Journal of Applied Sciences Research, 8(1): 420-430, 2012
ISSN 1819-544X
This is a refereed journal and all articles are professionally screened and reviewed

ORIGINAL ARTICLES

Micro/Nanoscale Biosensing in Microfluidics: Selection of Polymers and Microstructures

[1]Tijjani Adam, [1]U. Hashim, [2]Pei Ling Leow and [1]M.E. Ali

[1]Institute of Nano Electronic Engineering, Universiti Malaysia Perlis (UniMAP), 01000 Kangar, Perlis Malaysia.
[2]Faculty of Electrical Engineering, Universiti Teknologi Malaysia (UTM), 81310 Johor Bahru, Malaysia.

ABSTRACT

Microfluidic techniques based on nanotechnology for miniaturized lab-on-chip systems have recently received huge research attention because of its undisputable and widespread biomedical applications. For the development of a micro-total analytical system, the integration of an appropriate fluid delivery system to a biosensing apparatus is must. This review highlighted the recent developments in micro and Nanofluidics technologies for the state-of-art fabrication of microchannels, micromixer, microvalves, and micropumps on polydimethyl siloxane substrate. The impacts of micro/Nanofluidics on life sciences are also briefly discussed.

Key words: Miniaturization, biomedical, microfluidic, diagnosis, microchannels, micromixer, microvalves, micropumps. Polydimethyl siloxane.

Introduction

The manipulation of liquids and gasses in channels having cross-sectional dimensions on the order of 10-100μm will be a central technology in a number of miniaturized systems that are being developed for chemical, biological, and medical applications. These applications can be categorized into four broad areas; miniaturized analytical systems, biomedical devices, tools for chemistry and biochemistry, and system for fundamental research (McDonald *et al*, 2000). In order for these systems to be successful, they must have the attributes that are required for the particular application e.g. optical properties and surface chemistry and they must be also fabricated in materials that are inexpensive and rugged and use processes that are amenable to manufacturing (McDonald *et al*, 2000). Present a short review on fabrication and applications of microfluidic devices in one material-poly (dimethylsiloxane) (PDMS), The most basic fluidic structure to build microfluidic chip is an assembly of microstructures on a common substrate, used for the manipulation of the fluids (gases and /or liquids (Tjerkra *et al*,1997). A Lab-on-chip device is a combination of fluidic elements, sensor components and detection elements to perform the complete sequence of a chemical reaction or analysis, including sample preparation, reaction, and detection devices are microfluidics. These delivery structures provide the interconnection network between the fluidic elements of the device, but may have additional functions, like the channels in capillary electrophoresis and other separation techniques. Various shapes for the microfluidics are used. The shape of the of the device may be determined by the fabrication method and application (Tjerjra *et al*,1997; Gardiniers *et al*, 2000; Howitz *et al*, 1999).

There are three types of materials are common for microfluidic and Lab-on-chip devices: silicon, Glass and polymer materials. Polymers are the third type of material used in the manufacture of microfluidic devices (Becker *et al*, 200). The main reason why polymer become the best candidate of choice because of it's simple and cost- effective replication methods such as injection molding or embossing another advantage of the polymers is the broad range of material suited for these manufacturing methods, including PDMS, PMMA, PET, TPE, PC, Cyclic Olenfins, PEEK, POM. elastomers. and others. This allows a choice to be made for the material properties suitable for the specific application. The typical properties that may be of fundamental impotance include optical transparency, thermal expansion coefficients, thermal stability, permeability and stiffness (Becker *et al*, 2000; J. C. T. Eijkel and A. van den Berg, 2005).

Materials for fluidic components:

Since the prologue of microfluidic device in the 90s and due to the microfabrication of LOC was first realized by adopting fabrication techniques from microelectronics industrial; materials used for LOC were initially dominated by glass, quartz or silicon as the major material for microfabrication. However, polymers have slowly taken over the trend as the ease of microfabrication and cost effectiveness. The existence of

Corresponding Author: Tijjani Adam, Institute of Nano Electronic Engineering, Universiti Malaysia Perlis (UniMAP), 01000 Kangar, Perlis Malaysia.
E-mail: tijjaniadam@yahoo.com.

polymers has revealed as a better options for LOC fabrications (Tjerkra *et al*, 1997: Ramsey *et al*, 1995). Today, various methods and wide range of machines and techniques that have been developed to fabricate LOC that can meet the desired applications or geometry. Since the early work in the field, there has been a rapid expansion in into new types of materials(Van den Berg *et al*, 1995), especially polymers. Polymers, in contrast to silicon and glass, are inexpensive (Ogura *et al*, 1998; Ford *et al*, 1999; Kua-Kang Liu *et al*, 2010) channels can be formed by molding or embossing rather than etching and device can be sealed thermally or by using adhesive.

Some of the popular polymers used in microfluidic fabrication are poly (dimethylsiloxane) (PDMS) (Gardenires *et al*, 2000; Howitz *et al*, 2002) Poly(methyl methacrylate) (PMMA) (J. C. T *et al*, 2003); Aveek N *et al*, 2005) or called as Acrylate, thermoset polyester (TPE) (Siu SK *et al*,2003) polyethylene terephthalate (PET). cyclo-olefin copolymer (COC) (McDonald *et al*, 2002) and polyimide (Yue Fei *et al*, 20080). Most of the time, these polymer were chose according to the compatibility of their physical properties to the application of the microfluidic device, such as biocompatibility, optical properties that allow light transmission, surface properties whether hydrophilic or hydrophobic and also material stability in solvent. Besides that other reasons that come into consideration are the ease of fabrication, cost effective, availability and also flexibility of integration with other materials used in the fabrication. With the above scenario in mind, this materials interest of this study is poly(dimethylsiloxane) PDMS. The network polymer structure of PDMS makes it highly permeable relative to other materials, a property that can be put to use in cell culture applications to supply oxygen and remove carbon dioxide (Michael W *et al*, 2006) and also more, the this property will promote in dealing with bio species in their natural state especially in application area like Nano-Lab-On-Chip which a very small amount of sample. The porous nature of PDMS also enables small molecules to diffuse into the bulk polymer, which has allowed PDMS to be used in micro extraction applications for removing trace organic compounds from aqueous samples(G. Theodoridis *et al*,2004; J. N. Lee *et al*, 2003) The disadvantages of the polymers are that more care must be taken to control their surface chemistry than with glass or silicon; they are often incompatible with organic solvents and low molecular weight organic solutes; and they are generally incompatible with temperatures(Copper *et al*, 2000) But the good news about PDMS is that Some steps can be taken to modify the surface chemistry of the material; Low molecular weight silicone molecules can be removed from bulk PDMS through Aging and extraction which reduced hydrophobic recovery after plasma treatment and increased solvent resistance (W.J Chang *et al*, 2003; M. Bennett *et al*, 1997) in order to control the permeability of the PDMS, a cross linking agent and zeolite filler can be incorporated into PDMS in order to reduce evaporation which could lead to samples drying.

Fluidic Components:

The most basic fluidic structure to build microfluidic chip is an assembly of microstructures on a common substrate used for the manipulation of the fluids gases or liquids. A Lab-on-chip device is a combination of fluidic elements, sensor components and detection elements to perform the complete sequence of a chemical reaction or analysis, including sample preparation, reaction, and detection devices are microfluidics. These delivery structures provide the interconnection network between the fluidic elements of the device, but may have additional functions, like the channels in capillary electrophoresis and other separation techniques. Various shapes for the microfluidics are used. The shape of the of the device may be determined by the fabrication method and application and for the purpose of this review, the for components are briefly discussed.

Micro Channels:

The important parameters of microchannels include surface roughness and aspect ratio of the structure, which is defined as the ratio of depth to width. High-aspect ratio channel have a high surface to volume ratio and assume to less floor space on the microfluidic chip. Channel widths commonly vary between few millimetres to the micro range (Aveek N *et al*, 2005) aspect ratio of 10 is normally used. Fluidic communication between different regions of lab-on-a-chip devices by adjusting the channel diameter and the inverse Debye length of the channel and applying the appropriate external potential, the nanochannel arrays, can be made to behave like digital fluidic switches. Electrokinetic fluid flow in nanocapillary array (NCA) membranes reported in (Aveek N *et al*, 2005; Sia SK *et al*, 2003) between vertically separated microfluidic channels offers an attractive alternative to used mechanical action to achieve and the movement of molecules from one side of the array to the other side can be controlled Micro-channel can be realised by simple micro-fabrication technique that allows the rapid construction of complex 3-D micro-fluidic channels (Byung-Ho Jo *et al*, 2003) A parametric study of PDMS bonding via plasma activation is also reported. The techniques described can be applied to realize various kinds of 3-D micro-fluidic systems such as micro-mixers, micro-valves, capillary electrophoresis (CE) systems, and micro total analysis systems (TAS) (Byung-Ho Jo *et al*, 2000) figure 1 &2. Microchannels are commonly fabricated from (poly) dimethylsiloxane, or PDMS. The chemical and physical properties of PDMS allow for useful functionality and tolerances below 0.1 μm (McDonald *et al*, 2002).

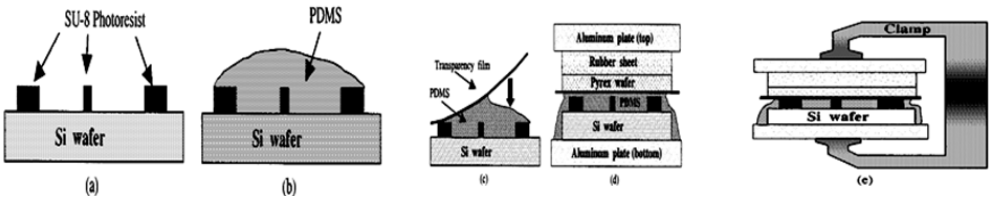

Fig. 1: Schematic illustration of the sandwich molding process for thin upper layers. (a) A master for each layer was formed on a silicon wafer using SU-8 photoresist and standard photolithography procedures. (b) Next, the PDMS prepolymer mixture was poured onto the master. (c) A transparency film was placed over the poured prepolymer mixture. (d) A multilayer stack of aluminium plates, the mold master, the PDMS prepolymer mixture, a transparency film, a rigid pyrex wafer, and a rubber sheet is used to form a compression mold. (e) Finally, all the layers are clamped tightly during the cure (Byung-Ho Jo *et al*, 2000).

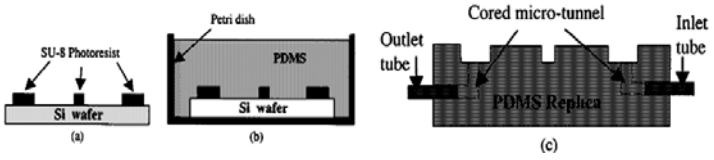

Fig. 2: Scheme for fabricating a thick bottom layer and off-chip connection via the bottom layer. (a) A master for the bottom layer. (b) Molding a thick bottom layer in a petri dish. (c) A bottom layer containing "L-shaped micro-tunnels and tube connections (Byung-Ho Jo *et al*, 2000).

The behaviour of fluid flow on a micro scale differs greatly from that of microfluidics and these differences can be beneficially exploited. Microchannels are commonly fabricated from Polydimethylsiloxane, or PDMS. The chemical and physical properties of PDMS allow for useful functionality and tolerances below 0.1m[9],another simple and flexible were reported using microwire-molding technique, without the use of large equipment and tedious process (Yue Fei *et al*, 2008). A straightforward idea to fabricate microchannels with simple structure would be that microwire could be embedded into and simply removed after PDMS curing. There are several reports about utilizing this idea in the micro fabrication of microchannels (Yan *et al*, 2003). A 3-D micro-channel fabrication process has been reported for PDMS elastomers material using a sandwich molding technique and stacking of many thin patterned layers. With a consideration of the many advantages of PDMS[39], it repeated that fabrication process is well suited for a wide range of applications in micro-fluidic component design. The process is rapid and simple. Thus, it allows rapid design interruptions to be performed, for example, to investigate the flow fields of a variety of complex channel structure (Byung-Ho Jo *et al*, 2000)

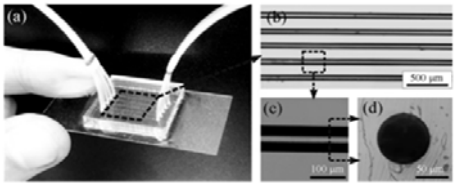

Fig. 3: Straight micro channel array. (a) Integrated PDMS micro channel chip; (b) microscope picture of microchannels; (c) micro channel in detail; (d) cross-section (Yue Fei *et al*, 2008).

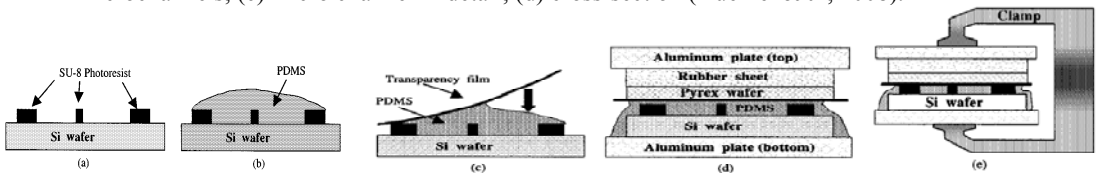

Fig. 4: Schematic illustration of the sandwich molding process for thin upper layers. (a) A master for each layer was formed on a silicon wafer using SU-8 photoresist and standard photolithography procedures. (b) Next, the PDMS pre-polymer mixture was poured onto the master. (c) A transparency film was placed over the poured pre-polymer mixture. (d) A multilayer stack of aluminium plates, the mold master, the PDMS pre-polymer mixture, a transparency film, a rigid Pyrex wafer, and a rubber sheet is used to form a compression mold. (e) Finally, all the layers are clamped tightly during the cure (Byung-Ho Jo *et al*, 2000).

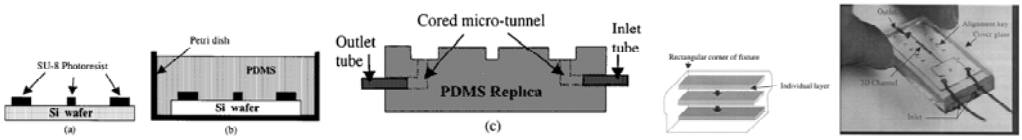

Fig. 5: Scheme for fabricating a thick bottom layer and off-chip connection via the bottom layer. (a) A master for the bottom layer. (b) Molding a thick bottom layer in a Petri dish. (c) A bottom layer containing "L-shaped micro-tunnels and tube connections.(d) Photograph of a finished 3-D passive micromixer(Byung-Ho Jo *et al*, 2000)

A novel method to fabricate micro structures under room temperature is reported from the review article of (Kuo-kang Liu *et al*, 2010) which could be used in Microfluidic system. This micro fluidic system can be used to automatically transport liquid by evaporation at the end without any external driving force; the driving force was generated by liquid evaporation at the exit of microchannels controlled by heaters. Lots of heater design was used to accumulate the generated force by liquid evaporation (Da-Leng Yo and Po-Yu Chen); Leminh *et al*, 2003) A new method named 'plasma polymerization on sacrificial layer' (PPSL) was describe. It consists in the direct polymerization of tetramethyldisiloxane (TMDS) on a photo patterned sacrificial layer. Channels are formed with only one lithographic mask and without any etching or bonding process. The use of polymerized TMDS allows rapid creation of capillarity-driven flow systems with the channel width ranging from 4 to 700 µm without pillars (Abbas *et al*, 2009) a micro-fabrication technique developed for constructing complex 3-D channel paths is based on the stacking of thin (100 m) two-dimensional (2-D) patterned PDMS layers is reported with the schematics of the process flow used to create the 2-D patterned layers shown in figure 4 and 6: which is imported from (Byung-Ho Jo *et al*, 2000).

Micromixer:

Mixing is a physical process to achieve homogeneity of the different components involved in the certain process (Kuo-kang Liu *et al*, (2010) In some cases, the mixing will be the rate determining step when the mixing time is in the same order or longer than the molecular reaction time. Because the fluid streams mainly appear naturally as laminar flow on a chip, the mixing will mainly depend on molecule diffusion. A good example is an immunoassay where miniaturization can lead to reduced reagent consumption, faster reactions and higher throughput (Asgar *et al*, 2007; Knight, 2000; Freemantle, 1999; Borman, 1999). Fully integrated microfluidic chips performing such reactions require fast homogenous mixing. Mixing small amounts of reagents and samples in microfluidic channels or structures is a challenging task Manz *et al*, 1990; Figeys *et al*, 2000; Kopp *et al*, 1998); Chow *et al*, 2000). Likewise, mixing in passive micromixer relies mainly on molecular diffusion and chaotic advection. To speed mixing process, the T-mixer or Y-mixer which consists of the inlets converging into a long microchannel has been developed as a simple and effective solution (Kamholz *et al*, 1999; Kamholz *et al*, 2002; Ismagilar *et al*, 2000). Other methods for fast mixing have been implemented through reducing the mixing path in a narrow mixing channel (veenstra *et al*, 1999) and realizing parallel lamination with multiple streams (Jackson *et al*, 2001; Koch *et al*, 1999). Besides diffusion, advection is another important form of mass transfer in flows with a low Reynolds number. However, advection is often parallel to the main flow direction, and is not useful for the transversal mixing process. The chaotic advection generated by special geometries in the mixing channel can improve mixing significantly. The basic idea is the modification of the channel shape for splitting, stretching, folding and breaking of the flow. The simplest method to get chaotic advection is to insert obstacles or structures in the mixing channel. However, it has been shown that eddies or recirculation cannot be generated in a microchannel, because of its low Reynolds number (Wang *et al*, 2002) The effective method to produce chaotic advection is to modify the wall of mixing channel with ribs, grooves and staggered-herringbone grooves. (Johnson *et al*, 2002) the paper reported as first investigator of this phenomenon. They ablated the grooves on the bottom wall of the channel by laser. This structure allows mixing at a relatively slow velocity of 300 µm/sec (Stroock *et al*, 2002) there were investigation of two different groove patterns, slanted groove and staggered The so-called staggered herringbone mixer can work well at low Reynolds number. Fabrication of MEMS based technology has been established with a solid foundation. Its ability to provide highly precise structures and compatibility with standard fabrication methods makes it very attractive to anyone working with microstructures. Recently, a surge in polymer-based Microsystems has taken off and allowed for rapid advancement in microfluidic technology (Beebe *et al*, 2000) At small scales, using conventional mixing methods (such as turbulence generation) is almost impossible yet diffusion can be too slow, While MEMS mixers, pumps, and valves have previously existed. However effective planar system utilizing novel mixing, valving, and bonding processes in order to deliver well mixed fluids at controllable flow rates is still required for many microfluidic devices, with applications ranging from drug solution dilution to reagent introduction for

chemical analysis. A fabrication of passive planar micromixer with obstructions for mixing at low Reynolds is reported(Asgar *et al*, 2007) show excellent mixing performance over a wide range of flow conditions, particularly in the low *Re* range (*Re* < 1) which is the characteristic of microchannel flows in LOC. Using the silicon bulk micromachining technology, a ring electroosmotic micromixer, which uses a novel arrangement of electrodes and flow obstacles to induce chaotic mixing, has been designed and fabricated. The design idea uses heavily doped silicon as the fabrication material, and SOI wafer to ensure the electrical isolation of the device from the substrate (Abbas *et al*, 2009) It was reported a design and fabrication of mechanically supported mixer through an ultrasonic vibration (yang *et al*, 2001; Kua-Kang Liu *et al*, 2010).

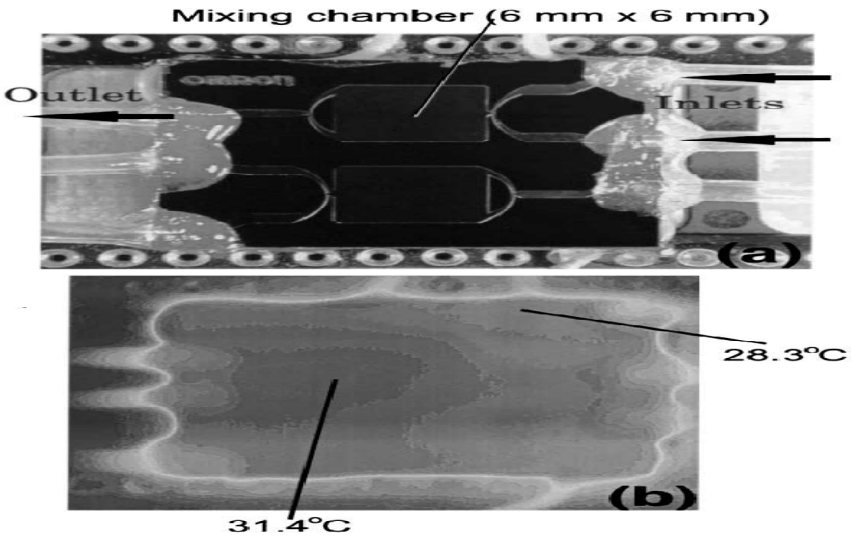

Fig. 7: Photograph of mixing device (Yang *et al*, 2001).

Micro pumps:

Controlling fluid flow is crucial in microfluidic devices, especially for processing biochemical reactions. Such a process generally relies on active control by mechanical pressure electroosmotic force. electro wetting. and electrochemical reaction. These active manipulations enable close control in a rapid and precise manner. Electrokinetic sampling has been widely used for microfluidic chip, especially for microfluidic chip electrophoresis, because the electric field can be easily and precisely applied to the reservoirs on the chip. The popular mechanism used for these active micropumps is electrokinetic force (Marmottant *et al*, 2001; Jun *et al*, 1998). Based on the mechanism, various micropumps such as Dielectrophoresis, asymmetric electric field, electroosmosis and electrophoresis (the latter two are considered as part of the electro hydrodynamic (EHD) phenomena) have been developed. Moving sample fluids and reagents on a biosensing microfluidic device requires developing a pressure difference in the flow path to direct fluid in one direction or another. Miniaturized versions of positive-displacement pump designs such as gear or peristaltic pumps have been proposed for microfluidic applications, but these all require some external power source or repetitive motion to control(Harrison *et al*, 1993; Huh *et al*, 2003). It is desirable for fluidic motion in a passive microfluidic system design to be driven by a readily available force such as gravity, capillary action, absorption in porous materials, chemically induced pressures or vacuums (e.g., by a reaction of water with a drying agent), or by vacuum and pressure generated by simple manual action. Wicking and capillary action have been widely used to motivate fluids for POC diagnostics. For example, low cost lateral flow tests demonstrate the elegant and inexpensive use of wicking to drive multiple sample types through all steps of an assay (Gallordo *et al*, 1999; Green *et al*, 2000). One of the simple methods for transporting fluids on microfluidic devices is to apply pressure manually to deflect a diaphragm (Brown *et al*, 2000; Morthy *et al*, 2004) Diaphragm membrane pumps have been demonstrated successfully in moving fluid on a microfluidic device. However, it is not easy to control the flow rate in a reproducible way. Reported a gravity microfluidic pump for producing constant flow rate (Zhu *et al*, 2002). This passive system employs a microchannel and a gravity-driven pump consisting of horizontally oriented reservoirs that supply fluid to the microchannel at a substantially constant rate. The passive device may be useful for numerous microfluidic applications such as cell-size sorting (Huh et at, 2002) The pumps have been developed based on osmotic pressure as the actuation mechanism have been used in many drug-delivery applications to deliver medication over a prolonged period of time (Su et al, 2002; Su et al, 2004). The advantages of these pumps include simple construction and the absence of moving parts. Another passive

system involves controlled evaporation of a liquid into a chamber with an absorption agent flow (Effenhauser *et al*, 2002) As fluid evaporates from the channel, capillary forces induce fluid flowing from reservoir to replace the evaporating fluid. This micro pump has advantages of low cost, high reliability and constant flow rate over a long period of time. The major disadvantage of the evaporation micro pump is the need to control environmental conditions for constant flow rates and lower flow rates. The micropumps have also been developed by employing fluid-responsive polymers to deliver fluids (Eddington *et al*, 2004). Fluid-responsive polymers swell when exposed to certain environmental conditions, such as changes in moisture, pH, or temperature. One recent fluid-responsive pump consists of an array of responsive polymers that deforms a flexible membrane made from PDMS and produces flow rates (Kua-Kang Liu *et al*, 2010) The disadvantage of the pump is the requirement of pressure to inject the buffer solution in order to active the pump.

The microfluidic system is one of the applications of MEMS, and the micro pump is a crucial device in a microfluidic system. Various types of micropumps have been developed. Earlier designs of micropumps were based on passive check valves (Kua-Kang Liu *et al*, 2010) When a diaphragm is actuated to supply fluid to a chamber, the inlet valve is open and the outlet valve is closed and the valve function is reversed when the diaphragm pumps the fluid to the outlet. This kind of pump has a high rectification efficiency, as defined for diffusion pumps ~see later!, which has a theoretical value of 1.0. However, fabrication of mechanical moving parts is complicated, and the probability of mechanical failure is high. As an alternative, valveless micropumps were proposed such as the electro-osmotic pump and the electro hydrodynamic pump for which electrokinetic phenomena are used to drive the fluid (Kua-Kang Liu *et al*, 2010) Normally, specific types of fluid are required for these pumps and the pumping efficiency depends on the ionic or charge level of the fluid, which limits the use of these pumps as a general purpose microfluidic device.

Design and fabrication of a multi-material high-performance micro pump was presented in. Exceptional flow rates of 80 ml/min were achieved by appropriate design optimization (Amirouche *et al*, 2009; Hetz *et al*, 2009; Heywang *et al*, 2009) figure 8a and b. Piezoelectric Actuated Valveless Micropumps (PAVM) has been designed and successfully fabricated using MEMS fabrication processes. A PZT: Pb (ZrTi) Ox (lead titanate zirconate) disc is used to actuate a silicon membrane by applying an alternating electrical field across the actuator. A report on laser machining technique to fabricate valveless diffuser micropumps using polymer as the base material (Kim *et al*, 2004) The micropumps showed a flow rate up to 50 mm3/min at a frequency of 180 Hz figure 8c and d.

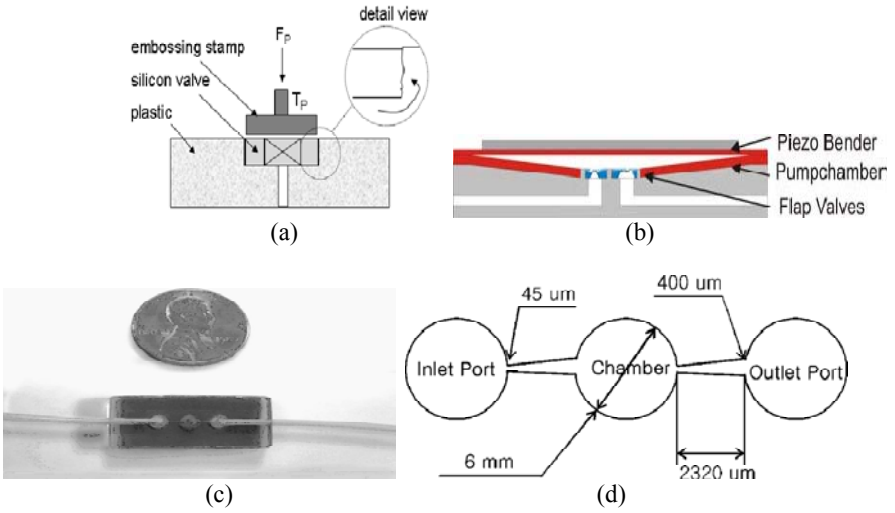

Fig. 8: Micropumps design and fabrication (a) micropumps fabrication by embossing stamp (b) Micropumps design for embossing stamp (c) Assembled diffuser polymer micropumps (d) Schematic of diffusers and the chamber(Amirouche *et al*, 2009; Hetz *et al*, 2009; Heywang *et al*, 2009; Kim *et al*, 2004).

Micro valves:

The development of valves for microfluidic systems has been progressing rapidly in recent years. The applications of the microvalves include flow regulation, on/off switching, or sealing of biomolecules, micro or nano particles, chemical reagents, oils, water, bubbles, gases, vacuum and many others. Most of them generally can be divided into two major categories: active microvalves and passive microvalves. Most active microvalves mechanically actuate moving parts using magnetic, electric, piezoelectric, thermal or other actuation methods.

However, the complexity, high cost and external supporting equipment has largely limited the application of active microvalves. Alternatively, passive microvalves are desirable due to their structure simplicity, easy integration and miniaturization of a system. Passive microvalves can normally be categorized as two categories as with and without moving parts. The passive microvalves with moving parts, also called check valves, are incorporated in inlets and outlets of micropumps as mechanical moving parts, such as flaps (Brain T *et al*, 2006) membranes spherical balls or mobile structures (Kua-Kang Liu *et al*, 2010). The passive valves with moving parts only open to forward pressure, excising diode-like characteristics. The one-way behaviour of check valves significantly affects the pumping performance of reciprocal displacement micropumps. Leakage in the check valves reduces backpressure and pumping rate in the micropumps. The passive microvalves without moving parts; e.g., using nozzle diffuser (Kua-Kang Liu *et al*, 2010) or Tesla (Morris *et al*, 2003; Feldt *et al*, 2002) elements, have been widely used in inlets and outlets of micropumps.

Another method to control fluid flow, taking advantage of the large surface-to-volume ratio in microfluidic systems, is the passive capillary microvalves which utilizes the geometries or the surface wetting properties in the microchannels (Kua-Kang Liu *et al*, 2010) The passive microvalves using capillary effects are useful for passive biosensing microfluidics since autonomous and spontaneous valving can be realized due to the geometry and surface wettability properties (Pan *et al*, 2005; Yamahata *et al*, 2005) of the microchannels. These passive capillary valves are used preferably to block and pass fluidic flows for avoiding the valve-actuation-induced interference with biofluids due to the actuation energy of microvalves (Leu *et al*, 2004) PDMS membrane microvalves with an in situ polymerized seal embedded in a rectangular channel. We locally fabricated the polymer sealed valve and compare it to a typical microvalves in a rectangular channel without a polymeric seal was presented in and demonstrated the equivalent functionality of the approach to curved channel microvalves by demonstrating a well functioning micropumps and droplet generator(Park *et al*, 20110) Membrane type pneumatic microvalves are the most common microvalves in PDMS microfluidic devices and are used in many applications(Ckoi *et al*, 2007; Wu *et al*, 2008; Monat *et al*; 2008; Zhang *et al*, 2008; Noort *et al*, 2009) When the fluidic channel is rectangular it is impossible to completely shut off the flow since the curvature of the expanding membrane is round. For this reason, rounded microfluidic channels are used. Rounded microfluidic channels are molded from rounded molds fabricated through a resist reflow process. Reshaping happens due to surface tension of the melted 'reflowed' resist on the unmelted resist. The maximum channel thickness that can be achieved by using conventional positive resist is tens of micrometres, limiting the height of the rounded fluidic channel. Other resists such as SU-8 can allow for high aspect ratio structures, but cannot be reflowed since they are highly cross-linked and thermally stable. Since thermal 'reflow' is not required using the method presented here, materials such SU-8 can be used (Anderson *et al*, 2004; Garcia-Alonso *et al*, 2009).

Microfluidics Applications for life sciences:

Microfluidic systems have provided new opportunities for the advancement in several emerging biomedical applications such as tissue engineering, drug delivery/testing, and stem cell therapy With the current technology in placed it is highly Tissue engineering aims to cultivate engineered tissues by harvesting cells from patient or donor and then seeding/culturing them on bio mimetic scaffolds, fabricated from natural or man-made biomaterials. However, creating 3-D engineered tissue has been limited by how to effectively arrange cells and distribute nutrients into the scaffold during the formation of tissue constructs. To tackle this problem, MFS has recently been used as a tool for fabricating novel "Microfluidic Scaffolds". As such, embedding microfluidic networks directly within cell-seeded scaffolds can facilitate convective mass transfer for control of the distributions and fluxes of solutes in the bulk of the 3D culture (Kua-Kang Liu *et al*, 2010) Microfluidic systems have also been used to develop perfusion-based micro 3-D cell culture platforms for high throughput drug testing (Ckoi *et al*, 2007; Wu *et al*, 2008) The microfluidic system fabricated based on soft lithography of PDMS and incorporated pneumatic-based pumping culture medium and cell-scaffold loading mechanism to form the cell culture platform has demonstrated to provide a homogenous and steady cell culture environment which will be useful for tissue engineering applications. Microfluidic system can be easily integrated with microphotonics such as optical trapping to form micro-opto-fluidic system (MOFS) for single cell manipulation (Monat *et al*, 200) Cultivating single cell in the MOFS can produce homogeneous daughter cells, which have a significant impact on stem cell therapy. The method can potentially apply for the stem cell delivery or the creation of stem cell niche that is to create a microenvironment consisting of various pluripotent cells, appropriate biochemical solutions and mechanical stimuli, e.g., flow shear stress, for fostering stem cells to differentiate into desirable tissues. Recently MFS incorporated with holographic optical tweezers to form a platform which can potentially be used as a reconfigurable force sensor array with Pico Newton resolution to investigate chemo-mechanical processes. This new technique may provide a powerful tool for multi-cellular manipulation in the cell arrangements and stimuli of engineered tissue. MFS has also been used for the development of *in vitro* physiological systems for studying fundamental biological phenomena for tissue growth. Microfluidic chips have also provided an excellent approach for cell-based screening and detection of

different toxicities. This technique can provide a low cost, fast speed, *Sensors* **2010**, *10* **6650** high throughput screening for testing different metabolic responses to drug on a cellular level and hence will be useful for *in-situ* tissue growth monitoring and drug testing. Microfluidic system can uniquely serve as a functional tool for studying cell mechanics which is important for the advancement of drug delivery and tissue engineering. A recent review has comprehensively highlighted its capabilities that are of significance for understanding the mechanical behaviours of cells (Anderson *et al*, 2004; Garcia-Alonso *et al*, 2009; Kua-Kang Liu *et al*, 2010)

Conclusion:

In the Micro and Nanofluidics technologies**,** the characteristics of PDMS are particularly useful in prototyping new systems and in studies of fundamental fluid mechanics. Since the fabrication of systems in PDMS is simple, chemists and biologists working at a bench top can make devices quickly and easily. As the focus of microfluidics shifts from demonstration of components and devices to development of fully functional devices, the ease of production of multi functional systems will become more important. Probably no single device will be able to take full advantage of the properties of PDMS, and as with all materials, some properties of PDMS may be advantageous or detrimental depending on the application. PDMS has been applied primarily to aqueous solutions, since non polar organic solvents swell it. The high solubility of non polar compounds (including organic solvents) can also be an advantage, for example, in removing small amounts of organic contaminants from an aqueous sample prior to analysis While PDMS is a useful material for prototyping microfluidic devices, its application to commercial systems remains to be established and also PDMS has the ability to seal reversibly and irreversibly to many materials and to encapsulate microelectronic and optical components. This ability to integrate systems easily is crucial to the development of complex, multifunctional microfluidic systems.

References

Abbas, A., P. Supiot, V. Mille, D. Guillochon and B. Bocquet, 2009. Capillary microchannel fabrication using plasma polymerized TMDS for fluidic MEMS technology, Journal of Micromechanics and Micro engineering, 19(4).

Ali Asgar S., Bhagat, Erik T.K. Peterson and Ian Papautsky, 2007. A passive planar micromixer with obstructions for mixing at low Reynolds numbers, J. Micromech. Microeng, 17: 1017-1024.

Amirouche, F., Y. Zhou and T. Johnson, 2009. Current micropump technologies and their biomedical applications, Microsystem Technologies, 15(5): 647-666.

Andersson, H., W.v.d. Wijngaart, P. Nilsson, P. Enoksson, G. Stemme, 2001. A valve-less diffuser micropump for microfluidic analytical systems. Sens. Actuator. B., 72: 259-265.

Andersson, H., A.v.d. Berg, 2004. Microfabrication and Microfluidics for Tissue Engineering: State of the Art and Future Opportunities. Lab Chip., 4: 98-103.

Aveek N. Chatterjee, Donald M. Cannon Jr., Enid N. Gatimu, Jonathan V. Sweedler, Narayana R. Aluru and Paul W. Bohn, 2005. Modeling and simulation of ionic currents in three-dimensional microfluidic devices with Nanofluidics interconnects, Journal of Nanoparticle Research, 7: 507-516.

Bien, D.C.S., S.J.N. Mitchell, H.S. Gamble, 2003. Fabrication and characterization of a micromachined passive valve. J. Micromech. Microeng., 13: 557-562.

Borman, S., 1999. Microchips deliver on command Chem. Eng. News, 5: 30-1.

Brian, T., N. Christopher, R.H. Davis, 2006. An effervescent reaction micropump for portable microfluidic systems. Lab Chip., 6: 659-666.

Brown, A.B., C.G. Smith, A.R. Rennie, 2000. Pumping of water with ac electric fields applied to asymmetric pairs of microelectrodes. Phys. Rev. E., 63: 16305.

Byung-Ho Jo, Linda M. Van Lerberghe, Kathleen M. Motsegood and David J. Beebe, 2000. Three-dimensional micro-channel fabrication in polydimethylsiloxane (pdms) elastomer, journal of icroelectromechanical systems, 9(1).

Choi, N.W., M. Carbodi, B. Held, J.P. Gleghorn, L.J. Bonassar, 2007. Microfluidic Scaffolds for Tissue Engineering. Nat. Mater., 6: 908-915.

Chow, A., A. Kopf-Sill, T. Nikiforov, A. Zhou, J. Coffin, G. Wada, L. Alajoki, M. Spaid, Y. Yurkovetsky, S. Sunberg and J.W. Parce, 2000. "High-throughput screening on microchips", Proceedings of the μ-TAS 2000 Symposium,Enschede, the Netherlands, May, 489-492.

Da-Jeng Yao and Po-Yu Chen, 2007. Room Temperature Microchannel Fabrication for Microfluidic System Proceedings of the 7th IEEE International Conference on Nanotechnology August 2 - 5, Hong Kong.

Beebe, D.J., J.S. Moore, Q. Yu, R.H. Liu, M.L. Kraft, B.H. Jo, C. Devadoss, 2000. "Microfluidic tectonics: A comprehensive construction platform for microfluidic systems," *PNAS*, Dec. 5., 97(25): 13488-13493.

Baltussen, E., P. Sandra, F. David and C. Cramers, 1999. Microcolumn Sep., 11: 737-747.

Eddington, D.T., D.J. Beebe, 2004. A valved responsive hydrogel microdispensing device with integrated pressure source. J. Microelectromech. Syst., 13: 586-593.

Effenhauser, C.S., H. Harttig, P. Kramer, 2002. An evaporating-based disposable micropump concept for continuous monitoring applications. Biomed. Microdevices, 4: 27-32.

Feldt, C., L. Chew, 2002. Geometry-based macro-tool evaluation of non-moving-part valvular microchannels. J. Micromech. Microeng., 12: 662-669.

Figeys, D. and D. Pinto, 2000. "Lab-on-a-chip: a revolution in biological and medical sciences", Analytical Chemistry- A page, 72(9): 330A-335A,

Ford, S.M., J. Devices, B. Kar, S.D. Qi, S. McWhoter, S.A. Soper, C.K.J. Malek, 1999. Biomech. Eng., 121: 13-21.

Freemantle, M., 1999. Downsizing chemistry Chem. Eng. News, 8: 27-36.

Gallardo, B.S., V.K. Gupta, F.D. Eagerton, L.I. Jong, V.S. Craig, R.R. Shah N.L. Abbott, 1999. Electrochemical principles for active control of liquids on submillimeter scales. Science, 283: 57-60.

Garcia-Alonso, J., G.M. Greenway, J.D. Hardege, S.J. Haswell, 2009. A Prototype Microfluidic Chip using Fluorescent Detection of Toxic Compounds. Biosens. Bioelectron., 24: 1058-1511.

Gerlach, T., 1998. Microdiffusers as dynamic passive valves for micropump applications. *Sens. Actuator. A.*, 69: 181-191.

Green, N.G., A. Ramos, A. Gonzalez, H. Morgan, A. Castellanos, 2000. Fluid flow induced by nonuniform ac electric field in electrolytes on microelectrodes: I. Experimental measurements. Phys. Rev. E., 61: 4011-4018.

Theodoridis, G., M. Aikaterini Lontou, F. Michopoulos, M. Sucha and T. Gondova, 2004. Anal. Chem. Acta, 516: 197-204.

Harrison, D.J., K. Fluri, K. Seiler, Z. Fan, C.S. Effenhauser, A. Manz, 1993. Micromachining a miniaturized capillary electrophoresis-based chemical analysis system on a chip. Science, 261: 895-897.

Becker, H., L.E Locatio, 2002. Talata, 56: 267.

LeMinh, H.W.J.H.P., J.W. Berenschot, N.R. Tas, 2003. A van den Berg, "Novel integration of a microchannel with a silicon light emitting diode antifuse," J. Micromech.

Herz, M., D. Horsch, T. Lueth, M. Richter, 2009. Modellierung, Optimierung und experimentelle Verifizierung piezoelektrischer Biegeaktoren für Mikropumpen, Conference Proceedings, MikroSystemTechnik Kongress, 12.- 14th October, pp: 274-277.

Huh, D., A.H. Tkaczyk, J.H. Bahng, Y. Chang, H.H. Wei, J.B. Grotberg, C.J. Kim, K. Kurabayashi, S.J. Takayama, 2003. Reversible switching of high-speed air-liquid two-phase flows using electrowetting-assisted flow-pattern change. J. Am. Chem. Soc. 125: 14678-14679.

Huh, D., H.H. Wei, O.D. Kripfgans, J.B. Fowlkes, J.B. Grotberg, S. Takayama, 2002. Gravity-Driven Microhydrodynamics-Based Cell Sorter (microHYCS) for Rapid, (2002) Inexpensive and Efficient Cell Separation and Size-Profiling. In *Proceedings of the 2nd IEEE-EMBS Special Topics Conference on Microtechnologies in Medicine & Biology*, Madison, WI, USA, May, pp: 466-469.

Ismagilov, R.F., A.D. Stroock, P.J.A. Kenis, G.M. Whitesides, H.A. Stone, 2000. Experimental and theoretical scaling laws for transverse diffusive broadening in two-phase laminar flows in microchannels. Appl. Phys. Lett., 76: 2376-2378.

Jackman, R.J., T.M. Floyd, R. Ghodssi, M.A. Schmidt, K.F. Jensen, 2001. Microfluidic systems with on-line UV detection fabricated in photodefineable epoxy. J. Micromech. Microeng, 11: 263-269.

Jang, W.I., C.A. Choi, C.H. Jun, Y.T. Kima, M. Esashi, 2004. Surface micromachined thermally driven micropump. Sens. Actuator. A. 115: 151-158.

Eijkel, J.C.T. and A. van den Berg, 2005. Microfluidics/ Nanofluidics, 1: 249.

McDonald, J.C., G.M. Whitesides, 2002. "Poly(dimethylsiloxane) as a Material for Fabricating Microfluidic Devices," *Accounts of* Chemical Research, 35(7): 491-499.

Cooper McDonald, J., C. David, Duffy, Janelle R. Anderson, Daniel T. Chiu, Hongkai Wu, Oliver J.A. Schuller, George M. Whitesides, 2000. Fabrication of microfluidics systems in Polydimethylsiloxane, Journal of Electrophoresis, 21: 27-40.MA. USA.

Gardeniers, J.G.E., R.W. Tjerkstra, A. Van den Berg, 2000. Fabrication and application of silicon-based Microchannels, in: W. Ehrfeld (ed), Microreaction Technology: Industrial Prospects, Springer, Berlin, 36.

YueFei, J.I.A., J.I.A.N.G. JiaHuan, M.A. XiaoDong, L.I. Yuan, HUANG HeMing, C.A.I. KunBao, C.A.I. ShaoXi and W.U. YunPeng1, 2008. PDMS microchannel fabrication technique based on microwire-molding, Chinese Science Bulletin.

Lee, J.N., C. Park and G.M. Whitesides, 2003. Anal. Chem., 75: 6544-6554.

Johnson, T.J., D. Ross, L.E. Locascio, 2002. Rapid microfluidic mixing. Anal. Chem., 74: 45-51.

Joohan Kim, Xianfan Xu, 2004. "Laser-based fabrication of polymer micropump" 2004 Society of Photo-Optical Instrumentation Engineers. [DOI: 10.1117/1.1631923]JM3, 3(1): 152-158.

Jun, T.K., C.J. Kim, 1998. Valveless pumping using traversing vapor bubbles in microchannels. J. Appl. Phys. 83: 5658-5664.
Kamholz, A.E., B.H. Weigl, B.A. Finlayso, P. Yager, 1999. Quantitative analysis of molecular interactive in microfluidic channel: the T-sensor. Anal. Chem., 71: 5340-5347.
Kamholz, A.E., P. Yager, 2002. Molecular diffusive scaling laws in pressure-driven microfluidic channels: deviation from one-dimensional Einstein approximations. Sens. Actuators B., 82: 117-121.
Knight, J., 2002. Honey, I shrunk the lab Nature, 418: 474-5.
Koch, M., A.G.R. Evans, A. Brunnschweiler, 2010. The dynamic micropump driven with a screen printed PZT actuator. J. Micromech. Microeng., 8: 119-122. *Sensors*, *10* 6653.
Koch, M., H. Witt, A.G.R. Evans, A. Brunnschweiler, 1999. Improved characterization technique for micromixers. J. Micromech. Microeng., 9: 156-158.
Kopp, M.U., A.J. deMello, A. Manz, 1998. "Chemical amplification: continuous-flow PCR on a chip", Science, 280: 1046-1048.
Kuo-Kang Liu, Ren-Guei Wu, Yun-Ju Chuang, Hwa Seng Khoo, Shih-Hao Huang and Fan-Gang Tseng, 2010. Microfluidic Systems for Biosensing, Sensors 10: 6623-6661.
Leu, T.S., P.Y. Chang, 2004. Pressure barrier of capillary stop valves in micro sample separators. Sens. Actuators A., 115: 508-515.
Bennett, M., B.J. Brisdon, R. England and R.W. Field, 1997. J. Membr. Sci., 137: 63-88.
Manz, A., N. Graber, H.M. Widmer, 1990. "Miniatured total chemical analysis systems: a novel concept for chemical sensing", Sensors & Actuators B-Chemical, B1, 244-248, Switzerland.
Marmottant, P., S. Hilgenfeldt, 2004. A bubble-driven microfluidic transport element for bioengineering. Proc. Natl. Acad. Sci., 101: 9523-9527.
Melin, J., N. Roxhed, G. Gimenez, P. Griss, W.v.d. Wijngaart, G. Stemme, 2004. A liquid-triggered liquid microvalve for on-chip flow control. Sens. Actuators B., 100: 463-468.
Michael W. Toepke and David J. Beebe, 2006. PDMS absorption of small molecules and consequences in microfluidic applications, Lab Chip, 6: 1484-1486.
Monat, C., P. Domachuk, C. Grillet, M. Collins, B.J. Eggleton, M. Cronin-Golomb, S. Mutzenich, T. Mahmud, G. Rosengarten, A. Mitchell, 2008. Optofluidics: a Novel Generation of Reconfigurable and Adaptive Compact Architectures. Microfluid. Nanofluid., 4: 81-95.
Moorthy, J., G.A. Mensing, D. Kim, S. Mohanty, D.T. Eddington, W.H. Tepp, E.A. Johnson, D.J. Beebe, 2004. Microfluidic tectonics platform: A colorimetric, disposable botulinum toxin enzyme-linked immunosorbent assay system. Electrophoresis, 25: 1705-1713.
Morris, C.J., F.K. Forster, 2003. Low-order modeling of resonance for fixed-valve micropumps based on first principles pump. J. Microelectromech. Syst., 12: 325-334.
Muhammad S. Virk1, Arne. E. Holdo2 and S. Kaennakham, 2007. "Numerical Analysis of Fluid Mixing in T-Shape Micro Mixer", Proceedings of the COMSOL Users Conference Grenoble.
Nguyen, N.T., T.Q. Truong, K.K. Wong, S.S. Ho, C.L. Low-N, 2004. Micro check valves for integration into polymeric microfluidic devices. J. Micromech. Microeng., 14: 69-75.
Noort, D.V., S.M. Ong, C. Zhang, S. Zhang, S. Arooz, H. Yu, 2009. Stem Cell in Microfluidics. Biotechnol. Prog., 25: 52-60.
Ogura, J.M., Y. Agala, K. Watanabe, R.M. McCormick, Y. Hamaguchi, Y. Aso, 1998. Mitsuhashi, M., Clin. Chem., 44: 2249-2255.
Pan, T., S.J. McDonald, E.M. Kai, B. Ziaie, 2005. A magnetically driven PDMS micropump with ball check-valves. J. Micromech. Microeng, 15: 1021-1026.
Ramsey, J.M., S.C. Jacobsen, M.R. Knapp, 1995. Nature Med., 1: 1093-1096.
Tjerkra, R.W., M.J. deBoer, J.B. Berenschot, J.G.E Gardeniers, M.C. Elenspoek, 1997. A. Van den Berg, Proc, IEEE workshop on MEMS, Nagoya, Japan, 147.
Sia, S.K., G.M. Whitesides, 2003. Microfluidic Devices Fabricated in PDMS for Biological Studies. Electrophoresis, 24: 3563-3576.
Howitz, S., 1999. Components and system for micro liquid handling, in: J. M. Kohler, T. Mejevaia, H.P Saluz, Microsystem Technology: A power Tool for Biomolecular studies, Birhkhauser Verlag, Basel, 31.
Stemme, E., G. Stemme, 1993. A valveless diffuser/nozzle-based fluid pump. Sens. Actuator. A., 39: 159-167.
Stroock, A.D., S.K.W. Dertinger, A. Ajdari, I. Mezi, H.A. Stone, G.M. Whitesides, 2002. Chaotic mixer for microchannels. Science, 295: 647-651.
Su, Y.C., L.W. Lin, 2004. A water-powered micro drug delivery system. J. Microelectromech. Syst., 13: 75-82.
Su, Y.C., L.W. Lin, A.P. Pisano, 2002. A water-powered osmotic microactuator. J. Microelectromech. Syst., 11: 736-742.
Uhrig, K., R. Kurre, C. Schmitz, J.E. Curtis, T. Haraszti, A.E. Clemen, J.P. Spatz, 2009. Optical Force Sensor Array in a Microfluidic Device based on Holographic Optical Tweezers. Lab Chip., 9: 661-668.
Van den Berg, A., P. Bergveld, (Ed.), 1995. Micro Total Analysis system, Kluwer, Boston.

Vanapalli, S.A., M.H.G. Duits, F. Mugele, 2009. Microfluidics as a functional tool for cell mechanics. Biomicrofluidics, 3: 012006.

Veenstra, T.T., T.S.J. Lammerink, M.C. Elwenspoek, A.v.d. Berg, 1999. Characterization method for a new diffusion mixer applicable in micro flow injection analysis systems. J. Micromech. Microeng, 9: 199-202.

Walter Heywang, Karl Lubitz, Wolfram Wersing, 2008. Piezoelectricity: Evolution and Future of a Technology, Springer Berlin.

Wang, H., P. Iovenitti, E. Harvey, S. Masood, 2002. Optimizing layout of obstacles for enhanced mixing in microchannels. Smart Mater. Struct., 11: 662-667.

Chang, W.J., D. Akin, M. Sedlak, M. R. Ladisch and R. Bashir, 2003. Biomed. Microdev., 5: 281-290.

Wook Park, Sangkwon Han and Sunghoon Kwon, 2010. "Fabrication of membrane-type microvalves in rectangular microfluidic channels via seal photo polymerization" Lab on a Chip, 29th July.

Wu, M.H., S.B. Huang, Z. Cui, Z. Cui, G.B. Lee, 2008. Development of perfusion-based micro 3-D culture platform and its application for high throughput drug testing. Sensor. Acuat. B. 129: 231-240.

Yamada, M., M. Seki, 2004. Nanoliter-sized liquid dispenser array for multiple biochemical analysis in microfluidic devices. Anal. Chem., 76: 895-899.

Yamahata, C., F. Lacharme, Y. Burri, M.A.M. Gijs, 2005. A ball valve micropump in glass fabricated by powder blasting. Sens. Actuator. B., 110: 1-7.

Yan, L.S., N. Liang, G.A. Luo, *et al*., 2003. Rapid fabrication of monolithic PDMS microchips and highly sensitive chemiluminescence detection for amino acids. Chem J Chinese Univ., 7(7): 1193-1197.

Zhang, H., K.K. Liu, 2008. Optical Tweezers for Single Cells. J. R. Soc. Interface, 5: 671-690.

Zhen Yang, Sohei Matsumoto, Hiroshi Goto, Mikio Matsumoto, Ryutaro Maeda, 2001. Ultrasonic micromixer for microfluidic system, sensors and actuators A, 93: 266-272.

Zhu, X., N. Phadke, J. Chang, B. Cho, D. Huh, S. Takayama, 2002. Gravity-Driven Microfluidic Pump with a Steady Flow Rate. In *Proceedings of the Micro Total Analysis Systems.* Nara, Japan, November, pp: 151-153.