euspen's 21st International Conference & Exhibition, Copenhagen, DK, June 2021
www.euspen.eu

Dimensional characterization of micro-milled polymer channels for acoustic blood plasma separation

Komeil Saeedabadi[1], Fabian Lickert[2], Henrik Bruus[2], Guido Tosello[1], Matteo Calaon[1]

[1]*Technical University of Denmark, Department of Mechanical Engineering, DK-2800 Kgs. Lyngby, Denmark*
[2]*Technical University of Denmark, Department of Physics, DK-2800 Kgs. Lyngby, Denmark*

komsae@mek.dtu.dk

Abstract

We here present development towards a novel cost-effective fully polymer-based acoustofluidic chip as a Point-of-Care diagnostic platform for blood plasma separation and analysis. Moving from glass chips to a polymer-based platform, prototype test samples were produced by injection moulding using four different polymers. PMMA (Lucite Diakon TD 525), COC (Topas 5013L-10), PC (Sabic Lexan EXL 1433T) and PS (BASF Polystyrol 158 K) were selected as potential candidates for the final commercial production. Finite element modelling of particle acoustophoresis behaviour in the PMMA channels provided information on optimal channel dimensions with an acoustic resonance frequency of 1.26 MHz for a water-filled channel. As a result, channels with design dimensions of 150 µm height, 375 µm width and 50 mm length were milled into the surface of the four different substrate materials. To ensure dimensional compliance of the micro-milled channels with design dimensions, post-milling dimensional metrology was performed using an Olympus LEXT laser confocal microscope. Ten samples of each of the four different substrate materials were inspected. In addition, analysis of surface roughness, S_a, of the channels was carried out. The results indicate a maximum dimensional variation of ±6 µm for height, ±3 µm for width and ±100 nm roughness. Dimensional and surface roughness variations have been characterized as reference values for different simulated acoustic energy density scenarios. The output from the metrological characterization is important for further simulation and optimization of the acoustic blood plasma separation chips, since the acoustic resonances are sensitive to the actual chip dimensions and their variation.

Injection moulding, micro-milling, lab-on-chip, metrology, acoustofluidic, PMMA, COC, PC, PS, FEM simulation

1. Introduction

Lab-on-a-chip systems have received immense attention in the recent years for their versatility, cost-effectiveness, reproducibility and last but not least, scalability. UV-lithography techniques have been the favourable process choice for manufacturing such platforms thanks to tooling procedures derived from the microelectronics industry. Moreover, over the past few years, the advancements in the field of rapid prototyping introduced a broad realm of capabilities that now links the field to lab-on-chips and organ-on-chips production [1].

Benefiting from rapid prototyping techniques on top of the advantages that polymers offer, especially with regards to the cost, has given rise to studies for manufacturing low-cost point-of-care diagnostics devices that separate and enrich cells using acoustic forces. The lack of a predictive model for resonant acoustofluidic platforms was, however, problematic and prevented research in this field from exploiting its full potential [2]. In 2012, Bruus presented a review of the theory of the acoustic radiation force and derived a second-order time-averaged relation to explain acoustophoretic motion of micrometre-sized materials inside an ultrasound field [3]. In 2019 Moiseyenko and Bruus [4], introduced a model for whole-system ultrasound resonances which could serve as a foundation for a full-polymer acoustophoresis platform. The advent of the recent manufacturing capabilities along with the theoretical groundwork gave birth to the AcouPlast project to design and manufacture an all-polymer device for acoustic particle separation using whole-system resonances in polymer chips. Through a well-tested and experimentally validated numerical method [5], it was demonstrated that good acoustophoresis can be attained inside a microchannel that is embedded within an all-polymer chip using excitation of whole-system resonances [4].

Prior to proceeding to the production stage using a micro-injection moulding tool that is designed and manufactured specifically for producing a chip with designated dimensions, micro-milling was considered as a rapid prototyping technology to help further analyse the process while optimizing resources. Milling as one of micro/meso mechanical manufacturing techniques confers new opportunities to develop microfluidic channels in both metals and plastics [6]. Other alternative methods, namely etching and energy beam processes are widely deployed to fabricate surface structures, however, they introduce other issues such as flexibility, cost and production rate and they are not exploitable for our study purpose. Compared to these methods, mechanical processes of cutting and forming offer a certain advantage in terms of flexibility of the shapes they can manufacture in high production rates [7].

In the present study, injection moulding is used to manufacture highly transparent polymer chips as the initial step. Micro-channels are machined using micro-milling with design dimensions optimized with respect to acoustic resonance frequency using FEM numerical simulation. The numerical simulations measure the particle focusing ability

Table 1. Injection moulding process parameters of the four different substrate materials namely, COC, PMMA, PC and PS.

Parameters	Value			
	COC	**PMMA**	**PC**	**PS**
Operating pressure (bar)	700	1600	2300	1400
Counter pressure (bar)	180	100	100	60
Tool temperature (°C)	80	80	80	45
Max barrel temperature (°C)	265	235	280	200
Injection rate (cm^3/s)	29	28	25	24
Injection time (s)	0.54	0.58	0.66	0.65
Holding time (s)	20	20	20	5
Dosage volume (cm^3)	14 100	15 450	15 650	15 100
Decompression (cm^3/s)	1.00	1.00	1.00	0.50

of suspended micro-particles as well as the acoustic energy density in a PMMA chip with the concept of whole-system resonance frequency introduced by Moiseyenko and Bruus [4,5,8]. The manufactured chips' dimensional measurements were characterized using both laser confocal microscope and Scanning Electron Microscopy (SEM) to ensure that the channels comply with the input dimensions and furthermore, to investigate the accuracy and precision of micro-milling as a prototyping tool.

2. Injection moulding equipment

The chips were manufactured via an injection moulding machine Allrounder® 370A from Arburg GmbH, Lossburg, Germany. The machine offers a maximum clamping force of 600 kN, a maximum injection pressure of 250 MPa and injection speed of 300 mm/s. The machine benefits from a reciprocating screw with a diameter of 18 mm and a length to diameter ratio of 24.5. The part produced with the mould, as illustrated in Figure 1, contains two separate but identical chips. Table 1 delineates the conditions under which the parts were produced for each of the four selected substrate materials.

3. Micro-milling of channels

Table 2. Process parameters of milling of the micro-channels on the injection moulded parts.

Parameters	Value/Description
Tool number	346
Diameter (mm)	0.3
Cutting length (mm)	50
Feedrate X,Y	300
Feedrate Z	150
Spindle speed (rpm)	28000
Toolpath length (mm)	1942
Toolpath time (min)	5.77

As a stepping stone towards acquisition of a polymeric chip with embedded micro-channels, the injection moulded chips were milled on their surface via Mikron HSM 400U LP in order to obtain a simple channel with dimensions of 150 µm deep, 375 µm wide and 50 mm long. The chips were milled as can be observed in Figure 1 with parameters specified in Table 2.

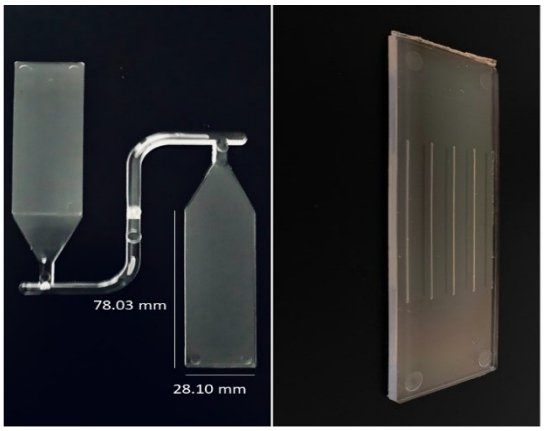

Figure 1. Injection moulded part of high optical transparency before and after milling the channels. The parts were molded with high optical transparency and later, five channels were micro-milled on their surface.

4. Parts quality control

The quality of the parts was evaluated with two methods of SEM and confocal microscopy to provide conclusive and complementary data shown in Figure 2 and 3. To evaluate the dimensional compliance of the milled chips and the replication fidelity of them, three positions were selected on three separate channels over the surface of the chip that resulted to nine separate locations per each polymeric chip. The aforementioned process was repeated for ten separate chips per each of the four substrate material and out of that ten, half possessed the chip thickness of 1.4 mm and the other half 1.9 mm. The depth, the width and the surface roughness value (S_a) of the bottom of the channels were measured using a laser scanning confocal microscope LEXT OLS 4100 using a 20x magnification lens. The obtained data was analysed using the processing software [9].

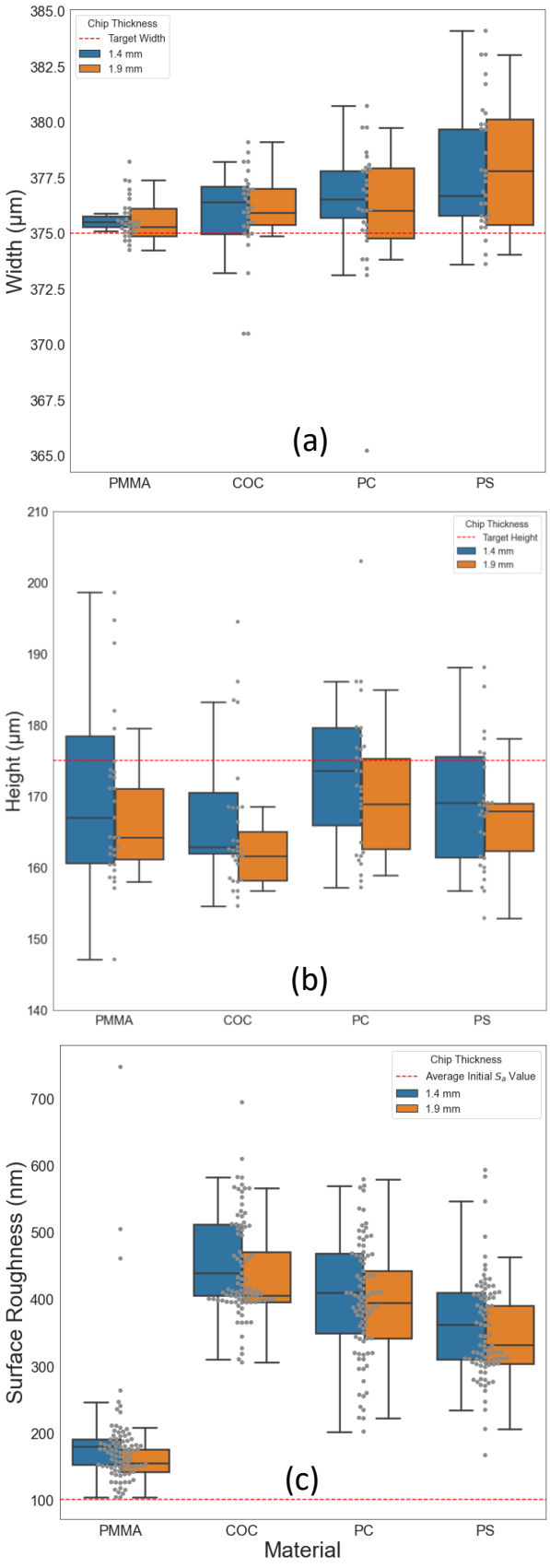

Figure 2. SPIP analysis data for width (a), height (b) and surface roughness (c) of the milled channels for four substrate materials. Error bars indicate standard deviation of repeated measurements. The data points marked on the graphs display the process reproducibility and express dimensional measurement accuracy for each of the four substrate materials and two chip thickness. The target values for height and width are marked with red dashed lines. For surface roughness the red line shows the average value for the surface roughness of the non-machined area.

Additionally, SEM analysis was performed via a Zeiss Supra VP 40 SEM in order to attain better metrological insight by scrutinizing the channels under a certain tilting angle. While conducting the SEM analysis, polymers face charging issues that produces instability of the secondary electron image intensity and therefore, may yield distorted and inaccurate footage [10]. Hence, the chips were coated with a thin gold-layer, with a thickness below 20 nm, using a Cressington 208HR sputter coater before further examination under the SEM. The samples were analysed on a level condition as well as tilted 30° to gain complementary information about the side walls and both ends of the channel as it can be seen in Figure 4.

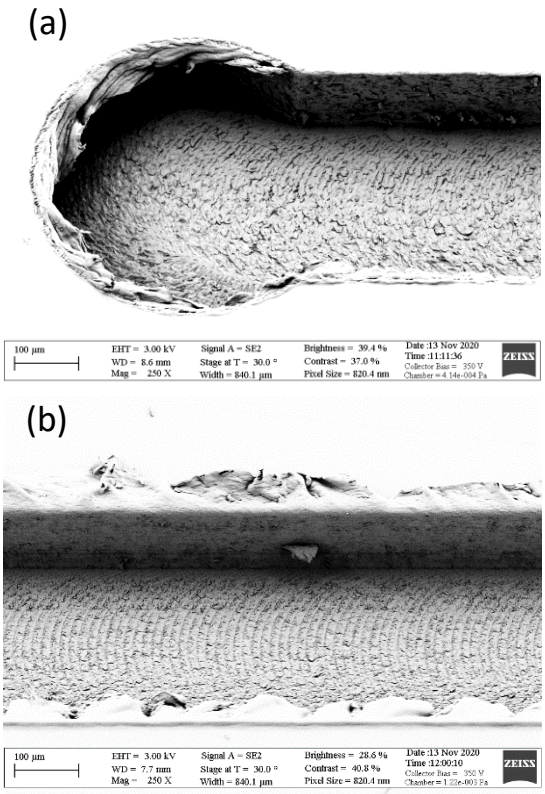

Figure 3. SEM examination of the channel's end (a); SEM analysis of the side of the milled channel with 30° stage tilt (b).

5. FEM simulation

Numerical simulations of the PMMA chips were performed using the finite element software COMSOL Multiphysics 5.5 and following the implementation described by Skov *et al.* [5]. PMMA was selected for the purpose of the simulations since the material parameters such as the transversal speed of the sound (c_T) and transversal attenuation coefficient (α_T), which are essential for numerical simulations have already been established for the material whereas this was not the case for the other three processed polymers. Simulations were performed on a 2D cross-section of the device geometry. In our simulations we included a piezoelectric transducer, made from lead-zirconate-titanate (PZT), used for driving the acoustic focusing. The actuation of the device is done with an anti-symmetric 30 V peak-to-peak voltage amplitude, using a phase-offset of 180° between the two electrodes of the PZT. We furthermore included a 20-µm-thin glycerol coupling layer between the PMMA and the PZT. A schematic of the simulated 2D cross-section of the device can be seen in Figure 4.

The outputs of the FEM simulations highlighted the optimized dimensions to be tested for milling of the channels. Results from the characterization of dimensional variation of the polymer channels were used to refine the FEM model to updated input parameters to appreciate the sensitivity of the acoustic parameters such as resonance frequency and acoustic energy. A sensitivity analysis on the channel width and height was performed in respect to the frequency and the acoustic energy density at resonance of the chip. The simulations were performed with frequencies ranging from 1 MHz to 2 MHz, close to the nominal 1-MHz-resonance of the used PZT transducer and while altering the width and height of the channel by ±10 µm around their specified values. The results of the sensitivity analysis are shown in Figure 5.

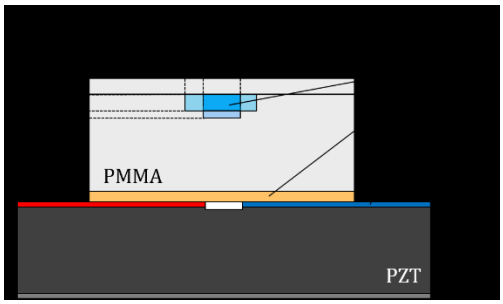

Figure 4. 2D cross-section of the simulated acoustophoresis device. The design consists of a piezoelectric transducer, a glycerol coupling layer (orange) and a PMMA chip including a water-channel. The microchannel has a width w_{ch} and a height h_{ch} and is altered by an amount Δw_{ch} and Δh_{ch} in our numerical simulations.

We observed only small deviations of below ±10 kHz in the resonance frequency of the main resonance, corresponding to a change of less than 1%, when changing the channel dimensions by 10 µm. Bigger changes were found in the acoustic energy density inside the channel at resonance when altering the channel cross-section. The acoustic energy density E_{ac} increased by up to 56% when increasing the channel width by 10 µm. Increasing the channel height h_{ch} on the other hand by the same amount, leads to a decrease of E_{ac} of about 17%.

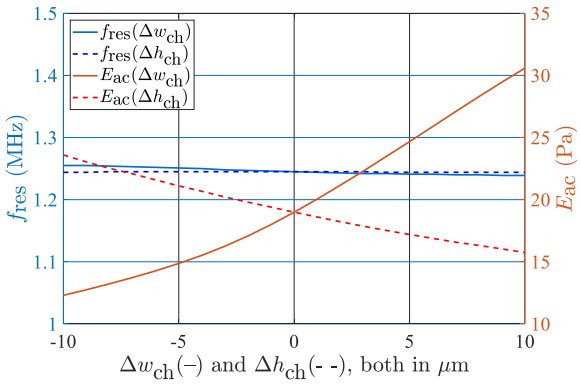

Figure 5. Simulated sensitivity analysis of the resonance frequency f_{res} (blue y-axis, left) and the acoustic energy density E_{ac} (orange y-axis, right) versus changes in the channel width Δw_{ch} (straight line) and channel height Δh_{ch} (dashed line) around the reference values of w_{ch} =375 µm and h_{ch} =150 µm are shown. While the resonance frequency remains almost constant in both cases, bigger changes in the acoustic energy density were observed when altering the channel dimensions.

6. Discussion

The analysis of three parameters of width, height and surface roughness (S_a) shows that respectively a dimensional variation of ±6 µm, ±3 µm and ±100 nm can be observed in the micro-milled channels. Microscopy of the chips was repeated for ten separate chips per substrate material where each chip itself encompasses five channels and only the three in the middle were dimensionally characterized. The acceptability of the established variance is contingent on the sensitivity of the experiment at hand on the given dimensions and in our case, this acceptability was appraised by the sensitivity analysis through 2D numerical modelling.

The results obtained from the numerical simulations show a higher sensitivity of the acoustic energy density at resonance inside the fluid channel towards variations of the channel width, while changing the height of the channel only lead to lesser variation in the energy. The lower variations in the fabrication of the channel width compared to the height are therefore beneficial at achieving energies close to the desired value. Furthermore, the numerical simulations can be used in combination with the known variance of the milling process to optimize the channel dimensions at a given resonance while only causing minute changes in the resonance frequency.

7. Conclusion

Micro-milling was performed as a prototyping tool to realise channels on four different polymers. The optimal dimensions for channels of PMMA was measured with FEM numerical simulations using COMSOL Multiphysics. The obtained measurements were 150 µm for height and 375 µm for width of the PMMA channel and using micro-milling, results with a dimensional variation of ±6 µm for the height and ±3 µm for the width was achieved. Additionally, surface roughness analysis (S_a) was also done which presented a maximum variation of 100 nm for each substrate material. To shed light on the effect of the measurement tolerance that micro-milling introduced to the system on acoustic parameters such as resonance frequency and acoustic energy, sensitivity analysis with the attained dimensional variation values was executed for both height and width of the microchannel. The sensitivity analysis revealed a negligible shift of the resonance frequency within the given dimensional variations. Higher changes were observed in the acoustic energy density, which can be used in combination with the known variations of the milling process to further improve the performance of the microfluidic device.

Acknowledgment

This work is part of the Eureka Eurostars-2 E!113461 AcouPlast project funded by Innovation Fund Denmark, grant no. 9046-00127B, and Vinnova, Sweden's Innovation Agency, grant no. 2019-04500.

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