LAB ON A CHIP

A high-pressure interconnect for chemical microsystem applications

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A PEEK interface for use in microfluidic applications is designed, fabricated and tested. The interface allows for the facile, non-permanent coupling of standard capillary tubing to silicon/glass micromixer chips. Importantly, the interface provides for a secure connection between capillary lines and chip reservoirs without the need for any adhesive materials. Furthermore, when used in conjunction with silicon/glass micromixer chips fluidic transport is stable over a wide range of volumetric flow rates (1–1500 μL min^{-1}), and the entire construct can be rapidly assembled and disassembled at any time during the course of experimentation.

Introduction

Over the past decade elementary microfluidic devices have been developed for a wide variety of chemical and biological applications.[1] Activity in this area has primarily been driven by a need for rapid, on-line measurements of small sample volumes within fields such as medical diagnostics, DNA analysis, drug discovery and screening, environmental analysis and chemical production. The advantages associated with downsizing are generally acknowledged and include improved efficiency with respect to sample/reagent usage, application, response times, cost, analytical performance, integration, throughput and automation.[2,3] Of these, perhaps the most interesting gain afforded through microfabrication of analytical devices is the functional integration of component processes that form a total analysis. One of the primary challenges associated with the successful realisation of fully integrated fluidic systems is the development of facile microfluidic interconnects, that allow coupling between the micro-environment of a microfabricated structure and the macro-environment of the 'real world' (*e.g.* capillary tubing, sample reservoirs and pumps).[4–7] Ideally a microfluidic interconnect should possess a low dead volume, provide chemi- and biocompatibility with the analytical system, be simple and cheap to fabricate, operate over a wide pressure range and be easy to implement.

One of the principal issues faced when designing microfluidic interconnects are dead volumes. Whilst handling picolitre quantities of sample is a relatively simple operation within a microfluidic network, typical dead volumes in an interconnect are several orders of magnitude larger. This limitation often leads to significant sample wastage and loss of analytical performance when processing within microfluidic environments.[8]

The use of micromachining technologies has more recently been applied to the development of microreaction systems.[9,10] The reduction in size and integration of functional elements allows the creation of microreactors with capabilities that vastly exceed those provided by conventional macroscopic systems. Microreaction environments provide a diversity of practical advantages when compared with more traditional synthetic systems. For example, the ultra-small volumes associated with most microreactors allow extremely small quantities of materials to be efficiently processed (advantageous in terms of both cost and safety, when processing particularly valuable or hazardous reaction components). On a more fundamental level, the unique reaction environments provided by microreactors allow for unprecedented control and manipulation of reactions. In many instances the high rates of thermal and mass transfer on the microscale allow for more aggressive processing and higher yields than attainable in conventional systems.[11,12] Consequently, the potential benefits of performing on-chip synthesis as a route towards high-throughput chemical production, for example, are compelling.

When using microfabricated devices as reaction vessels for molecular synthesis, compatibility between chip/interconnect materials and common solvents systems becomes an issue of concern. Most synthetically useful reaction systems involve the use of organic (chlorinated and non-chlorinated) solvents, high thermal gradients and large variations in solution pH. Consequently, all substrate materials must be robust to the experimental conditions required. To date, the most common (and indeed simplest) approach to connecting reagent supplies to monolithic microfluidic reaction devices is *via* the use of glued capillaries. This approach has been successfully applied to fluidic coupling in many studies, and indeed today, most leading-edge microfluidics devices are still being joined with epoxy based adhesives. For example, Kovacs and co-workers have developed interconnection strategies for interfacing microfluidic systems to standard capillary tubing.[4] Using deep reactive ion etching techniques reservoir ports are defined in silicon substrates, allowing precise fitting of connecting capillaries. Different variations on this theme allow for minimal dead volumes and reduce the risk of particulate entry into microfluidic channel networks. In addition, Smith *et al.* have demonstrated modular interconnection, assembly and packaging of individual microfabricated devices. Both vertical and horizontal assembly methods afford the formation of three-dimensional microsystems.[5]

In general, the use of adhesives at connections is non-ideal since the process of gluing is ill-defined, time-consuming, inflexible and provides a potential contamination source during analytical measurements. For these reasons we have developed an interface to allow for the facile coupling of standard capillary tubing to silicon/glass microreactor chips currently used in our

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laboratories.[13,14] The interface provides for a secure connection between capillary lines and chip reservoirs without the need for a permanent seal. In this paper we define the design and construction of the interface and describe its use at a wide range of volumetric flow rates.

Design and principle of presented micromixer

The micromixer devices used for all experiments operate according to the principle of distributive mixing.[15] The microstructure is a two-layer device made up of a glass/silicon/glass sandwich. It has an internal volume of 600 nL and measures 1.3 × 5 × 10 mm. Fabrication and design methods have been discussed in detail elsewhere.[8,13] Briefly, two inlet flows are split into a series of separate multichannel streams (16–64 partial flows). This is achieved by repeated splitting of the channels in such a way that an array of symmetrical elements results. Wafer-through nozzles connecting the two fluidic layers allow the two liquid streams to converge and mix. Channels are then sequentially combined in a reverse network until all partial flows are united in one broad outlet channel. The extremely large diffusional surface areas created within the devices have been shown to allow for rapid, efficient mixing.

Design and fabrication of the interface

Design issues

From a mechanical design perspective, the problems associated with interfacing the micromixer chip with conventional fluidic tubing stem from the following factors: (1) The featureless shape of the micromixer unit (thin rectangular solid) makes it relatively difficult to add external modules. The absence of features such as holes (except inlet/outlet ports) or recesses does not easily allow integration to the macro-world. (2) The external dimensions of the chip are small and result in a number of practical problems. (*a*) Access ports are smaller than the vast majority of off-the-shelf parts (*e.g.* fingertight connectors). (*b*) Manual handling of the chip is difficult and tedious. (*c*) The distance (pitch) between the inlet and outlet holes is 1400 μm. This value, although arbitrary, dictates to a great degree the final design of the interface and affects the cost of manufacturing enormously. The smaller the pitch, the more complicated the interface design has to be, the more difficult the sealing is and the more difficult is to manufacture the interface structure. (3) From a mechanical viewpoint, the micromixer chip is not a robust structure. Consequently, high pressures cannot be applied during clamping, nor can the microstructure be relied upon as a structural element of an assembly. Since clamping is unavoidable, it dictates the need for high tolerance when fabricating the components of the interface. Typical tolerances of the order of ±5 μm were consequently used in manufacture.(4) The location of the inlet/outlet holes in relation to the external edges of a chip are not precisely defined (general tolerance of ±30 μm). This meant that external edges of the chip could not be used as datum or reference edges for positioning. As the separations of the port holes are the only precisely located features of the chip, a clamping method utilising the holes as locators needs to be devised to effect assembly.

Design requirements

Based on the design issues above, the ideal micromixer/capillary interface needs to fulfil the following requirements: (1) *Facile assembly*: The design should provide a platform that facilitates assembly of the capillary/interface/chip construct. Assembly time should be kept to a minimum and the end user should not require any specialist training. (2) *Reliability*: As stated, one of the primary drawbacks associated with existing interconnection methods is unreliability. Often a leak-free connection can only be achieved after several attempts. In addition, the connection may not survive prolonged use. A new chip interface should provide a stable leak-free connection with a success rate >97%. Furthermore, once assembled, it should remain sealed for the duration of experimentation. (3) *Rapid assembly*: A severe disadvantage associated with adhesive-based interconnection methods is long assembly times (several hours). Ideally secure assembly should be established within a time frame of seconds to minutes. (4) *Chemical Compatibility*: All interface materials should be chemically compatible with a wide range of laboratory solvents and reagents. (5) *Low dead volumes*: To avoid sample wastage and a reduction in analytical performance use of the interface should introduce minimal dead volume. (6) *Replaceability*: Adhesive-based interconnection methods prove limited when capillaries or microchannels become blocked or damaged. Normally the complete assembly has to be discarded. Consequently, the ability to replace specific chip or interface components is an important requirement of the new design. The new interface should cater for replacement of individual components, without the need for complete disassembly. (7) *Operation over a range of flow rates*: Previously, as a result of poor connections between the micromixer chip and capillary tubing, only volumetric flow rates between 0.01–100 μl min^{-1} could be used without significant leakage. The new interface should allow for efficient (leak free) operation at flow rates in excess of 1000 μl min^{-1}. (8) *Ability to observe on-chip processes*: An observation window should be incorporated into the interface design, to allow for on-line monitoring of mixing processes.

Final design

When fully assembled the chip interface measures 38 × 35 × 30 mm. A schematic of the assembled device is illustrated in Fig. 1. An exploded view of the interface, showing its various components, is given in Fig. 2.

The identity and composition of the components listed in Fig. 2 are as follows: (1) 375 μm od fused silica capillary tubing

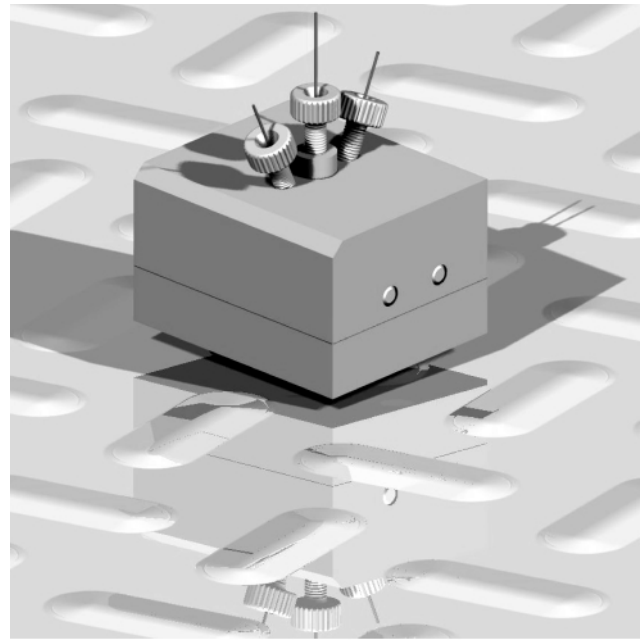

Fig. 1 Schematic (to scale) of the assembled chip interface (external dimensions 38 × 35 × 30 mm).

(Composite Metal Services, Worcester, UK); (2) custom made fingertight connectors (PEEK450G-medical-grade: AZTEC Precision Engineering, Letchworth, UK); (3) M3 × 25 Long Socket Head Screw (Stainless Steel 316: RS Components, Corby, UK); (4) back half of main body (PEEK450G: AZTEC Precision Engineering, Letchworth, UK); (5) front half of main body (PEEK450G: AZTEC Precision Engineering, Letchworth, UK); (6) 3 mm od structural rods (Stainless Steel 316: AZTEC Precision Engineering, Letchworth, UK); (7) sealing membrane (silicon elastomer: GOODFELLOW, Huntingdon, UK); (8) micromixer chip; (9) precision spacer (Aluminium Alloy 6082-T6: AZTEC Precision Engineering, Letchworth, UK); (10) back plane to micromixer chip (selected float glass: SPANOPTIC Ltd, Glenrothes, Fife, UK); (11) base with observation window (PEEK450G: AZTEC Precision Engineering, Letchworth, UK); (12) M3 × 14 long cheese head screw (White Acetal: RS Components, Corby, UK).

Design analysis

I. Main body (parts 3–6). The main body of the interface is designed in two halves (parts 4 and 5) that are brought together permanently. This was necessary due to restrictions imposed by the hole-to-hole pitch of 1.4 mm in the micromixer chip. Straight-through holes on a single piece of plastic could not be implemented, since the short pitch distance would prohibit any use of fingertight connectors. Instead, this distance was artificially increased using the interface, making the use of custom-made connectors feasible. Each half of the body is machined to shape a path for the capillaries to follow and find their 'target' (inlet and outlet holes of micromixer chip). Each path has a half-circular cross sectional area, so that when parts 4 and 5 are brought together, they form a complete circular cross sectional area (400 μm diameter). As the capillaries are pushed from the top through the sub-assembly block, they follow the path defined by the newly formed sub-assembly. By that point they are accurately positioned and in the right pitch. When the two halves are brought together by means of the structural rods and screws (items 6 and 3, Fig. 2) the lower flat surface of the subassembly (the face on the micromixer chip side) is machined to form a totally flat surface (flatness tolerance $< \pm 5$ μm). This sub-assembly is then permanent and if taken apart, additional machining of the bottom surface is required.

II. Remaining assembly. One of the most important elements of the complete assembly is the sealing membrane (part 7, Fig. 1). This is made from a silicon elastomer (~ 100 μm thick) and has a dual purpose. First, when the assembly is complete, it compresses and seals the edges of the inlet and outlet holes of the micromixer chip, thus prohibiting any sample leakage. More generally, its flexibility absorbs various machining tolerances, when the micromixer chip, the precision spacer, the glass back-plate and the base (parts 8–11) are assembled. The sealing membrane has the same footprint as the micromixer chip and contains 3 pre-cut holes (of approximately 200 μm od). These holes are created using a jig consisting of two plates with the same footprint as the chip. Each of the 2 plates has the 3 holes of the chip mapped to it. A larger piece of the Silicone elastomer is firstly sandwiched between the 2 plates and cut to the chip footprint. Finally, using a 300 μm drill bit diameter, the 3 holes are transferred to the membrane, which is then ready for assembly.

The precision spacer (part 9) is used to maintain the relative parallelism between the glass back-plate, the micromixer chip and the base (part 11). The micromixer chip interface is designed to be used in conjunction with 375 μm od capillary tubing (part 1). Nevertheless, it has been used with stainless steel capillaries (of the same od) with equal success.

Assembly of interface

Step 1: Capillaries (part 1) are passed through the fingertight connectors (part 2) and then through the three portholes of the interface so as to protrude approximately 2 mm from the bottom surface of the main body. *Step 2*: The precision spacer (part 9) is introduced to the assembly. *Step 3*: The sealing membrane (part 7) is fitted over the three protruding capillaries (by means of one half of the jig). *Step 4*: The 3 portholes of the chip are self-aligned with the capillaries. *Step 5*: The glass back-plate (part 10) and the base with the observation window (part 11) are

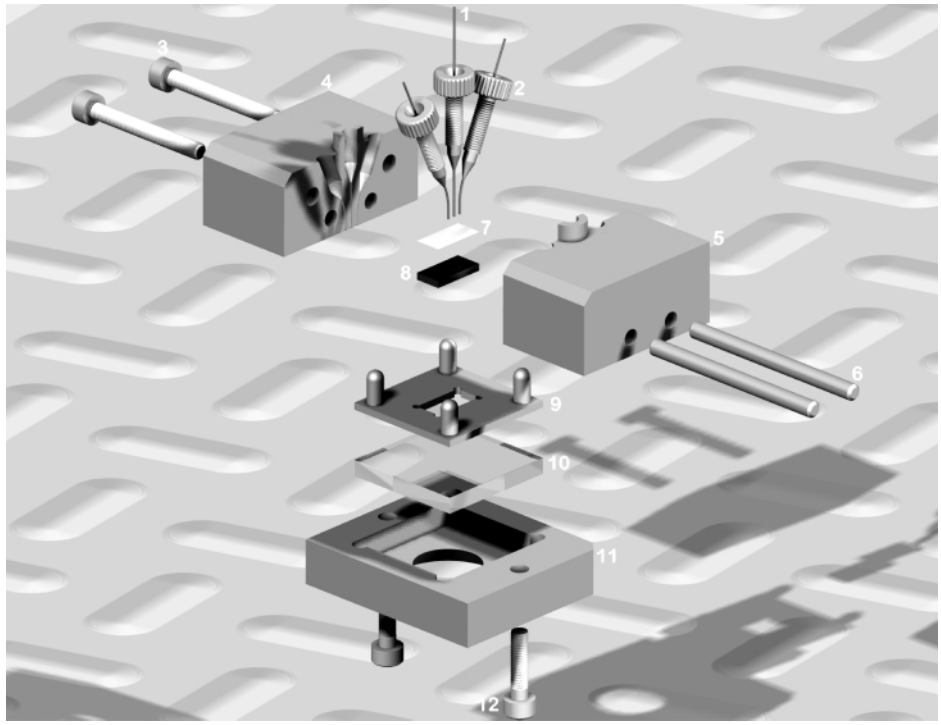

Fig. 2 Schematic (to scale) of the exploded chip interface. Identities of components 1–12 given in main body of text.

fitted to the assembly. Tightening of the M3 plastic screws (part 12) pushes the capillaries back out a little, precisely forcing them to the right depth relative to the chip. *Step 6*: The three fingertight connectors are tightened. In addition, if replacement of the micromixer chip is required, only steps 4 and 5 need to be repeated. If any of the capillaries need to be replaced, then all steps must be repeated.

Assessment of mixing quality

Characterisation of distributive mixing phenomena in the micromixer has been described elsewhere. Nevertheless, flow visualisation studies are a useful tool in characterising the quality of mixing and gaining information about flow behaviour on chip. For flow visualisation experiments, the microchip/interface is connected to a syringe pump (PHD2000 Infusion, Harvard Apparatus, Edenbridge, UK) *via* fused silica capillaries and fluid driven through the chip from two 25 μL syringes. A microscope (Leica DMIL, Milton Keynes, UK) with a light source for reflected light is then used in conjunction with a video camera (SONY, CCD XC-999P) for image capture. Fig. 3 shows a black-and-white image of a typical fluorescence quenching reaction performed on-chip. Here quenching is accomplished using buffered aqueous solutions (pH 9.4) of 2M KI and 20 μM quinidine hydrochloride (99% Fluka, Gillingham, Dorset, UK). Quinidine (fluorophore) is introduced through the network system on the same layer as the observation channel, whereas the iodide solution (quencher) enters from the back side *via* a series of wafer through holes. Fluorophore and quencher solutions are mixed in a 1:1 ratio. As expected, lamination and flow patterns can clearly be observed and information about dead volumes (areas of stagnant or slowly flowing liquid in the corners of channels as can be seen from the streamlines), asymmetries, and boundary effects can be elucidated. These issues and analyses have been described in detail elsewhere. More importantly, it is apparent that the interface facilitates the introduction of fluids into the chip from capillary tubing, without the need for adhesives. To assess the fidelity of the capillary/chip connection fluid, streams were passed through the chip at a variety of flow rates. The fluid exiting the chip (after a given time interval) was then collected in a sealed container and its volume calculated (according to the weight of fluid collected). As can be seen in Fig. 4 the variation of volume collected with volumetric flow rate is essentially linear for flow rates between 0.001 and 1.50 mL min^{-1}. At flow rates above 1.57 mL min^{-1} appreciably fluid leakage was observed at the capillary/chip interface (data not shown due to a large variation in collected fluid volumes). This is not surprising due to the large back-pressures generated at higher flow rates. Nevertheless, an acceptable volumetric flow rate of 1.5 mL min^{-1} yields a total volumetric throughput of 90 mL in 1 h.

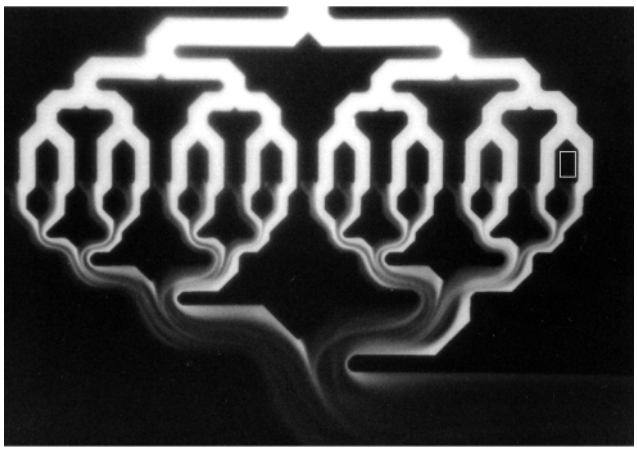

Fig. 3 Visualisation of the fluorescence quenching of a buffered aqueous solution (pH 9.4) of quinidine hydrochloride (20 μM) using 2M KI at a total volumetric flow rate of 200 μL min^{-1}. The hashed rectangle marks the position of one of the wafer-through holes connecting the two layers of the microfluidic device.

Discussion

The studies presented herein describe the successful design and fabrication of a high-pressure interconnect for use in microfluidic applications. The interface allows for the facile, non-permanent coupling of standard capillary tubing to silicon/glass micromixer chips.

The chip/interface construct can be assembled in less than 5 minutes (this time includes replacement and piercing of the silicone gasket). Initial success rates were approximately 75%. However, this has since been improved with practice and subsequent re-machining to >97%. Importantly, the total dead volume associated with the interface is effectively zero. This is due to the fact the capillaries enter the chip directly, and therefore any dead volume in the system is due to a mismatch in the chip inlet hole and the capillary, and not due to the device.

An additional characteristic of the interface is that it provides for a secure connection between capillary lines and chip reservoirs without the need for any adhesive materials. Furthermore, the interface is stable over a wide range of volumetric flow rates (1–1500 μL min^{-1}) and the connections have been demonstrated to operate effectively at pressures in excess of 6 atm.

Recently, the interface has been successfully applied to continuous-flow, solution-phase compound library generation using the described micromixer chip.[12,14] The ability to disassemble the entire construct has proved invaluable on a practical level. As stated, a common problem faced when using microfabricated structures for synthetic processes is the propensity for both capillaries and channels to block (as a result of precipitation or particle contamination). The temporary nature of the capillary/chip interface allows facile cleaning of the chip and replacement of capillary tubing. However, probably the most important benefit of the current interface design is its ability to efficiently operate at high flow rates. A maximum flow rate of 1.5 mL min^{-1} is approximately an order of magnitude greater than that achievable using adhesive based coupling schemes.

From the engineering design perspective, future development of the interface/chip construct will most likely focus on increasing the pitch distance between the inlet and outlet holes

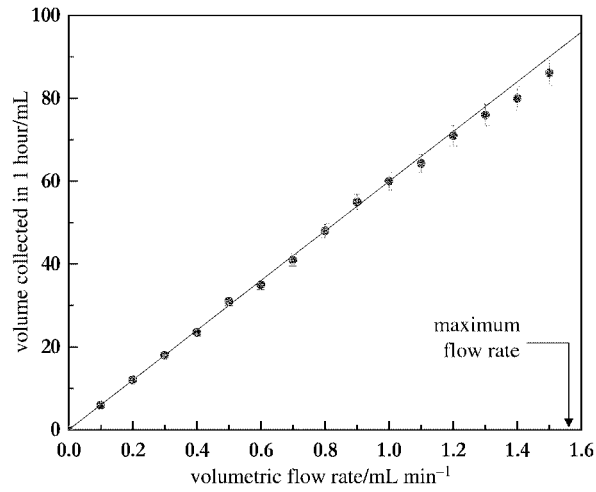

Fig. 4 Variation of the volume of fluid (water) collected (off-chip) in a 1 h period as a function of total volumetric flow rate.

of the micromixer chip itself. As it has already been mentioned, this dimension greatly affects the complexity of the interface design and consequently manufacturing costs. As a rough approximation, we expect that a threefold increase in pitch (to 4.5 mm) would reduce the manufacturing costs by a half. These cost savings will become increasingly important when using multiple micromixer units in both serial and parallel processing applications.

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