Hedvika Maxová*, Stephan Behrens, Mandy Petzold, Jürgen Philipp and Florian Schmieder

Scalable manufacturing of microphysiological systems to extend the production volume

When is the right time to switch to injection moulding?

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Abstract: Microphysiological systems (MPS) have emerged as a valuable tool in preclinical drug testing. These systems are capable of simulating *in vivo* conditions and physiological functions within an *ex vivo* tissue culture setting, resulting in improved accuracy of the obtained data. However, the lab-scale manufacturing processes of MPS are associated with high manufacturing time and costs, and are thus unable to sustain high-throughput studies [1]. Thus, we have to rethink the design of MPS considering high-volume production technologies from the beginning on. In this study, we examined which design features can help to translate the production process of MPS from a small scale micro-milling process to high-volume injection moulding. Moreover we compared the manufacturing costs of both manufacturing processes to figure out the right time to switch to injection moulding. To compare both manufacturing processes, we designed a tissue culture MPS by using common design features that fit to both manufacturing processes and compared design features that have to be changed, when transitioning from micro-milling to injection moulding. The break-even point was investigated using public pricing tools suggesting, that injection moulding has considerable potential in enhancing the scalability of MPS production starting from a production volume of 200 units. This could help further projects reducing manufacturing costs and time and foster the early switch to injection moulding, thus yielding in an enhanced accessibility of new MPS concepts.

Keywords: micro physiological systems, microfluidics, injection moulding, micro-milling, break-even point

***Corresponding author: Hedvika Maxová:** Hochschule für Technik und Wirtschaft, Dresden, hedvika.maxova@mailbox.tu-dresden.de
Stephan Behrens, Mandy Petzold: Fraunhofer Institute for Material and Beam Technology IWS, Dresden, Germany
Florian Schmieder: Fraunhofer Institute for Material and Beam Technology IWS, Dresden, Germany

1 Introduction

1.1 Microphysiological systems

Microphysiological systems (MPS) are miniaturised microfluidic chips used in preclinical studies to evaluate the efficacy and safety of drugs. Therefore they combine a technical periphery (mostly microfluidic cartridges) with cell based artificial tissue or organ equivalents and the substance that should be tested, to generate preclinical data on efficacy and safety (figure 1). To offer an advantage compared to *in vitro* experiments in standard cell culture lab ware, MPS emulate the natural environment of individual tissues and simulate vital functions, such as blood flow, specific oxygen levels, or heart muscle contraction [2].

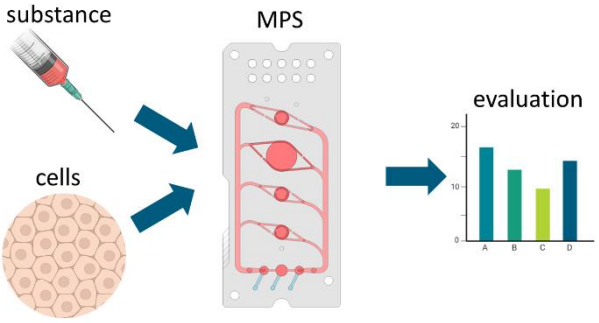

Figure 1: The use of MPS in preclinical studies; cells are cultured on a MPS enabling accurate evaluation of substances; created in BioRender.com

This can be used to create co-culture model systems of different artificial organs like a liver-kidney model to evaluate the toxicity by emulating metabolization and excretion [3], yielding in a better prediction when compared to *in vitro* experiments in well plates. MPS can replicate human tissue in a miniaturised form, with one thousandth to one millionth of the size of human organs making preclinical testing more cost efficient [4]. Thus, MPS already pave the way into a new area of preclinical testing. Nevertheless, the adequate prediction of toxicity and safety of different drugs requires specifically adopted MPS that perfectly fit to the clinical question they should replicate. Therefore, researchers permanently reinvent

MPS systems and prototype them with different manufacturing methods.

1.2 Manufacturing of Microphysiological Systems

In recent years, a wide range of manufacturing methods has been developed for the production of microfluidic cartridges on a laboratory and industrial scale. The selection of the appropriate manufacturing process is based on several aspects ranging from the technical function of the cartridge to the complexity of the design and the desired production volume (see Figure 2:).

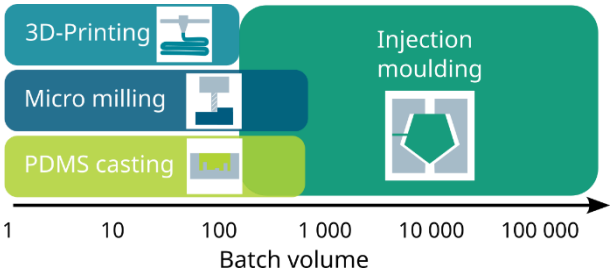

Figure 2: Suitable production volume for different fabrication methods (modified from [5])

Widely established manufacturing processes in the lab-scale production include silicon casting (PDMS), 3D printing (mostly FDM and stereolithography) and micro-milling. While the casting of silicon is mainly used for fabrication of flexible parts (e.g. lung-on-chip allowing a stretching of the material) [6], 3D printing facilitates the fabrication of complex components (such as micromixers, multichambered chips, and microtraps) with minimal setup costs [7]. Micro-milling is especially suited for the processing of hard materials with complex geometries and tight tolerances (used for rapid prototyping and fabrication of moulds) [8]. As a subtractive manufacturing process, micro-milling utilizes rotary cutting tools to remove material from a workpiece. The trajectory of the cutting tool is controlled by a computer (CNC) based on a 3D model to create the desired design. CNC milling automates the process and increases the repeatability of parts. However, compared to generative manufacturing, this method is associated with higher material costs and tool wear [8]. In serial production, injection moulding is the standard fabrication method, due to the short production time and low manufacturing costs (used for devices for high-throughput screening) [9]. Injection moulding is a manufacturing process in which molten material (typically thermoplastic) is injected into a mould (manufactured by milling). This method allows for the production of complex parts with tight tolerances and high repeatability, fully automatically and in a matter of seconds.[10]

Considering the differences of micro-milling and injection moulding, it seems necessary to develop feasible strategies to switch from lab-scale to serial production. Hence, the objective of this study was:

1. to design a microfluidic cartridge that can be manufactured using both injection moulding and milling
2. to compare design features that have to be changed, when transitioning from micro-milling to injection moulding
3. to examine the manufacturing costs and to determine the production volume at which it is economical to switch from milling to injection moulding

2 Material and Methods

To scale the manufacturing of MPS it is necessary to have a deeper look on their basic structure. The MPS used for this study consists of a microfluidic cartridge, which allows the cultivation of up to ten tissue or organ equivalents. The microfluidic cartridges consists of three components: a microfluidic main body, a micropump and a bottom layer to enclose the pump and seal the channels of the main body. Hence, the bottom layer and pump are not suited for translation of manufacturing processes, the present study focuses on the manufacturing of the main body.

2.1 Design of the microfluidic main body

The overall dimensions of the main body of the microfluidic cartridge are 40 mm x 90 mm x 15 mm. The main body is equipped with ten reservoirs, each with a capacity of up to 1500 µl of fluid. The reservoirs positions are derived from a 48-well plate. The bottom side incorporates an opening for a micropump, which is connected to the reservoirs through fluidic channels ensuring fluid flow within the reservoirs.

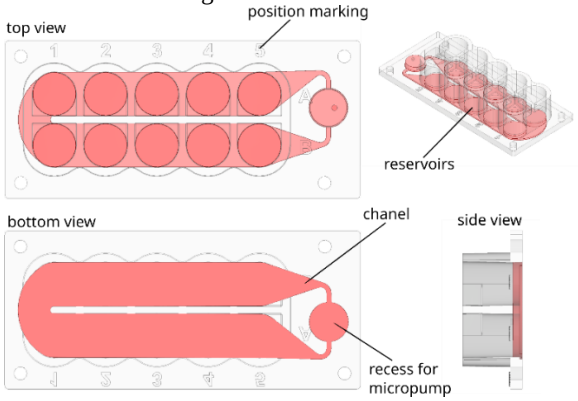

Figure 3: Design of the main body featuring a micropump and ten reservoirs connected through a fluidic channel

The material of choice was polycarbonate (PC) because of its wide availability, biocompatibility, transparency, proper cell attachment and resistance to chemicals used for sterilisation [11].

2.2 Evaluation of manufacturing costs

To determine the manufacturing costs of the microfluidic main body, we obtained quotes for both injection moulding [12] and micro-milling [13]. Since the quotes for both manufacturing processes were obtained from an external provider, the cost of the machine was excluded from the calculation. Therefore, the cost of the milled part equals the manufacturer's price per piece and the shipping cost. Additionally, the cost of the injection moulded part also include the mould and the setup cost. The total costs per unit was calculated for production batches starting from 100 units and ending with 1000 units with a step width of 100 units. The preliminary results obtained were then used to estimate the minimum production volume at which transitioning to injection moulding becomes economically feasible (break-even point).

3 Results

3.1 Comparison of common design features

To optimize the design of the microfluidic main body for both manufacturing processes, we have modified some features of it. It is important to note that these modifications do not change the interface with the micropump and have no impact on the overall functionality of the chip. They are however imperative when transitioning from one manufacturing method to another. The critical geometrical features are fillets, markings, side wall angle and surface finish (see Figure 4).

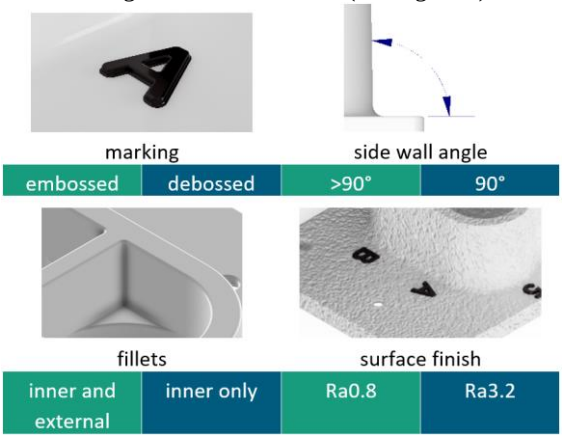

Figure 4: Comparison of critical features in micro-milling (blue) and injection moulding (green)

Because of the rotary cutting tool, inner edges of milled parts need to be rounded (fillets). For injection moulding, a negative of the part (mould) is milled und therefore external fillets are necessary. For easier injection, inner fillets are incorporated as well. To minimize the cost of the part or mould the trajectory of the cutting tool has to be minimized. Therefore, it is best for markings on injection moulded parts to be embossed whereas milled parts have to be debossed. For easier demoulding, all the sidewalls of the moulded body are slanted (degree >1°), whereas sidewalls of the milled body are parallel to the cutting tool if possible. For a smoother surface finish, an additional step in the milling process of the part itself or the mould for injection moulding is required. Polishing of the one-time mould has smaller impact on the cost in comparison to polishing of every piece, resulting in a smoother surface finish of injection moulded parts (Ra0.8) compared to micro-milled parts (Ra3.2).

3.2 Comparison of manufacturing costs

A comparative analysis of the costs indicated by the quotations was conducted for the two fabrication methods. The results of this analysis are presented in Figure 5.

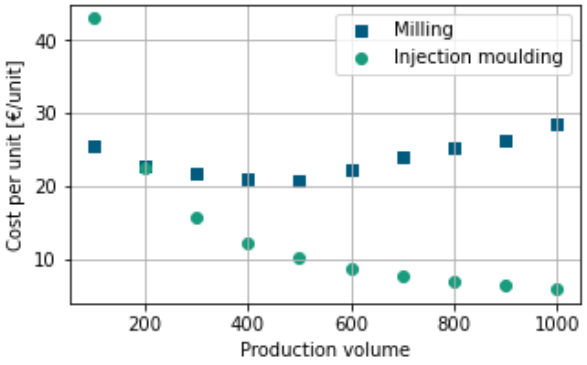

Figure 5: Break-even point analysis comparing the cost [€/unit] of injection moulding (green) and micro-milling (blue) for different production volumes, N=1

For micro-milling the total costs (Ct) range between €20.57 and €28.50 per unit. A minimum cost per unit occurs at a production volume of 500 units. The cost of micro-milling varies only due to transport costs (which increase per unit with lower production volumes) and the need to restructure orders (which increases with higher production volumes). The difference between the highest and lowest costs per unit in the range between 100 and 1000 units is 27.8%.

The total costs of injection moulding consist of two components: variable costs (C_v) and fixed costs (C_f). The fixed costs are a one-time expense and consist of the costs to

manufacture the mould (€3605.00) and the set-up costs to equip the machine with the mould (€499.50). The mould is made from aluminium, predominantly because of the lower procurement costs in comparison to a traditional steel mould. Additionally to the lower cost, aluminium moulds offer superior heat dissipation capabilities over steel moulds. [14]. Conversely to the fix costs, variable costs are incurred per unit and exhibit a decline with increasing production volumes, ranging from €1.97 to €1.67 per unit. The total cost (C_t) per unit can be calculated from the variable cost (C_v), the fixed cost (C_f) and the production volume (n) using the following formula:

$$\boldsymbol{C_t = C_v + C_f/n} \quad (1)$$

Due to the fixed costs of injection moulding being distributed over the units produced, the total costs of injection moulding decrease exponentially as the production volume increases (cost reduction of 86.6% from 100 to 1000 units).

The break-even point, i.e. the minimum production volume at which a manufacturing transition is feasible, is approximately 200 units. For greater production volume, injection moulding is the more economical option. Conversely, for production volumes below or equal 200 units, the more cost-effective option is micro-milling.

4 Conclusion

The objective of this study was to evaluate the transition of the manufacturing of MPS from micro-milling to injection moulding, with a focus on cost-effectiveness and scalability. By designing a part that can be manufactured by both methods, we conducted a comparative cost analysis based on manufacturer quotes. The findings indicate that while milling remains cost-effective for small production volumes (≤200 units), injection moulding becomes significantly more economical at larger scales (>200 units). However, we are aware, that the costs can vary based on chosen manufacturer, delivery time and particular tolerance requirements. Thus, these results could differ if other distributers are compared or internal manufacturing capacities are utilized. Therefore, subsequent studies should take a deeper look into the manufacturing landscape and also validate other manufacturing options like 3D-printing. Overall, the findings of this study indicate that transitioning to injection moulding could play a crucial role in the wider availability of MPS for high-throughput drug testing and biomedical applications. However, for lab-scale production of small batch sizes micro-milling remains the manufacturing process of choice.

Author Statement

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References

[1] Pandey CM, Augustine S, Kumar S, et al. Microfluidics Based Point-of-Care Diagnostics. Biotechnology journal 2018; 13.

[2] Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. Nature reviews. Genetics 2022; 23: 467–491.

[3] Theobald J, Ghanem A, Wallisch P, et al. Liver-Kidney-on-Chip To Study Toxicity of Drug Metabolites. ACS biomaterials science & engineering 2018; 4: 78–89.

[4] Wikswo JP, Curtis EL, Eagleton ZE, et al. Scaling and systems biology for integrating multiple organs-on-a-chip. Lab on a chip 2013; 13: 3496–3511.

[5] Schmieder DF, Dipl.-Ing. Stephan Behrens, Mikro- und Biosystemtechnik, Fraunhofer-Institut für Werkstoff- und Strahltechnik IWS. In-Vitro-Diagnostik – maßgeschneidert und massentauglich. LABORPRAXIS 2022 Nov 8.

[6] Shrestha J, Ghadiri M, Shanmugavel M, et al. A rapidly prototyped lung-on-a-chip model using 3D-printed molds. Organs-on-a-Chip 2019; 1: 100001.

[7] Geffert ZJ, Xiong Z, Grutzmacher J, et al. Multipath Projection Stereolithography for Three-Dimensional Printing Microfluidic Devices. ACS applied materials & interfaces 2024; 16: 69807–69817.

[8] Guckenberger DJ, Groot TE de, Wan AMD, Beebe DJ, Young EWK. Micromilling: a method for ultra-rapid prototyping of plastic microfluidic devices. Lab on a chip 2015; 15: 2364–2378.

[9] Morelli L, Serioli L, Centorbi FA, et al. Injection molded lab-on-a-disc platform for screening of genetically modified E. coli using liquid-liquid extraction and surface enhanced Raman scattering. Lab on a chip 2018; 18: 869–877.

[10] Hopmann C, Michaeli W, Greifeld HR, Ehrig F, Greif H. Technologie des Spritzgießens: Lern- und Arbeitsbuch. 4th ed. München: Hanser 2017.

[11] Le Grand DG, Bendler JT, editors. Handbook of polycarbonate science and technology. New York, Basel: Marcel Dekker Inc 2000.

[12] Protolabs | Rapid Prototyping & On-demand Production Services; 2025 [cited 2025 Mar 31].

[13] Spanflug. Einfach beschaffen, effizienter fertigen mit Spanflug; 2025. Available from: URL:https://spanflug.de/ [cited 2025 Mar 31].

[14] [Marconi P, Amarante E, Ferreira C, Beal V, Ribeiro Júnior A. Steel and Aluminum Molds: The Effect of Thickness on Productivity and Part Quality. Materials and Manufacturing 2024; 17.