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## TECHNICAL NOTE

# Adhesive bonding of microfluidic chips: influence of process parameters

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## Abstract

In this note, the influence of process parameters for adhesive bonding as a versatile approach for the sealing of polymer microfluidic chips is investigated. Specifically, a process chain comprising pre-processing, adhesive transfer as well as post-processing is presented and parameter recommendations are provided. As a device for adhesive transfer, a modified laminator is utilized which transfers thin layers of adhesive onto the chip surface, only *via* a silicone roll. Using this device and a high temperature ( $T_g > 100$  °C) epoxy adhesive, adhesive layers in the range of 2–4  $\mu\text{m}$  can be reproducibly transferred ( $CV < 4\%$ ). For best bonding results, it is recommended to provide 2.5  $\mu\text{m}$  thin layers of adhesive in combination with a subsequent evacuation step at 10 mbar for 3 h. Further, it is proposed to integrate capture channels near large, featureless areas to compensate for variations in processing and thus prevent clogging of channels.

(Some figures in this article are in colour only in the electronic version)

## 1. Introduction

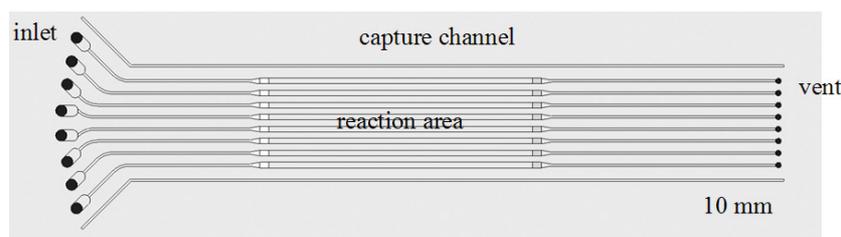
So-called lab-on-a-chip systems for diagnostic technologies attract a growing interest due to their immanent benefits of reduced turn-around times, increased reliability and minimized costs [1]. For some time, there has been a strong trend towards disposable polymer labs-on-a-chip [2–4] specifically due to their amenability for low-cost mass production. The bonding of polymer substrates however can prove to be highly challenging and can ultimately decide on the functioning or even commercial success of the chip [5].

Multiple approaches for bonding of microfluidic chips like laser welding [6], thermal bonding [7] or adhesive bonding [6, 8–13] currently exist. Depending on the boundary conditions for lab-on-a-chip development, e.g. material used,

different approaches are more or less feasible and providing a universal approach for different applications is a non-trivial task but still highly desirable. Laser welding for example requires an absorber at the interface between the chip and lid [6] while thermal bonding requires high temperatures or specific material combinations [7]. Thus, bonding *via* adhesives is still the most uniform approach as it primarily relies on the wetting of the chip surface by the adhesive and is therefore applicable on various polymer materials.

A standard approach for adhesive bonding is the coating of the lid with adhesive. This way however, a large amount of the adhesive gets in direct contact with the sample. Further, no bioreagents can be immobilized on the lid. Thus, different approaches to only selectively cover the chip surface with adhesive have been reported, namely contact printing [6, 9, 10, 13], the use of guide channels [8, 12] or by a laminator [11]. The so far presented work allows for selecting a

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**Figure 1.** Microfluidic test chip featuring eight parallel channels comprising inlets, reaction areas and vents. The capture channels are discussed in section 3.3.

general approach for bonding. However, in most cases no quantitative data or in-depth investigation has been provided which prevents a head start in bonding development. This work therefore investigates the influence of different process parameters for the adhesive bonding of a microfluidic test chip while trying to abstract the parameters from the utilized device and chip geometry.

## 2. Materials and methods

### 2.1. Microfluidic test chip

The chip with outer dimensions of standard microscope slides comprises eight parallel channels with a sample volume of  $7.5 \mu\text{L}$  each (figure 1). The reaction area features a width/depth of  $500 \mu\text{m}$  while the supply channels exhibit a width/depth of  $200 \mu\text{m}$ . The chips are currently fabricated by CNC-micromachining from a cyclic olefin polymer (COP, E480R, Zeonor, Zeonox Corporation). The chip assembly additionally comprises a lid (1 mm thick, made from E480R, not shown).

### 2.2. Pre-processing

Before bonding, the chip and lid are first ultrasonicated for 10' in 2-propanol to remove debris from the channels. This is followed by a drying step utilizing pressurized nitrogen. Finally, the surfaces to be bonded are activated in an oxygen plasma for 4' with a power of 200 W (Picollo, Plasma Electronic, Germany).

### 2.3. Adhesive

For adhesive bonding, reactive adhesives (two-component, e.g. epoxy) [6, 9, 10] and UV-curable adhesives [8, 11–13] are most frequently applied. However, the UV light in the bonding process of the latter can possibly denature stored bioreagents if not masking the respective areas and preventing reflection or scattering. Thus, only reactive, epoxy-based adhesives have been considered for this work which feature excellent resistance against most acids and solvents after cure. For bonding development, Epo-Tek 375 (Polytec-PT, Germany) is selected which features a very high glass transition temperature  $T_g = 135 \text{ }^\circ\text{C}$ . This is imperative for the target application of this study, i.e. polymerase chain reaction (PCR), as to ensure no decrease in bond strength during cycling. Further, the high viscosity of the adhesive ( $\sim 4 \text{ Pa s}$ ) reduces the risk of clogging

the channels. To confirm the proposed bonding parameters, a less viscous adhesive ( $\sim 1.2 \text{ Pa s}$ ), namely Epo-Tek 302-3M (Polytec-PT, Germany), is also evaluated.

### 2.4. Adhesive transfer

The applied technology is based on the previously presented transfer of an adhesive layer onto the microfluidic chip via rolls [11]. Any contact between the adhesive layer and bioreagents on the lid can thus be prevented. When the substrate comes into contact with the rotating transfer roll, about half of the amount of adhesive present on the roll will be taken up by the chip. Thus, the process is independent of the chip features. The transferred amount of adhesive depends on the distance between the definition roll and the transfer roll, the viscosity of the adhesive as well as the transport velocity. For a fixed distance, the layer thickness can be extrapolated according to [14] as  $d_{\text{adh}} \sim (\eta_{\text{adh}} \cdot v_{\text{roll}})^{0.64}$ .

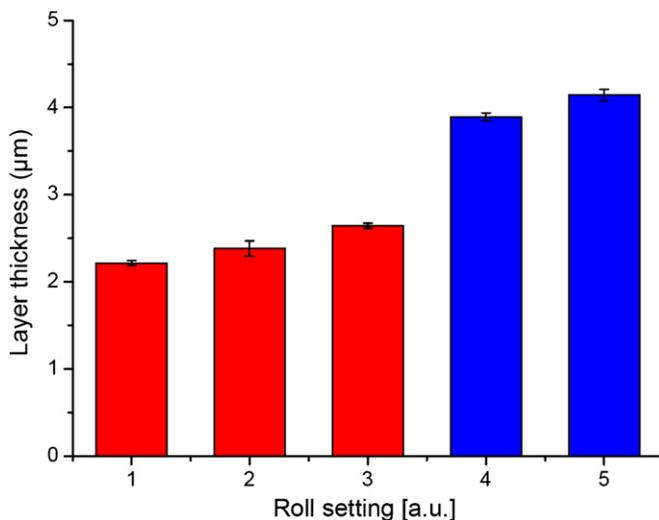
As a device, a custom-built laminator is utilized (NMI, Germany) [11]. It features an aluminum (Al) definition roll and a silicone transfer as well as a transport roll. The process is abstracted from the device by measuring the influence parameters, i.e. adhesive layer thickness, transport velocity and distance between the substrate and roll. Thus, the results are applicable for arbitrary laminators based on a soft (e.g. silicone or rubber) transfer roll.

### 2.5. Adhesive layer thickness

The amount of adhesive is measured gravimetrically using a high-precision microbalance (SC2, Sartorius, Germany) and the layer thickness is extrapolated based on these data. For a good wetting (i.e. activated) surface, a homogenous distribution of adhesive over the chip surface can be assumed.

### 2.6. Post-processing

After adhesive transfer, the chip is placed in an Al chip holder (not shown) comprising cavities for the chip/lid assembly. The depth of the cavities is  $200 \mu\text{m}$  less than the total thickness of the assembly. Then, the lid is aligned on top of the chip. An Al plate is subsequently pressed on the holder via screw clamps (Bessey, Germany) which are able to exert a force  $> 1 \text{ kN}$ . The chip holder is then evacuated to 10 mbar. Finally, the chip holder is put into a lab furnace (Binder, Germany) for 3 h at  $70 \text{ }^\circ\text{C}$  for curing.



**Figure 2.** Extrapolated adhesive layer thicknesses. The three lower values were achieved by moving adhesive-covered substrates through the laminator without any adhesive on the transfer roll.

### 3. Experimental results

#### 3.1. Adhesive layer thickness

With the selected adhesive and device, the minimum transferred layer thickness amounts to 3.5 µm. This can be explained by the incompressibility of the adhesive and the elasticity of the transfer roll. For achieving thinner layers, a larger amount is first transferred onto the chip surface followed by a second run through the laminator with no adhesive present thus effectively halving the amount of adhesive on the chip surface. Alternatively, an additional roll could be installed on the laminator. The results of the adhesive transfer, exhibiting a good reproducibility (coefficient of variation CV < 4%), are summarized in figure 2. Further, it has been evaluated that the transferred layer thickness is basically independent of the feeding orientation of the chip into the laminator (tested for a given transfer roll velocity of 20 mm s<sup>-1</sup>). Additionally, the same amount of adhesive is transferred onto the smaller features (500 µm wide spacers between the channels in the center chip area) as well as on the outer chip area. However, a small adhesive meniscus may be present at the interface between channel and lid.

#### 3.2. Bonding influence parameters

For successfully bonding microfluidic chips, a high number of influence parameters have to be taken into account. The primary parameters for adhesive bonding, their influence and possible consequences are summarized in table 1 (in the order of processing). It should be noted that the chip design is the major influence parameter for bonding, i.e. chips featuring large (>1 mm) and deep (>500 µm) channels, only, will require less bonding process development due to the reduced risk of clogging than chips comprising small (≤500 µm) and shallow (≤200 µm) channels as well as isolated features. The other parameters of major influence are evaluated in

**Table 1.** The primary parameters for adhesive bonding, their influence and possible consequences.

Property	Influence	Consequence
Chip design	++	–
Chip surface planarity	++	More adhesive required
Variation in thickness	+	Higher pressure required
Rinsing	+	Residual fat prevents adhesion
Surface activation	++	No wetting of the chip surface with adhesive
Layer thickness	++*	No bond versus clogging of channels
Transport velocity	0**	–
Distance substrate roll	0***	–
Cleanliness of atmosphere	+	Dirt particles, local leaks
Alignment	+	Smearing of adhesive into channels
Apply pressure	++*	No bond
Evacuation	++*	Leaks around small features
Cure	0	–

++: major impact, i.e. a failure in bonding can occur; +: minor impact, i.e. can reduce yield; 0: no impact; \*: test parameter. Please refer to table 2; \*\* influences adhesive layer thickness [14] and \*\*\* possibly increases risk of clogging shallow (<100 µm) features.

the following paragraph except for chip surface planarity and surface activation. The latter can be considered binary because either there is adhesion or not which depends on the wetting properties of the adhesive on the chip material. The chip surface planarity can be a major issue when using injection-molded chips specifically if the master exhibits two layers of different heights on the chip surface to facilitate fabrication. Then, the amount of transferred adhesive must be sufficient to compensate for the height difference. This however increases the risk of channel clogging.

For the parameters of minor influence, the rinsing, cleanliness of atmosphere as well as the alignment relate to the processing in general or handling. A variation in thickness, if existent, requires the bonding partners to be in intimate contact during post-processing and cure. For ideal substrates (e.g. silicon wafers), the basic adhesion between chip, adhesive and lid may be sufficient to result in a strong bond. The following can be seen as a rule of thumb for adhesive bonding: the less ideal the surfaces of the bonding partners, the more the pressure and/or adhesive is required.

#### 3.3. Chip bonding results

In general, all successfully bonded chips did not exhibit any leakage even if operated for 2 h at 100 °C with an overpressure of 4 bar. Further, no cross-flow between channels could be observed (12 h @ 4 bar) when alternately priming the eight channels with dyed liquid and DI-water.

For the presented test chip, the different microfluidic channels can be seen as independent units, i.e. clogging of one channel does not result in chip failure. Thus, the results of the bonding have been classified in the following way.

**Table 2.** Bonding results for different process parameters. If not stated otherwise, adhesive (Epo-Tek 375) layers with  $d_{adh} \sim 2.5 \mu\text{m}$  are transferred, the chip and lid assembly are evacuated for  $t_{vac} = 3 \text{ h}$  under a constant pressure of  $\sim 1 \text{ kN}$  and cured directly afterward for  $t_{cure} = 3 \text{ h}$ . Best results are achieved for chips featuring capture channels. The last two rows refer to experiments based on Epo-Tek 302-3M as adhesive in combination with capture channels.

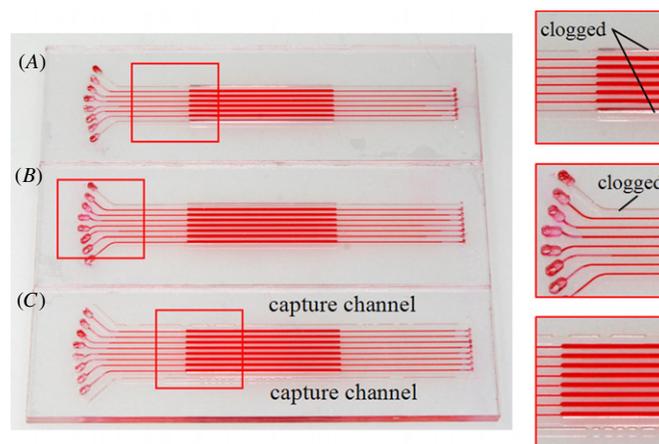
Process Variation	Perfect	Good	Working	Fail
No pressure @ cure	0	0	0	3
$t_{vac} < 2 \text{ h}$	0	0	1	7
$t_{vac} > 12 \text{ h}$	0	0	0	3
$d_{adh} < 2 \mu\text{m}$	0	0	0	5
$d_{adh} > 3 \mu\text{m}$	0	0	11	3
$d_{adh} \sim 2.5 \mu\text{m}$	0	0	5	0
$t_{store} = 48 \text{ h}$	0	3	0	0
Remove adhesive	0	3	0	0
Capture channels	35	2	3	0
302-3M, $d_{adh} < 2 \mu\text{m}$	1	0	0	5
302-3M, $d_{adh} \sim 2.4 \mu\text{m}$	10	0	0	2

- Fail: multiple leaks and/or  $>2$  channels clogged
- Working: no internal leaks, up to two channels clogged
- Good: no leaks, one channel clogged
- Perfect: no leaks, all channels operational

The results of the chip bonding are summarized in table 2. First, it is imperative to apply a high pressure on bonding partners during post-processing and cure. Second, for the presented chip geometry, no good bonding results could be achieved without an evacuation step after the adhesive transfer. The evacuation step can lead to a redistribution of adhesive on the interface between the chip and lid and thus can compensate for process variations. It should however be noted that a very long evacuation leads to clogging as the adhesive is also pulled into the channels over time. Further, transferring  $\sim 2.5 \mu\text{m}$  onto the chip surface is the recommended layer thickness for the selected adhesive. A higher amount results in more clogged channels (figure 3(A)) while a smaller amount does not exhibit sufficient cohesive forces to result in a strong bond.

Still, even based on optimal parameters, it has not been possible to achieve a ‘perfect’ bonding result (figure 3(B)). The results can be improved by storing the chips at room temperature after evacuation. This however reduces the throughput and thus different ways are desirable. It has been observed that for the presented chip, only the outer channels tend to clog in most cases. It is thus assumed that the distance between a feature and the next larger, adhesive-covered area is the dominating factor for clogging of channels. Some excess adhesive has to be present on the chip surface to compensate for e.g. a variation in surface planarity. Adjacent channels can thus be clogged if near to a larger area covered with adhesive, i.e. near a supply.

To test this assumption, the adhesive has been manually removed from the sides of chip after transfer with an acetone wipe which again lead to improved results. A more defined approach however is the integration of capture channels (figure 1) which collect excess adhesive and thus prevent the outer channels from clogging (figure 3(C)). For the applied test chips,  $200 \mu\text{m}$  wide and deep channels are milled in a distance of  $1 \text{ mm}$  to the respective outer reaction area. The dimensions



**Figure 3.** Example images and close-ups of bonded chips filled with food dye for better visualization. (A) Chip sealed by a  $3.5 \mu\text{m}$  adhesive layer. The outer channels are clogged. (B) Chips sealed with optimal parameters. A single channel is clogged. (C) Perfectly bonded chip featuring capture channels.

of the capture channels should be equal to or smaller than the shallowest or least wide functional channel. Otherwise, excess adhesive would flow into channels exhibiting the highest capillary pressure and not into the capture channels. Additionally, it could be feasible to add a vent to each capture channel to further promote the adhesive flow and thus the collection of excess adhesive.

It should be noted that a yield  $> 90\%$  has not been achieved so far (table 2). Still, it should be possible by optimizing the position of the capture channels.

For the less viscous adhesive (Epo-Tek 302-3M), about the same layer thickness has to be transferred with respect to the primarily evaluated adhesive (Epo-Tek 375) to achieve perfect bonding results based on chips featuring capture channels. The failed chips correlate to the increased risk of channel clogging.

### 3.4. Process chain

- Ultrasonicate chips for 10' in 2-propanol
- Dry with pressurized nitrogen
- Surface activation in  $\text{O}_2$  plasma, 4 min, 200 W
- Transfer  $2.5 \mu\text{m}$  of Epo-Tek 375 onto the chip surface
- Align the chip and lid in the chip holder
- Apply force  $> 1 \text{ kN}$  on chip assemblies
- Evacuate assembly for 3 h @  $10 \text{ mbar}$
- Cure assembly for 3 h @  $70 \text{ }^\circ\text{C}$

## 4. Conclusion

In this note, the influence parameters for the adhesive bonding of polymer chips have been evaluated. Consequently, a process chain with parameter recommendations is provided which can greatly reduce the time and costs for bonding development of a custom lab-on-a-chip. Further, the bonding principle in combination with the selected adhesive allows for applications where high temperature stability and reagent storage on-chip are required e.g. a solid-phase PCR.

## Acknowledgment

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