers on top of the oxygen sensor. In a glucose sensor for example, the glucose molecules are converted to gluconic acid; thereby, hydrogen peroxide is generated in the presence of glucose oxidase enzyme. A similar principle applies for lactate measurement in the presence of the lactate oxidase enzyme. In order to construct the micro/nano biosensor array over a disposable substrate, various fabrication techniques were investigated and introduced so that the mass-production of fully-integratable biosensor array can be realized as shown in Figure 6.



(a) (b)

(c)

Figure 6. Biosensor array incorporated into the polymer smart lab-on-a-chip: (a) sensor array; (b) nanoelectrodes as biosensor; and (c) smart biochip.

ANALYZER AND MEASUREMENT

The control and detection circuitry were implemented on a multilayer PCB using SMT (surface mount technology) IC's to minimize the size of the analyzer. The LCD used for displaying the concentration of fluid analyte was a 3-1/2 digit static duty, elastomer version LCD that met the low

Figure 7 shows a wristwatch analyzer with a biochip cartridge.

(a) (b)

Figure 7. Health monitoring wristwatch: (a) disposable smart lab-on-a-chip and (b) wristwatch analyzer [10].

The disposable biochip developed in this work was tested with the developed SMT electronics system. The actual testing with blood samples was conducted. Figure 8 shows the test results of the biosensor array with whole blood for glucose and lactate measurement. The results clearly indicate that our sensor array has a very linear response in the normal detection limits for both glucose and lactate. The normal physiological limits (daily average) for glucose are 90-120 mg/dL. The glucose sensors developed in this work can detect glucose concentrations from 50-250 mg/dL and the lactate sensor has been successfully tested for 2-12 mg/dL. These results clearly prove the utility of the developed biosensor array and the disposable biochip for clinical diagnostic applications.

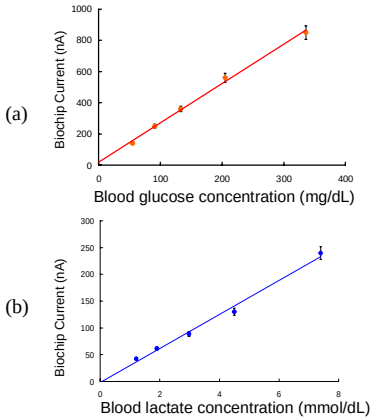


Figure 8. Measured results for different human blood samples: (a) glucose concentrations and (b) lactate concentrations.

CONCLUSION

This work illustrates a platform of an innovative smart lab-on-a-chip for various blood microfluidic system, the disposable polymer smart lab-on-a-chip developed in this work has made a significant contribution toward the development of rapid and affordable point-of-care testing. The biosensor arrays developed in this work are well suited to mass production approach and have been optimized towards accurate and fast measurements. We believe the results of this work can have a significant impact over the development of rapid and affordable point-of-care testing in clinical diagnostics.

Acknowledgements

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