Video Article

High Throughput Microfluidic Rapid and Low Cost Prototyping Packaging Methods

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Abstract

In this work, 3 different packaging and assembly techniques are presented. They can be classified into two categories: one-time use and reusable packaging techniques.

The one-time use packaging technique employs UV-based and temperature curing epoxies to connect microtubes to access holes, wire-bonding for integrated circuit connections, and silver epoxy for electrical connections. This method is based on a robust assembly technique that can support relatively high pressure close to 1 psi and does not need any support to strengthen the microfluidic architecture.

Reusable packaging techniques consist of PDMS-based microtube interconnectors and anisotropic adhesive films for electrical connections. These devices are more sensitive and fragile. Consequently, Plexiglas support is added to the microfluidic structure to improve the electrical contact when anisotropic adhesive films are used, and also to strengthen the microfluidic architecture. In addition, a micromanipulator is needed to maintain tubes while using a thin PDMS layer to connect them to the access holes. Different PDMS layer thicknesses, ranging from 0.45-3 mm, are tested to compare the best adherence versus injection rates. Applied injection rates are varied from 50-300 µl/hr for 0.45-3 mm PDMS layers, respectively. These techniques are mainly applicable for low-pressure applications. However, they can be extended for high-pressure ones through plasma-oxygen process to permanently seal the PDMS to glass substrates. The main advantage of this technique, besides the fact that it is reusable, consists of keeping the device observable when the microchannel length is very short (in the range of 3 mm or lower).

Video Link

The video component of this article can be found at http://www.jove.com/video/50735/

Introduction

Recent progresses in microfabrication have led to more complex microfluidic devices including a large number of electrodes and different types of control algorithms. However, these advances highlighted new challenges in packaging. Furthermore, Lab-on-Chip (LoC) is a multidisciplinary concept where microfluidic devices, microelectromechanical systems (MEMS), microelectronic chips among other parts are connected together. Consequently it is impossible to develop a packaging process without considering different constraints of LoC components such as microelectronics circuitry sensitivity and protection, tubing, and mechanical aspects. In addition, packaging the components of a given LoC is closely related to the application[1,2]. As an example, in optical applications, the transparence of the device is crucial, especially for testing purposes. Thus, it is important to monitor system behavior by keeping the device observable. In applications related to cell or particle manipulations, using low-voltage techniques is more attractive, with the emergence of new microfabrication technologies which facilitate reduced electrode dimensions (from few a micrometers to submicron scale[3-5]) but considerably increase the number of electrodes to 100 or more.

On the other hand, LoCs dedicated for chemical and biological analysis require long-term observation. Thus, the system packaging and test bench must avoid biological contamination as well as any failure in the electronic devices of LoC in addition to keeping the system observable.

In recently published papers, microfluidic and MEMS are the main parts of a LoC, but other modules may be used for the monitoring of the system. Consequently, testing and validating microfluidic architectures became a challenging issue with the new microfabrication approaches and the high complexity and throughput architectures. Up to now there are no standard testing platforms or supports for microfluidic system, as it is the case for microelectronics dies.

Researchers proposed different packaging techniques for specific uses, such as Xie *et al.*[6] who designed a bio-microfluidic packaging including a microelectronics chip to control DNA separation in microfluidic channels. Beebe *et al.*[7] designed a microfluidic channel with integrated fluid reservoirs and stimuli-responsive hydrogel valves to manipulate fluid samples. Other systems propose the use of electrolytic bubble-based flow sensors to detect pressures through an electrical field to generate air bubbles and measure corresponding pressure[8]. The sensing system measures the impedance of the bubble and then determines the pressure, which requires special packaging designed to avoid introducing any interference into the measurements. In another work, a room temperature microfluidic packaging method was introduced based on sequential plasma activation process[9]. Despite the fact that this process could lead to a strongly assembled device, it has limitations when it is used for prototyping purpose or when the device is used several times. The latter may imply frequent replacement of some parts of the system. Moreover, Lee *et al.* introduced a new packaging technique, called Biolab-on-IC, based on using magnetic fields for individual magnetic bead manipulation, where the microfluidic architecture is designed on the top of the integrated circuit[10]. In addition, the reliability of packaging and integration of microfluidic systems, considering the system size, optical aspects, and connection parts, are critical issues as detailed by Han and Frazier[11]. This latter work reflects a typical approach for LoC systems, where several parameters must be precisely fixed and measured during the packaging.

Consequently, microfluidic packaging is a challenging issue for new a generation of microfluidic devices. Packaging includes heterogeneous parts such as tubing, electrical connections and microfluidic support. For tubing, the main issue is the very limited space available to connect the tubes to access the microfluidic holes. The diameter of the current commercially available connectors is in the range of 6 mm; however, the distance between the two access holes is becoming smaller with the reduction of overall system dimensions[12-13.] Therefore, we have proposed a tubing technique based on PDMS. This tubing process is specially elaborated for the prototyping phase. In fact, owing to the chemical constraint, changing the connection tube after each usage is mandatory to avoid and minimize liquid leakage inside the microstructure and to clean the microchannels. For these purposes, the described process in this paper is particularly applicable for a fast prototyping design.

On the other hand, electrical connections are critical for microfluidic devices that utilize direct or indirect electrical manipulation or measurement. Due to the wide range of microfluidic applications, device dimensions, shape, and number of electrical contacts may vary considerably. Therefore, a versatile method is required, which can be used for different applications. Kaler *et al.* reported results from their microfluidic rapid prototyping platform, which is based on zero insertion force (ZIF) connectors[14]. Instead of these later connectors, the presented methods use an anisotropic adhesive conductive film, which can be easily adapted to any shape.

Many researchers do not take into consideration the testing constraints when designing their microfluidic device. In microelectronics, there is many supports used for prototyping purpose and testing, which are called IC holders. These are mainly designed to reduce prototyping and testing times, and offer researchers and engineers an easy way to replace devices in case of failure. Similar to microelectronics, we are also proposing a new testing package for microfluidic devices limited to a 45 mm x 90 mm device size.

Our proposed techniques are targeting to cover a large number of microfluidic devices and applications. These methods can be adapted, extended and upgraded to other applications. We aim to provide one of the first versatile packaging methods for microfluidic devices that are optimized for microfluidic manipulations. For example, one end application for devices packaged with these techniques is separation of polystyrene and carboxyl modified microspheres with artificial cerebrospinal fluid. Nevertheless, they can be used in other applications with different solutions.

In the remainder of this article, three different tubing techniques, 2 electrical connection methods and one microfluidic packaging method are presented and compared.

Protocol

1. Removable PDMS-based Interconnector for Low-pressure Microfluidic Applications[15-16]

1. **Preparation**

   This section describes different steps to prepare the glass and PDMS in order to produce the interconnector.
   1. Prepare the PDMS: Mix the PDMS and curing agent with (10:1) ratio.
   2. Ensure that the oven temperature is stabilized at a constant temperature of 80 °C. Depending on the oven, use a measurement device to sense the temperature of the oven and then manually monitor it.
   3. Thoroughly clean the Petri dish with ethanol.
   4. Clean the surface of the microfluidic access holes where the PDMS interconnector will be placed.

2. **Fabrication**

   The interconnector described in this paper is essentially a compliant gasket. This gasket is formed from PDMS and contains holes into which microtubes may be inserted. It self-adheres to the surface of a microfluidic chip, to form a leak-proof seal between the microtube and access holes to microchannels in the chip.

   Use the following steps to fabricate the interconnector.
   1. Pour a thin layer (approximately 2 mm) of the PDMS (liquid) into a Petri dish.
   2. Let the PDMS slightly polymerize at a temperature of 80 °C in the oven for 12-15 min. Place the microfluidic chip to which the connection will be made in the oven at the same time, so that it will be at the same temperature.
   3. When the PDMS starts to polymerize, remove it from the curing oven.
   4. Use a biopsy punch to form holes of the desired diameter in the microfluidic chip surface.
   5. Using the blade, cut the required piece of PDMS.

      Note: It is recommended to initially cut out a larger piece of material than that will eventually be required. To avoid using multiple connectors, it is desirable that any given PDMS interconnector be cut to a square shape, and holes punched, so as to conform to the maximum possible number of holes on the user's chip.
   6. Keep the holes slightly smaller than the outside diameter of the microtube.
   7. Quickly remove the PDMS from the Petri dishes and place it onto the microfluidic chip.
   8. Ensure that there is no dust on either the PDMS or chip and ensure that the access holes on the microfluidic chip are aligned with those of PDMS.

9. Using a micropositioner, insert tubes (*e.g.* Teflon tubes) through the PDMS interconnector. The tubes should be 110% of microfluidic access hole diameter to prevent liquid leakage. The same tubes can be connected to the liquid injection system depending on the user's application.

   Note: Always place the tubes using a micropositioner, the PDMS layer is not very thick and can be detached if the tubes are twisted.
10. If necessary, add epoxy between the tube and the PDMS for better adherence.

   An example of the completed interconnector is shown in the figures and in Ghallab and Badawy[2].

2. Interconnecting Microtubes in Microfluidic Applications with Epoxy[17]

When fabricating an interconnector, ensure the edge of the microtube is correctly cut. Use a new sharp blade to cut the edge of the microtube straight and to ensure that the contact between microtubes and access hole is uniform.

1. Using the micropositioner, carefully place the microtube in the access hole of the microfluidic chip.
2. Apply a small pressure on the epoxy dispenser to deposit epoxy on the access holes or manually place it.
3. Allow the epoxy to cure using the following steps:
   1. UV curable Epoxy: Expose the UV epoxy to a UV source for 3-10 min, depending on the quantity of the epoxy used. For more details, refer to the epoxy specifications.
   2. Standard epoxy: If the microfluidic substrate is to be used only at RT, keep epoxy curing during 24 hr at RT. If the substrate is required to withstand high temperatures, rapidly solidify the epoxy by exposing it to 100 °C using an oven or a heater, depending on the application. For more details, refer to the epoxy specifications.

3. Assembly Technique for Reusable Microfluidic Chips with Electrical Interface[17]

1. **Assembling the Components**

   Figure 2 shows the links between the electrical connectors on the PCB and the electrical pads on the microfluidic chip. To assemble the PCB/microfluidic chip/Plexiglas components, follow these steps:

   CAUTION: Avoid excessive compression pressure, which can break the microfluidic chip.
   1. Solder the surface-mount multipin electrical connectors to the PCB.
   2. If there is surface contamination on the microfluidic chip's electrical pads, clean with plasma oxygen; otherwise clean the pads with ethanol.
   3. Use a sharp blade to cut the conductive tape into small pieces with the same dimensions as the microfluidic chip's electrical pads, as shown in **Figures 1** and **2**.
   4. Using forceps, place the conductive tape on the PCB electrical pads.
   5. Align and then place the microfluidic chip onto the PCB.

      Note: For placement precision, use an alignment machine.
   6. Place an insulation layer (such as paper) on the PCB to avoid short circuits before installing the metal brackets, depending on the location of the PCB traces.
   7. Attach the metal bracket using machine screws and nuts.

2. **Disassembling**
   1. Remove the machine screws, nuts and the metal brackets.
   2. Gently separate the microfluidic chip and the PCB.
   3. Use ethanol to remove the conductive tape adhesive from the electrical pads on the PCB and microfluidic chip prior to reassembly.

Representative Results

Figure 3 illustrates a detailed schematic of the proposed packaging technique. The packaging solution was tested with several PDMS thicknesses and sizes to characterize a transparent and efficient packaging process for hybrid microelectronics/microfluidic microsystems as shown in **Figures 4** and **5**. The dimensions of the designed PDMS interconnector layer are 6 mm x 6 mm and it is used to connect two access holes. However, with major commercially available connectors, it is not possible to connect more than one hole within these dimensions if space between access holes is 5 mm or less. Thus epoxy and PDMS are the best choices for tubing in this case. Different thicknesses of the PDMS interconnector are tested such as 0.45 mm, 1 mm, and 1.75 mm. The best adherence is achieved with thin PDMS layers (0.45 mm). Finally, the fabrication of the PDMS-based interconnector requires approximately 20 min.

The liquid flow speed is monitored through a microsyringe pump. Both the 0.45 mm and 1 mm PDMS layers are tested with 50 µm channel depth on a glass substrate. The PDMS adherence to glass is broken when the injection speed is 30 ml/hr and 150 ml/hr for the 0.45 mm and 1 mm PDMS layers, respectively. **Table 1** is a comparison with recently published results. In Saarela *et al.*[22] the PDMS layer is glued to the glass chip. To overcome this inconvenience, a new approach is proposed, which is based on control of the thickness of the PDMS layer interconnector.

Table 1. Main interconnector comparisons.

	Gray[24]	Lee[20]	Kua[21]	This work[1]	This work[2]
P. (psi)	315	57	30	0.07[3]	0.21[3]
V. R. (ml/hr)	N.A	N.A	N.A	30[4]	150[4]
Features	H.P	N.R	C.F.P	R	R

P.: Pressure, V.R.: Volume rate, N.A: Non Applicable, H.P.: High Pressure, C.F.P.: Custom Fabrication Process, R: Reusable, N.R: Non Reusable

[1] 0.45 mm PDMS thickness

[2] 1 mm PDMS thickness

[3] Simulation results

[4] Experimental results

This method allowed achieving good results for low-pressure liquid injection, which is why in previous works[19,20] the comparison was based on the pressure, but in this case, it was based on volume rate and pressure.

Table 2 presents a comparison between different tubing techniques detailed in this work. This comparison helps the designer to choose a suitable technique for their design, according to its use and the application of the system:

Table 2. Assembling technique comparison.

	PDMS	UV epoxy	Standard epoxy
Removable	Yes	No	No
Preparation temperature	80 °C	UV	24 °C~100 °C*
Preparation time	20 min	3 min~10 min	30 min~24 hr
Pressure	<0.5 psi	high pressure >1 psi	high pressure >1 psi
Adherence	Good	Very good	Very good
Need support system for microtubes	Yes	No**	No**
Risk of microchannel obstruction	No	Yes***	Yes***
Transparency	Yes	No	No
Accuracy	Good	Very high	Good
Alignment	Yes	No	No

Notes:

PDMS is suggested for use with low-pressure applications when the microfluidic design must be uncovered and requires fast prototyping. If it is necessary to fix the PDMS interconnector permanently to the microfluidic design; this can be achieved by using a plasma oxygen process.

Standard epoxy provides a strong interconnection technique that can be used for both low- and high-pressure applications, but it is not recommended for prototyping because it cannot be removed from the microfluidic chip. Furthermore, it is not suitable for designs where the distance between the access holes is less than 5 mm because during the fabrication, the epoxy may spread over the chip surface.

UV epoxy has the same properties as standard epoxy but has the advantage of solidifying in just a few minutes depending on the UV light.

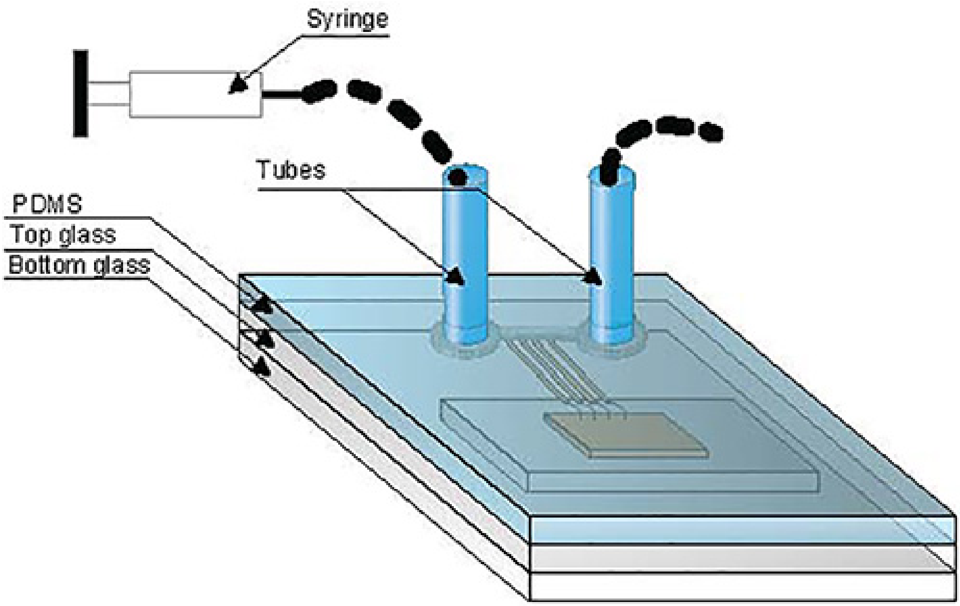

Figure 1. Microfluidic-PCB connection. (**a**) No established connection, (**b**) Microfluidic-PCB connection with good alignment and (**c**) bad alignment.

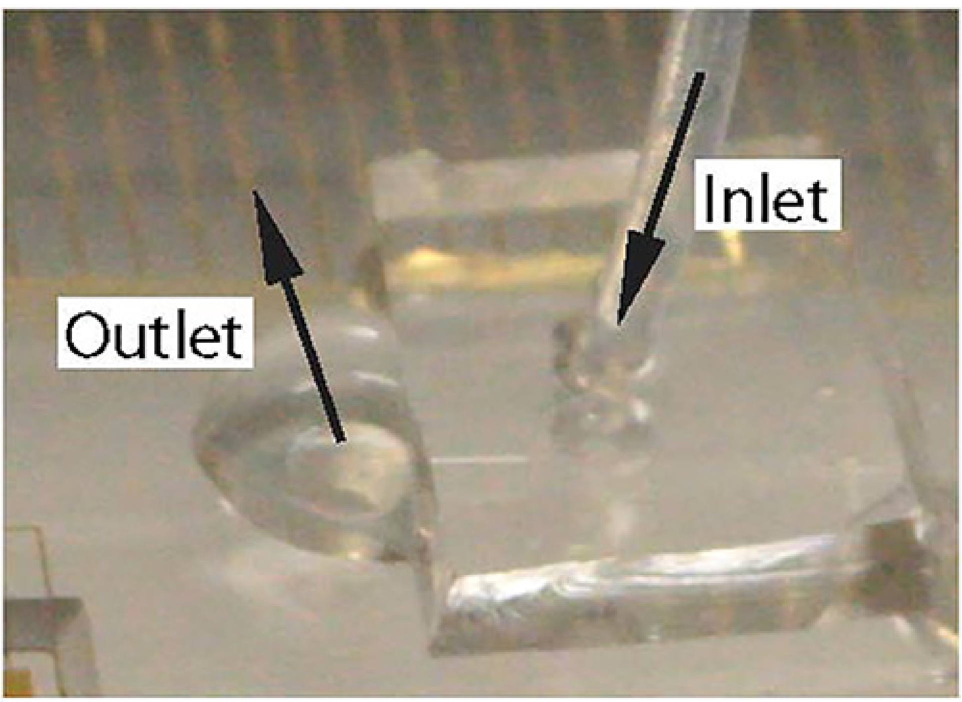

Figure 2. Example of assembled device using ACF.

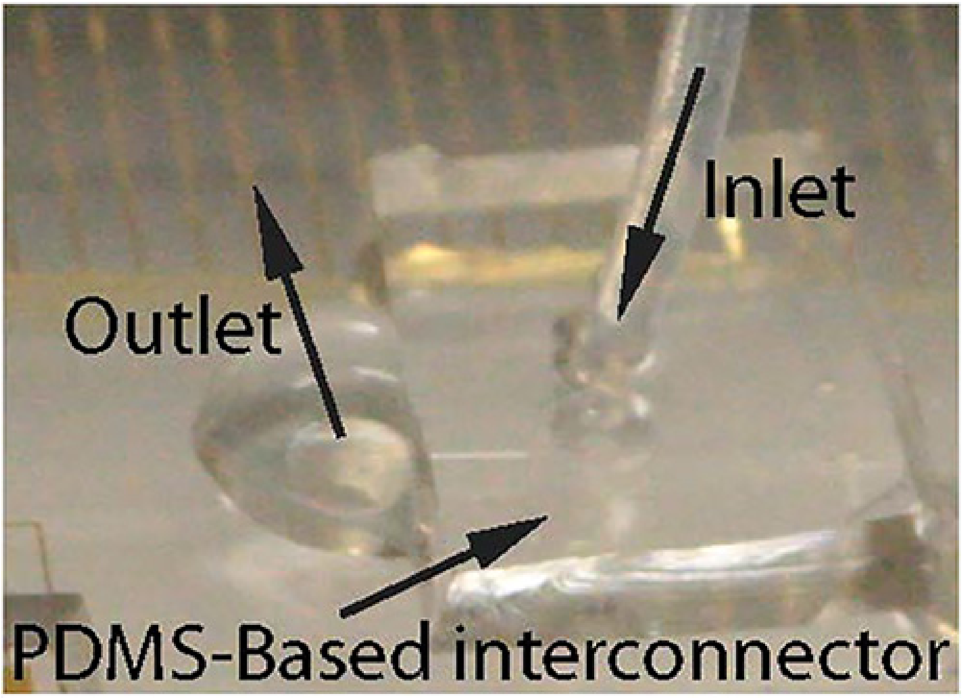

Figure 3. Fast prototyping assembly. (**a**) global device architecture (**b**) microfluidic architecture and (**c**) microfluidic-PCB contacts.

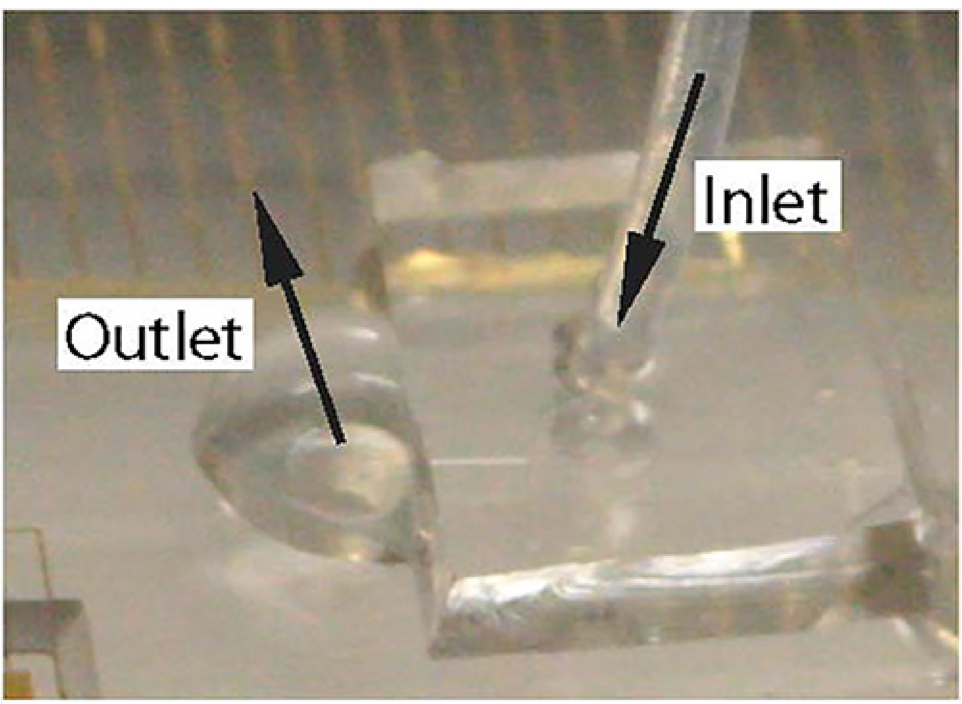

Figure 4. PDMS interconnector. (**a**) only one access hole is covered by a PDMS interconnector, (**b**) both access holes are covered.

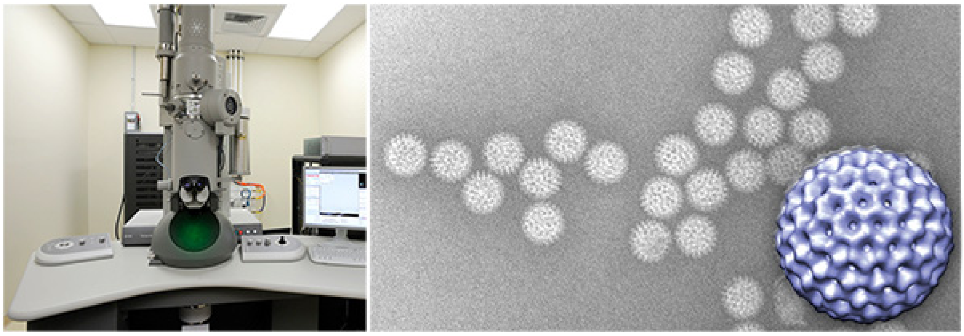

Figure 5. Fast Prototyping Platform for microfluidic devices.

Discussion

The PDMS interconnector is intended for low-pressure applications, liquid leakage into the chip access hole when the PDMS interconnector is subsequently placed on the access hole must be prevented. Therefore, the recommended thickness of PDMS is less than 2 mm. A greater thickness can induce a weak adhesion of the PDMS to the microfluidic chip surface and is not recommended. An unsuccessful trial was made using a thickness of 4 mm. This work focuses on the adherence of the PDMS interconnector to the glass while syringe pumps control the liquid injection. Solution leakage refers to the loss of adherence, which limits the maximum liquid flow rate. Thus, the solution leakage refers to the maximum liquid flow rate that can be used with the design PDMS interconnector.

The interconnector described in this method may not be ideal if, during the microfluidic chip or system prototyping phase, a removable interconnector is required. This interconnector is often single-use only, and once it is removed from the microfluidic chip it is difficult to be put back in place with the same initial adherence and must be replaced by a new one. However, in general, this interconnection technique is versatile and can also be adapted to any microfluidic chip and thus remain reusable. To place a permanent interconnector, the PDMS can also be bonded through a plasma-oxygen process. Although this is useful when the device is finalized, it is not useful when the system is for prototyping purposes and if changes and improvements are expected, which is usually the case with prototypes.

Attaching tubing is a challenging step in a system assembly when liquids are injected into MEMS, microfluidic or LoC devices. The complexity comes from the very limited space to connect tubes to access holes in this work. The smallest diameter of the currently commercially available connectors is in the range of 6 mm; however, the distance between the two access holes is 3 mm[22–24]. Therefore, we have proposed a tubing technique based on polydimethylsiloxane (PDMS) as shown in **Figure 4**. This new tubing process is specially elaborated for the prototyping phase. In fact, owing to the chemical constraint, changing the connection tube after each usage is mandatory to avoid and minimize liquid leakage inside the microstructure. For these purposes, the described process in this paper is particularly employed for a fast prototyping design.

In the case of epoxy-based interconnectors, the biocompatibility was not considered in this work, however different types of biocompatible epoxy are available in the market and can be used with the proposed technique. In addition in-channel electrodes may need to be biocompatible depending on injected liquid[25].

Disclosures

There is nothing to disclose.

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