Thermally Bonded Microfluidics for Healthcare

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Abstract

Microfluidic chips aim to allow for larger processes to occur in a smaller controlled environment with applications ranging across many industries. Microphysiological systems or Organs-on-a-chip specifically recapitulate complex biological phenomena, typically utilizing polydimethylsiloxane (PDMS). Limitations in PDMS-based chips (e.g. vapor permeability, lipophilic absorption) recently motivated fabricating thermoplastic-based chips connected via adhesive layers which theoretically do not suffer from these limitations[1,2]. Adhesive-based chips may induce a level of cytotoxicity, motivating the investigation of other bonding techniques. In this work, we developed a protocol for replicating the adhesive-based chip geometries through a thermal-bonding technique. We then compared bonding strength between adhesive and thermal bonding across several materials and found that thermal bonds had an average of 77.66% higher yield stress. Finally, an initial test of biocompatibility using a human cancer cell line (Caco-2) revealed comparable metrics of both qualitative confluence and adhesion analysis within chips. We also unexpectedly discovered during initial seeding that confluence was improved by 68.42% in thicker channels due to a residual, oscillatory flow effect. We found after 48 hours, adhesion was similar across chips with corresponding channel thickness, confirming the efficacy of thermal fusion bonding as a suitable alternative to the use of adhesives. This work offers the capability to better study biological systems, specifically in the field of disease modeling for pharmaceuticals.

Introduction

- 6.2% overall success rate in pharmaceutical clinical trials[3]
- Microfluidic chips are able to use human cells and simulate organs in three dimensions, potentially improving research efficacy in comparison with animal testing
- Current industry standards in microfluidic chips with biomedical applications involve layering polydimethylsiloxane (PDMS) with different bonding methods, including a double-sided adhesive[1,2]
- Thermoplastics emerged as a favorable alternative with their resistance to lipophilic molecule absorption and ability to maintain a gas gradient
- One concern raised with the current assembly method of thermoplastic microfluidic chips – adhesives – is its potential to be cytotoxic
- Our project focused on thermal fusion bonding as an alternative assembly method
- Thermal bonding involves heating thermoplastics to their glass transition temperatures so bonds between polymer chains break and an exchange between materials occurs[4]

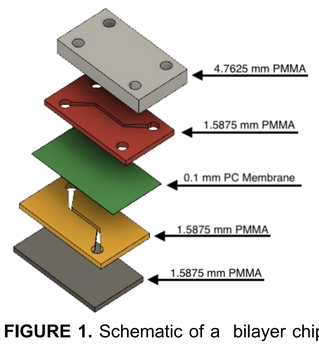

FIGURE 1. Schematic of a bilayer chip used in the Koppes Lab which includes a 3⁄16" PMMA layer with Luer Lock fittings (allowing the insertion of fluids), a 1⁄16" PMMA layer with a channel, a 0.1 mm PC membrane layer, another 1⁄16" PMMA layer with a channel, and a PMMA bottom cover.

Assembly Methods

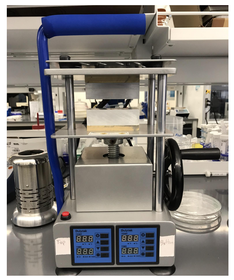

FIGURE 2. Manual heat press with adjustable temperatures used to thermally bond chips. Thermoplastics are pressed between heated top and bottom components.

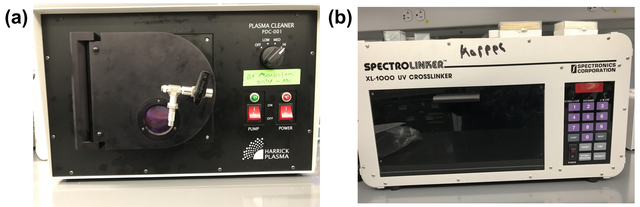

FIGURE 3. Applied surface treatment to chip layers to increase surface energy and allow additional interlocking of polymer chains, the formation of covalent and polar bonds, and electrostatic interactions[4]. **(a)** Air plasma treatment of membrane for 2 minutes on each side. **(b)** UV light treatment on other layers on each side at 100,000 or 150,000 J/cm², depending on material.

Results

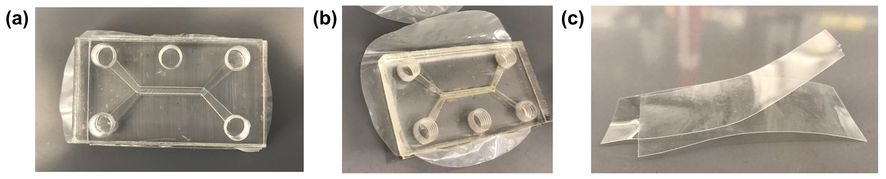

FIGURE 4. (a) Polymethylmethacrylate (PMMA) chip was fabricated at 145°C for 10 minutes following surface treatments. PMMA chips had decent optical clarity but were prone to air bubbles. **(b)** Polycarbonate (PC) chip was fabricated at 160°C for 10 minutes following surface treatments. PC chips had similar optical clarity but were less prone to air bubbles. **(c)** Attempted thermal bonding of polyethylene terephthalate (PET) was unsuccessful.

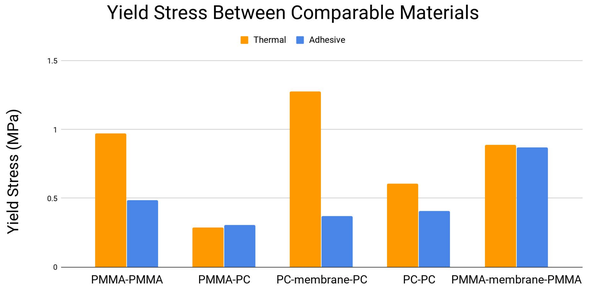

FIGURE 5. Using a tensile strength machine, thermal bond strengths were compared to their respective adhesive bonds. Yield stress is the amount of pressure a material can withstand before permanent deformation occurs. Thermal bonds on average had 77.66% higher yield stresses.

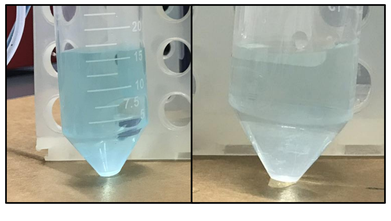

FIGURE 6. We flowed 20 mL of blue-dyed water through a thermally bonded chip and an adhesive chip as a control. The dye permeated the membrane in both with the adhesive chip (left) showing higher coloration than the thermally bonded chip (right); however, the comparable concentrations of dye affirmed a degree of membrane permeability in both chips.

Results (continued)

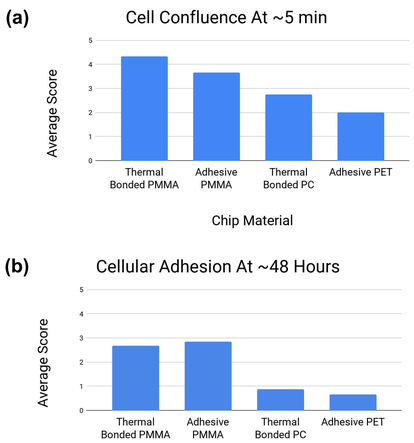

FIGURE 7. To test biocompatibility, Caco-2 cells were seeded in adhesive and thermally bonded chips under static conditions. **(a)** Central channels on each chip were observationally quantified on a scale of 0-5. **(b)** After inducing oscillatory stimulation at 48 hours to remove unadhered cells, chips were scored again as an additional biocompatibility metric. On average, thermal bonding yielded a biocompatibility improvement of 20.26% in scoring.

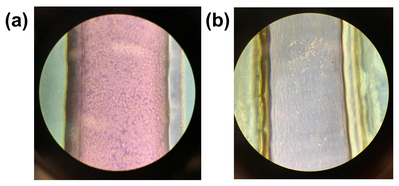

FIGURE 8. (a) Thermally bonded PMMA chip with confluence score of 5. **(b)** Thermally bonded PC chip with adhesion score of 1.

Conclusion and Future Steps

- Mechanical testing of chips with the thermoplastics PMMA and PC demonstrated higher durability in thermal bonds.
- While thinner channel heights in chips are preferable for biomedical applications, the limited space results in higher fluid velocities and more shear stress, decreasing the cells' ability to adhere and decreasing biocompatibility scores by an average of 62.59%.
- Our results suggest that thermal bonding of microfluidics presents a suitable alternative to adhesive; however, larger scale trials with more controlled quantitative analysis must be performed.

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