The Application of Microfluidic Devices/Systems

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1.0 INTRODUCTION

The functional elements in technical systems are integrated and miniaturised using microtechnology. In this article, the microtechnology in microfluidic systems by emphasising on the various applications of the systems is reviewed. The potential merits of industrialising this technology are discussed, and its potential future is analysed.

Microfluidics, which could be devices, systems, and methods for manipulating fluid flows with characteristic length scales in micrometer range, is a powerful tool in chemistry, physics, and biology. Microfluidic systems possess the capability to execute operations more quickly than macroscopic systems, while consuming much smaller amounts of chemicals and solvents [1]. Thus, less waste is generated and energy use is reduced. Moreover, with the potential for packing a large number of experiments in a few cubic centimetres [2] and their potential portability and disposability [3], microfluidic systems become very attractive particularly in biological applications.

The world saw the bicentenary of the development in the field of microfluidic systems since Manz *et al*. (1990) [4] introduced miniaturised total analysis systems (μTAS). μTAS refers to miniaturised chemical analysis system of laboratory functions or lab-on-a-chip that integrates sample preparation, reaction, injection, separation and detection system on a single chip that is small enough to be handheld, and robust enough to be used by non-professionals [5, 6].

2.0 APPLICATIONS OF MICROFLUIDIC SYSTEMS/DEVICES

The review of microfluidic applications is divided into sections based on their common resemblance.

General Bio-Applications of Microfluidics

DNA analysis is one of the primary applications of μTAS technology, involving cell sorting, cell analysis, DNA extraction and purification, polymerase chain reaction (PCR) and capillary electrophoresis (CE). Microchip formats of PCR and CE were shown to be an ideal combination for fast DNA analysis [5]. Figure 1 shows the microfabricated PCR–CE device.

In the process of drug discovery, implementation of microfluidics technologies into cell-based assays that are used can develop tests that provide data representative of biological responses, where the results are ideally comparable to those obtained from animal models or clinical trials [1].

In liver tissue engineering, Leclerc *et al*. (2004) [7] addressed the efficiency of microstructures by introducing microfluidic bioreactors to the perfusion culture of fetal human hepatocytes. This saw good cell growth over the inner surfaces of the bioreactors and enhancement of the cellular albumin production. Also, Leclerc *et al*. (2005) [8] attempted to study osteoblastic cells behaviour cultured within microdevices allowing continuous and homogenous feeding of cells. The study is promising for bone cell growth and differentiation as well as tissue regeneration.

In the work by Sadani *et al*. (2005) [9], they described the fabrication of a lab-on-chip devoted to the analysis of the cells to be fertilised in in-vitro fertilising (IVF). IVF is an exciting subject of research for human assisted reproduction and veterinary medicine. The determination of the cell to be fertilised (oocyte) is perhaps the most critical among the various steps of gamete manipulation. The choice is generally the results of a visual estimation of the morphological properties of the cell. The system, as illustrated in Figure 2, is able to capture the cell on the lab-on-chip surface, transport it to different analysis stages, and establish an objective catalogue of the oocyte characteristics.

In diabetes treatment, glucose dialysis is of particular interest. Continuous monitoring of various metabolites such as glucose, lactate, sodium, etc. in patients is vital. Hsieh and Zahn (2005) [10] highlighted recent efforts to characterise

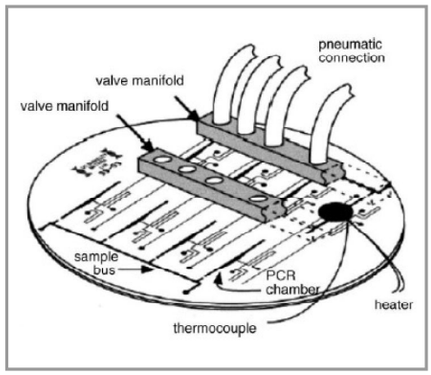

Figure 1: Microfluidic PCR–CE device. The PCR chambers are directly connected to the cross channel of the CE system for product injection and analysis [5].

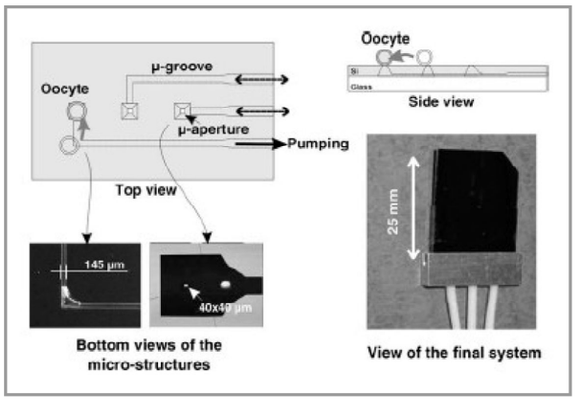

Figure 2: Microfluidic platform for trapping the cells. When the cell is close to an aperture, pumping in the corresponding micro-channel efficiently traps the oocyte [9].

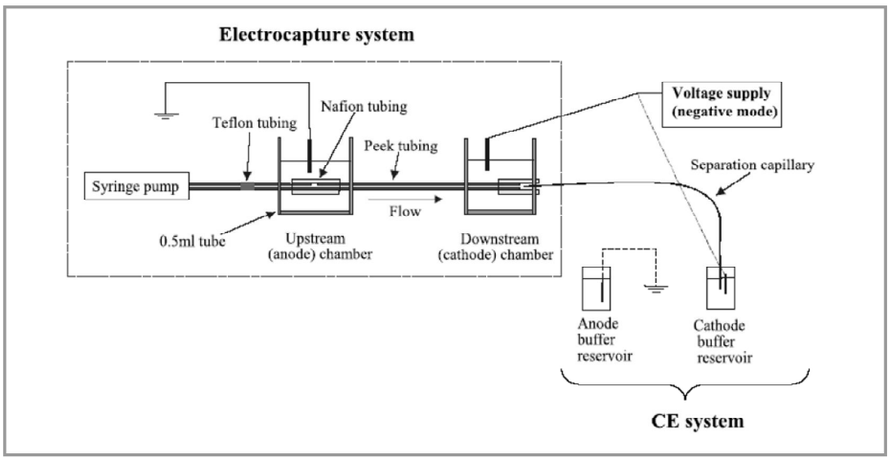

Figure 3: Schematic representation of the electrocapture device-CE system. A syringe pump provides continuous injection of sample into the microfluidic device. After concentration, the sample is injected into the separation capillary. The capillary is located at the CE anode reservoir, and the electrophoresis is started [13].

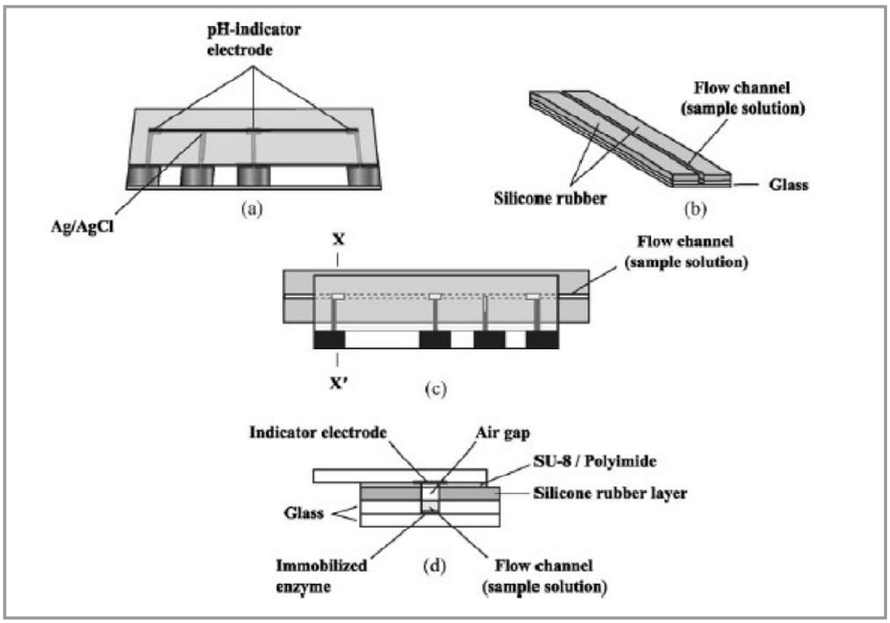

Figure 4: Structure of the integrated sensing system to determine ammonia, creatinine and urea: (a) glass substrate with detecting electrodes. (b) flow channel. (c) electrode substrate (a) placed on the flow channel (b). The opposite side of the electrode substrate is seen (d). Cross-section of the system (c) along the line X–X' [14].

mass transport in a miniaturised microdialysis system to create a microdevice for continuous glucose sensing.

In macromolecular crystallisation (e.g. protein crystallisation), among the successful applications of lab-on-a-chip is batch crystallisation by temperature variation by Christopher *et al.* (1998) [11]. Following this, the potential of microfabrication in active nucleation and crystal growth control was demonstrated by Sanjoh and Tsukihara (1999) [12].

Electrocapture technology, a tool in protein and peptide analysis, constitutes a strategy to perform sample preparation in microfluidic devices. The combination of microfluidic technologies and this powerful analytical tool (CE combined with electrocapture system as shown in Figure 3) has been foreseen as the solution for integrated and versatile high-throughput analysis of polypeptides [13].

An integrated sensing system incorporating microflow channel has also been microfabricated by Suzuki and Matsugi (2005) [14] for simultaneous determination of ammonia, creatinine, and urea, which is required in routine health-care analysis because the analytes are critical indicators of renal function. The system consists of air-gap ammonia sensors as the transducers, three pH-indicator electrodes and an Ag/AgCl reference electrode patterned on a glass substrate, as shown in Figure 4.

In summary, the technology of microfluidics has been observed in almost every bio-related application, especially in human-health analysis. It is undoubtedly seen that microfluidics will play important role in discovering more and higher quality drugs through cell-based assays, as well as growing various cells in tissue engineering area and determining the cells to be fertilised in IVF. Additionally, the development of compact, disposable and automated diagnostic systems that can be used in a clinical laboratory will enable microfluidic systems to revolutionise the DNA diagnostic tests, and also recover various metabolites when used in continuous monitoring of metabolites in patients. Besides, microfluidics also offers a powerful alternative approach to the growth of macromolecule crystals. Furthermore, an integration of microanalytical systems as demonstrated by Wells *et al.* (2005) [13] in an electrocapture-CE system for proteins and peptides analysis has proven that a microfluidic system can also be multifunctional. Integrated microanalytical systems have the potential in the future to become standard platforms for analysis of not only peptides and proteins, but also other molecules.

Applications of Capillary Electrophoresis – Electrochemical Detection (CE-ECD) Systems

The microchip capillary electrophoresis system with end-channel electrochemical detection is established for effective separation and sensitive detection of various chemicals. It has been applied widely in pharmaceutical analysis and environmental monitoring purposes. The high sensitivity and selectivity, miniaturisation, portability and low cost of electrochemical detectors are of particular interest in microchip systems. The rapid progress of electrochemical detection for analytical microchips over

the past few years shows that it may have a major impact in the present decade as a powerful tool for microscale analytical systems.

A microchip CE-ECD system was investigated by Liu *et al.* (2005) [3] in a pharmaceutical analysis to determine and rapidly separate acetaminophen and its hydrolysate, where the trace of p-aminophenol in paracetamol tablets has been successfully detected. Additionally, the recent advances and the key strategies in microchip CE with ECD are developed for separating and detecting a variety of environmental pollutants including phenols, aromatic amines, hydrazines, nerve agents, nitroaromatic compounds, and inorganic and organic ions [15]. CE-ECD systems also provides an approach to portable methods of analysis in in-situ real-time measurement for environmental monitoring, using suitable chemical methods that are simple, fast, and stable, and could produce sufficient quality data [16].

Applications of Microreactors

Pattekar and Kothare (2005) [17] have developed a novel radial flow packed-bed microreactor to deliver hydrogen from methanol reforming in miniature fuel cells, for portable power generation. This opens the path for fuel-cell-based portable energy systems, with energy storage capacities of 10 times higher than current battery technology. Miniature fuel cells provide the solution to the problems faced by today's portable rechargeable batteries, as the demand for high energy density power sources grows.

Another application of microfluidics as microreactors is enzymatic microreactors. Applications of enzymatic microreactors with immobilised enzymes include analysis of proteins and nucleic acids. Besides, microreactors also find applications in organic synthesis. Moreover, microreactors are also useful in kinetic characterisation of enzymes, where the key kinetics parameters, K_m and v_{max}, could be determined. Enzymatic microreactors have the potential to be introduced into industrial-scale synthesis, where the prospective fields of application are wide including biotechnology and enzyme-targeted drug search. Commercialisation of enzymatic microreactors would aid standard analytical and micropreparative procedures [18].

Applications of Microfluidics in Analytical Chemistry

Microfluidic systems also find applications in analytical chemistry. Shih *et al.* (2005) [19] fabricated the first chip-based temperature gradient liquid chromatography (LC) system which integrates an LC column, a electrochemical sensor, a resistive heater and a thermal isolation structure on a single silicon chip using parylene-strengthened thermal isolation technology as shown in Figure 5.

On the other hand, a microfluidic chip employing the electrochemical sensing method illustrated in Figure 6 is capable of performing precise continuous pH measurements as demonstrated by Lin *et al.* (2005) [20]. This provides a valuable tool to examine pH values in a wide range of biomedical and industrial applications, such as monitoring the variation of pH levels of blood. The pH-sensing chip not only provides a valuable tool for rapid and accurate pH sensing, but it also has the potential to be extended to other forms of miniature electrochemical sensors.

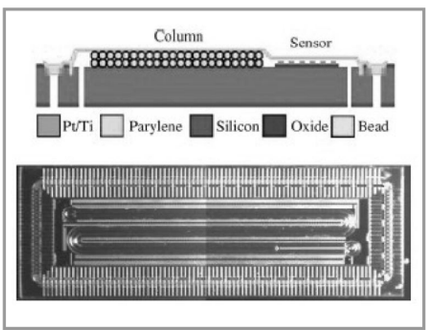

Figure 5: On-Chip temperature gradient liquid chromatography device. Dash-lined rectangle in the bottom picture defines the separation column zone, thin white lines are parylene cross-linking structure, running between the separation columns is the platinum resistive heater [19].

Liquid–liquid (L–L) extraction is among the oldest of preconcentration and matrix isolation techniques in analytical chemistry. A robust L–L extraction chip system using two microfabricated glass plates and a microporous membrane as shown in Figure 7 was developed by Cai *et al.* (2005) [21]. Gravity was employed to drive the aqueous and organic flows in the microporous membrane liquid–liquid extraction system as shown in Figure 8. Indeed, the present system has the potential to be further extended by coupling it to flow injection analysis, gas chromatography and high pressure liquid chromatography systems to serve as a sample pretreatment system.

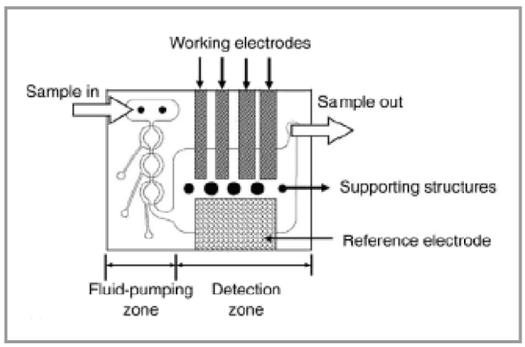

Figure 6: Microfluidic pH-sensing chip. (Supporting structures designed to avoid adhesion of PDMS membranes. Single pneumatic pump used for fluid control) [20]

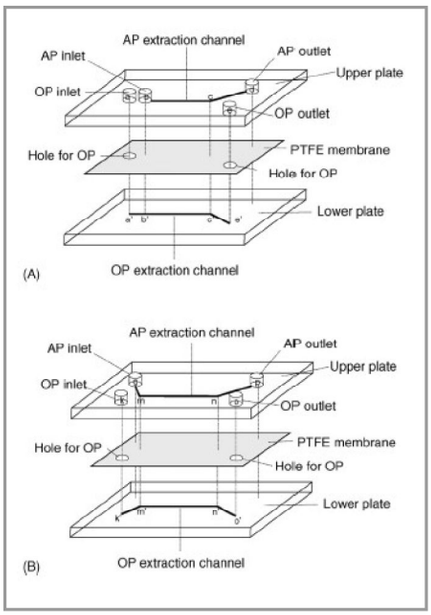

Figure 7: Schematic diagram of the microfluidic chips for liquid–liquid extraction with different shaped extraction channels, A and B [21].

3.0 CONCLUSIONS

The development of the field of microfluidics is stimulated by the trend to miniaturise chemistry, especially in biological and medical analyses. The small-scale, low-cost systems result in an amazing reduction in solution

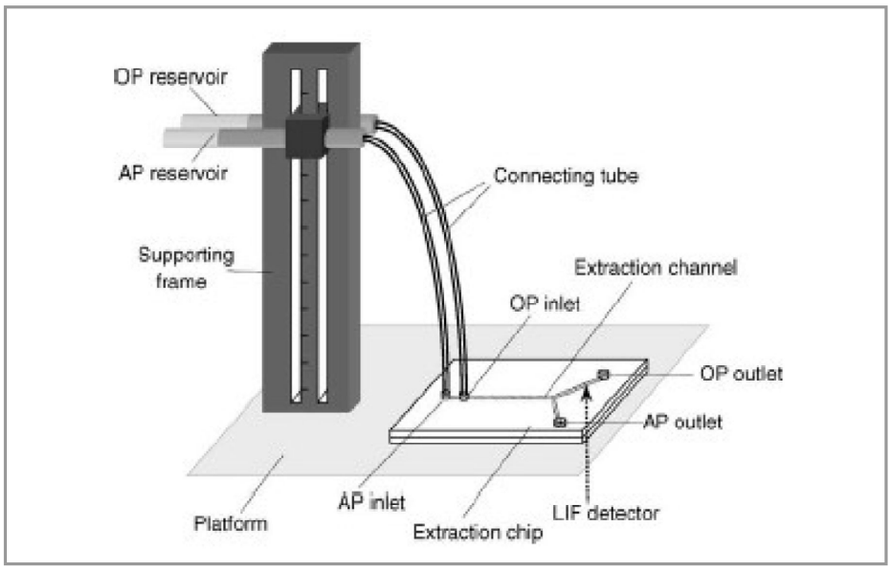

Figure 8: Schematic diagram of the chip based microporous membrane liquid–liquid extraction system [21].

consumption and waste generation as well as a high degree of integration, portability, disposability, high performance, and speed. Besides the research that have been investigated so far, a lot of other research are still ongoing and need to be undertaken to further improve the microfluidic systems, as well as to study any possible new applications, to make the industrialisation of this technology a reality. The upshot for any large scale use of microfluidics is ease use and robustness. ■

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