Ultra-thin Microfluidic Devices Built via Thermal Lamination

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Ultra-thin Microfluidic Devices Built via Thermal Lamination

Abstract
Widespread adoption of lab-on-a-chip technologies may be encouraged by the development of methods and devices that require minimal investment and expertise. Here we describe a type of device that makes exclusive use of consumer-grade components and equipment. The devices consist of as little as three layers of a polymer film, with microchannels shaped by an inexpensive craft cutter, and sealed by thermal lamination. Fabrication time is in the order of minutes, and the method does not require any prior training. To showcase the properties and demonstrate the versatility of the devices, we describe their use to generate fully biocompatible lipid-based nanoparticles, and present an example of a multi-layered device. Our approach lowers the barrier-to-entry for reliable microfluidic devices that are flexible and ten to thirty-times thinner than the common PDMS/glass alternative.

Keywords
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Disciplines
Biology | Mechanical Engineering

Comments
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“There is an intellectual merit to asking how do we make things as simple as we can, as cheap as we can, as functional as we can, and as freely interconnectable as we can.”

G. Whitesides 2010 TED TALK: Towards a Science of Simplicity
Ultra-thin Microfluidic Devices Built via Thermal Lamination

Fernando Ontiveros, PhD St. John Fisher College
Building PDMS/glass chips for research and teaching
Building PDMS/glass chips for research and teaching
How this project started

Building PDMS/glass chips for research and teaching

Eliminate the need of photolithography?
Building PDMS/glass chips for research and teaching

How this project started

Eliminate the need of photolithography?
How this project started

Building PDMS/glass chips for research and teaching

Eliminate the need of photolithography?

Use a craft cutter (xurography, Bartholomeusz et al.)
How this project started

Building PDMS/glass chips for research and teaching

Eliminate the need of photolithography?

Use a craft cutter (xurography)

PDMS sheet + Glass
Eliminate the need of photolithography?

Use a craft cutter (xurography)

PDMS sheet + Glass

Can we eliminate rigidity, make it thin, flexible?
Eliminate the need of photolithography?

How this project started

Building PDMS/glass chips for research and teaching

PDMS sheet only

Can we eliminate rigidity, make it thin, flexible?

Use a craft cutter (xurography)

PDMS sheet + Glass
How this project started

Building PDMS/glass chips for research and teaching

PDMS sheet only

Problems: access to channels, cost and bonding

Eliminate the need of photolithography?

Use a craft cutter (xurography)

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Problems: access to channels, cost and bonding

Can we eliminate the need for bonding equipment?

Eliminate the need of photolithography?

Use a craft cutter (xurography)

PDMS sheet + Glass

Can we eliminate rigidity, make it thin, flexible?
Can we eliminate the need for bonding equipment?

Use thermal lamination

Eliminate the need of photolithography?

Use a craft cutter (xurography)
Can we eliminate the need for **bonding equipment**?

Eliminate the need of **photolithography**?

- Use thermal lamination
- Use a craft cutter (xurography)

**Affordability**
How this project started

Can we eliminate the need for **bonding equipment**?

Eliminate the need of **photolithography**?

Use thermal lamination

Use a craft cutter (xurography)

Affordability
Rapid iteration
How this project started

Can we eliminate the need for **bonding equipment**?

Eliminate the need of **photolithography**?

Can we eliminate rigidity, make it thin, flexible?

**Affordability**

**Rapid iteration**

*Use thermal lamination*  
*Use a craft cutter (xurography)*
How this project started

Can we eliminate the need for **bonding equipment**?

Eliminate the need of **photolithography**?

- Use thermal lamination
- Use a craft cutter (xurography)

Affordability
Rapid iteration
Thin, flexible

Can we **eliminate rigidity**, **make it thin, flexible**?

Eliminate glass, use sheets, film
PETLs

Affordability
Rapid iteration
Thin, flexible
PET Laminated Chips (PETLs)

Channel heights of 25, 76 & 127 micrometers

Channel width of >150 micrometers*

Measured burst pressures (delamination) of 30 to 57 PSI
Polyethylene terephthalate (PET)

Synthetic fibre and resin, used in a wide variety of applications, from food packaging to biological tissue replacement to astronaut suits.

- 25 micrometers (1 mil)
- 76 micrometers (3 mil)
- 127 micrometers (5 mil)

Ethylene-vinyl acetate (EVA)

An elastomeric polymer, it can be used as a hot-melt adhesive with waterproof properties for a variety of purposes including plastic wraps, padding (rubber) and drug delivery.
PET + EVA

25 micrometers (1 mil) roll

76 micrometers (3 mil) laminating pouch
PET Laminated Chips (PETLs)

Channel heights of 25, 76 & 127 micrometers

Channel width of >150 micrometers*

Measured burst pressures (delamination) of 30 to 57 PSI

Rapid, inexpensive prototyping
Non-specialist user
Applications where gas exchange is a concern
Applications where device flexibility is desirable
Educational & Research setting

Vinyl + adhesive

PET + EVA
Using hydrodynamic focusing to produce nano-sized lipid vesicles (liposomes)
Using hydrodynamic focusing to produce nano-sized lipid vesicles (liposomes)

Jahn et al.

Figure 1. (a) Schematic of liposome formation process in the microfluidic channel. Color contours represent the concentration ratios of IPA to aqueous buffer. (b) 3-D color contour map of DiIC$_{18}$ fluorescence intensity at focused region during liposome formation.

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Nanoparticle production via microfluidic devices

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3690 East Ave. Rochester, NY 14618

Abstract

The development of nanoparticles ranging in the size of 10-100 nm using microfluidics is highly reproducible and useful in many biological applications. Advancements in microfluidics (the study of how fluids and gases behave at the micro & nano-scale) have made it possible to produce microfluidic devices. Essentially, these devices contain channels (roughly 50 micrometers deep and 50 micrometers wide) that induce the formation of fluid-fluid interfaces that can result in the formation of nanoparticles. Stable lipids such as phosphatidylcholine (PC) dissolved in ethanol and fed through a microfluidic chip, in the presence of a simple buffer solution is just one method to produce lipid-based nanoparticles. Pressure and particle physics inside the channel cause the lipid to self-assemble into a spherical shape. During this process, lipophilic or hydrophilic compounds can be incorporated inside or around the liposome membrane. Here we have used microfluidic technology to make nanoparticles and are now working on incorporating an lipophilic compound. Pantothenic acid has been shown to act as an anti-inflammatory in vivo, but nanoparticles have not been used as a mode of delivery. The next action is to incubate cells in vitro with this nanoparticle and test this method of delivery as an anti-inflammatory therapy.

Methods

Initially a silicon wafer is coated with a polymer SU-8, which acts as a photolithography. A sheet with the microfluidic chip design (to scale) was then placed in a UV-photolithography device with the wafer beneath it. UV light shines through the photolithography in the sheet and causes the SU-8 to harden and remain on the wafer. The remaining unmodified SU-8 is washed off, leaving a residue in the form of the microfluidic chip patterns. The wafer acts as the mold for microfluidics chips which are composed from a silicone, polydimethylsiloxane (PDMS).

Phosphatidylcholine (PC) was dissolved in ethanol (1 mL EtOH per 25 mg PC). 1 mL of ddH2O was pumped through the device at a rate of 0.50 mL/min to the channels of air bubbles. 1 mL of PC/EtOH mixture was added to a syringe and then put into the lipid entry port. 2 syringes were filled with 1 mL of buffer (PBS) and loaded into the two buffer entry ports. The system is then activated by turning each of the pumping units on. The ideal flow rate ratio to produce liposomes is approximately 5 times the volume of buffer to lipid.

Results

After developing the nanoparticles from lipids using a microfluidics chip, they are then measured for size using a Zetasizer, a tool that uses dynamic light scattering to determine average diameter. The goal is to produce particles that are 50-100 nanometers in size. The image above shows our nanoparticles in this sample were around 46 nm, with a tolerable distribution. We found that increasing the ratio but increasing the flow (290%) in more reliable sizing between batches of nanoparticles.

Discussion

Nanoparticles offer much promise to the scientific community, however problems with reproducibility have halted advancements in this field. Microfluidic devices have been shown to aid in the production of nanoparticles of the same size, batch to batch. We were able to produce many microfluidic chips and through trial and error develop the ideal procedure for maintaining liposome batch uniformity.

Harnessing this technology with the familiarity gained using these devices over the summer, we plan to incorporate lipophilic compounds inside liposomes, while maintaining a similar size. The lipophilic compound of choice is pantothenic acid, an anti-inflammatory agent. In our pilot experiment, the pantothenic nanoparticle was recently administered to cells and via cytoxyn assays it may be determined if the anti-inflammatory properties apply when encased in a liposome.

Future Direction

Once the pantothenic liposome has been shown its efficacy, its future will serve as a proof of principle that most lipophilic compounds can be incorporated into a lipidosome and safely delivered to cells. This success makes the possibilities endless. For example, lipophilic anti-cancer drugs like vincristine, can be incorporated into these liposomes and then delivered to the tumor directly or systemically.

Acknowledgements

We are thankful to Dr. James McDowell for the support in this project and the generous support from the laboratory. We are also grateful to graduate students in the lab (Jared Miller and Jack Gaglardi). This project was supported by the Summer Science Scholars Program at Fisher and a supplement grant from the National Science Foundation.

References


Figure 7: Deposition of the liposome. We use the liposomes produced with anti-inflammatory compounds to be delivered to cells in vivo with the objective of blocking anti-inflammatory components with this molecular complex.
Using hydrodynamic focusing to produce nano-sized lipid vesicles (liposomes)
Production of nanoliposomes: Comparison between PDMS/glass & PETLs
We use **nanoliposomes** to modulate the sterile inflammatory response
Phospholipid composition of nanoliposomes impacts the production of inflammatory cytokines by immune cells.
OTHER  Applications ?
Applications

Mixers and droplets
Applications

Cell culture
Fabrication
Fabrication

PET laminate chips (PETLs)

- PET film (76.2 or 127μm)
- EVA thermoset adhesive

i) Channel cutting

ii) Layer alignment

iii) Thermal lamination

Laminator

~120 °C

≥ 230 μm

≥ 150 μm
Layer composition:

Basic devices require 3 layers of film. The result is a device with a total thickness of 3x the height of the channel.

Additional layers can be used to separate overlapping channels, add depth and/or maximize the use of space.
3 layer - basic device (3 x 76 μm)
3 layer - basic device (3x 76µm)
4 layer device for cell culture
7 layer device
Access the channels

Initial efforts used PDMS blocks and ferrules attached using a variety of adhesives

*Frequent leakage, adhesive clogging*
Self-adhesive vinyl bumpers with orifices ranging from 1/32” to 1/4”
4 layer device for cell culture
Applications

EDUCATION
pH 9 solution

Indicator (phenol red)
Microfluidics Laboratory for High School & College Students

Students design their own channel configurations and submit a screen capture

Craft cutter creates channels and outlets/inlets (3 minutes)

Students align the layers and laminate (3 minutes)

Students attach perforated bumpers to inlets/outlets (3 minutes)

Students test their devices
High School and College Student Designs

Fabrication time once design is drawn is 10 - 15 minutes.
Alternative to syringe pump

Burets + adaptor (tubing+barbed luer adaptor)
PETLs are microfluidic devices fabricated via thermal lamination using polyethylene terephthalate (PET) film, coated with the adhesive ethylene-vinyl acetate (EVA). These ready-to-use materials are commercially available in the form of laminating pouches of varying thickness (3 and 5 mil, or 76.2 and 127 micrometers respectively). Access to the microchannels is facilitated by inlet and outlet ports built using vinyl furniture bumpers. The devices have a thin profile, are flexible, reproducible, robust, of extremely low cost and easy to fabricate. A finished device takes under 15 minutes from design to fabrication.

![PETL Fabrication and Use Image](image)

Figure 1. PETL fabrication and use

1. **Device Design**

   1.1 Start by sketching on a piece of paper ideas for the channels that will form part of the device.

   1.2 Using any computer program that allows for drawing (e.g. Powerpoint), draw the device using lines and other shapes like curves or circles. Make lines black, solid, and with a thickness of around 4 pts.

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### List of Equipment, Tools and Reagents Used

<table>
<thead>
<tr>
<th>Task</th>
<th>Equipment/Reagent</th>
<th>Specifications</th>
<th>Brand/Seller</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device design</td>
<td>Computer</td>
<td>Drawing software (PPT, Keynote, Illustrator, etc.)</td>
<td>Any</td>
</tr>
<tr>
<td>Channel cutting</td>
<td>Craft Cutter</td>
<td>Silhouette Cameo</td>
<td>Silhouette</td>
</tr>
<tr>
<td></td>
<td>Cutting mat + blade</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PET/EVA film</td>
<td>3 or 5 mil laminating pouches</td>
<td>Scotch/3M</td>
</tr>
<tr>
<td></td>
<td>Powder-free gloves</td>
<td></td>
<td>Any</td>
</tr>
<tr>
<td>Thermal lamination</td>
<td>Thermal laminator</td>
<td>Standard/basic home/office model</td>
<td>Scotch/3M</td>
</tr>
<tr>
<td></td>
<td>Double-sided tape</td>
<td>Any size</td>
<td>Scotch/3M</td>
</tr>
<tr>
<td></td>
<td>Scissors</td>
<td></td>
<td>Any</td>
</tr>
<tr>
<td>Device assembly</td>
<td>Vinyl furniture bumpers</td>
<td>Round, clear, self-adhesive (9.5mm to 1/8 inch diameter)</td>
<td>Everbilt Home Depot</td>
</tr>
<tr>
<td></td>
<td>Biopsy punch (optional)</td>
<td>1 mm punch</td>
<td>Millen/Proto-Pellet</td>
</tr>
<tr>
<td></td>
<td>Drill (preferred)</td>
<td>1/32&quot; drill bit (we use a Dremel rotary tool)</td>
<td>Any</td>
</tr>
<tr>
<td>Device testing</td>
<td>50 mL glass burettes w/ stopcock</td>
<td>Regular burettes on stands</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Syringe pump</td>
<td>Allows for precise control of flow (will require 1ml syringes+blunt needles, 16G)</td>
<td>New Era</td>
</tr>
</tbody>
</table>
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Kelsey Moore
Nick Passero

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Applications

RESEARCH

PC/ethanol before PETL

PC/ethanol after PETL

Diameter (nm)

chip 1  chip 2  chip 3  chip 1  chip 2  chip 3

*  **
widths were measured via an optical profilometer. Channels of pre-shrunk widths of 1.0, 0.6, and 0.2 mm were characterized as having post-shrunk widths of 211, 128, and 95 μm respectively (Fig. 2a). It was previously assessed that the Quickutz Silhouette’s lateral feature resolution was 0.2 mm.\textsuperscript{15} Our method of utilizing shrink polymers was able to achieve a significant improvement in lateral feature resolution.

The topographical analysis of the multi-width channels (Fig. 2) depicts near vertical side walls, high aspect ratios, and smooth surface features. The channel walls were on the order of 600 μm for

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