RAPID PROTOTYPING, MANUFACTURING AND APPLICATION OF ORGAN-ON-A-CHIP AND CELL BASED LAB-ON-A-CHIP SYSTEMS

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INTRODUCTION

Nowadays there are basically two pre-clinical ways to gain a better understanding how physiological parameters and drugs can influence the human organism: well-established 2D cell culturing and complex animal models. Organ-on-a-chip and lab-on-a-chip devices has been developed to create more complex 3D cell models which are exposed to dynamic ambient conditions and a proper readout of the cell behavior.

Through the last years several ways has been investigated to model a more physiological environment and to include non-invasive sensors to better predict influences on the cells in culture.

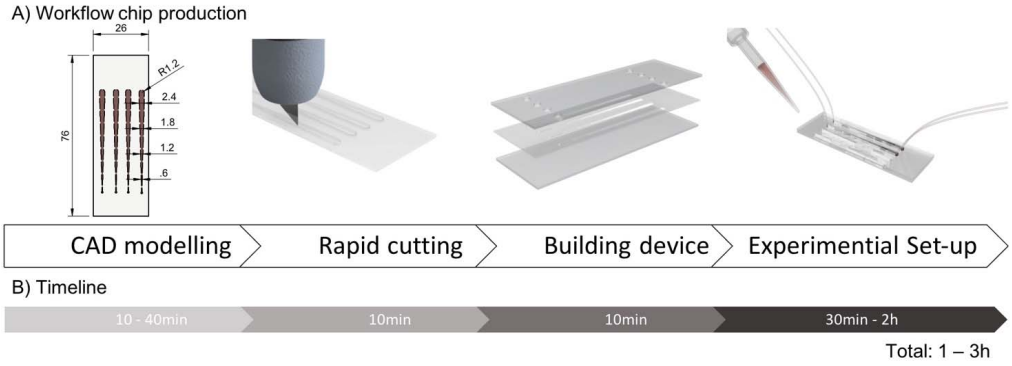
A major challenge the research of microfluidics systems are the many iteration steps which have to be taken from the first design up to the working device.

EXPERIMENTS / FUNDAMENTAL OF THE PROBLEM / EXAMINATIONS

Furthermore through the commercialization of several device the industry is seeking for suitable methods to produce cheap and robust devices with designs in the scale of micrometers. Therefore there is still a gap between the rapid manufacturing for research purpose and the industrial manufacturing for commercial devices.

To hit the challenge and overcome the gap new rapid prototyping methods has to be investigated and evaluated.

This work will investigate the applicability of new materials for the rapid prototyping and the application of those in organ-on-a-chip and lab-on-a-chip devices.



Picture 1:
A) Rapid prototyping of biocompatible pressure sensitive adhesives

B) Time line for concept-to-chip-time

One promising method is to use biocompatible pressure sensitive adhesives to establish microfluidic system for a physiological cell-like environment.

This method to assemble and built those device must be rated in regards of effort and accuracy in microfabrication as well as the bonding ability to other materials to build up multi-featured devices. Beside mechanical and chemical properties the investigation of biocompatibility is necessary to establish a proper valid cell model with in the device.

The following pressures sensitive adhesives are investigated:

Name	Total thickness	Layer thickness	Adhesives thickness	Adhesives type
ARcare 92712®	48.26 µm	12.7 µm polyester	17.78 µm	MA-93 acrylic pressure sensitive
ARcare 90445®	81.28 µm	25.4 µm polyester	27.94 µm	AS-110 acrylic medical grade
ARcare 90106®	142.24 µm	25.4 µm polyester	58.42 µm	MA-69 acrylic hybrid medical grade
ARseal 90880®	142.24 µm	50.8 µm polypropylene	45.72 µm	SR-26 silicone adhesive

Table 1 Pressure sensitive tape

RESULTS AND DISCUSSION

To analyse the cutting behaviour of pressure sensitive adhesive tapes a defined structure was cut, residual material removed and the deformation of the edges of the structure was measured.

When the digital model for the given chip design already exist, the chip structures can be cut with in minutes. By primary evaluation of the plotting resolution structures down to 100 µm are cut. The limiting factor for the machining of the pressure sensitive double-sided adhesive tapes is how easy and under which deformation the residual material of the designed structure can be peeled off. This represents the limit of the scale for cutting structures within pressure sensitive double sided adhesive tape.

The chip was built easily within 3h as described in Figure 2. The chip stayed leakage free for 7 days was perfused at the second day with 2 µl/min maintained at 37ºC. The seeded BeWo b30 cells adhered after 24h to the collagen treated membrane (see Figure 4) until day 7. Through the establishment of a monolayer of BeWo b30 cells the resistance of the cells and the membrane increases up to 0.12 kOhm and 0.17 kOhm at day 2 (see Figure 27 A). The TEER increases significantly with developing of tight junctions between the cells. This can be observed at day 2 where the slope of the TEER measurement increases and a confluent monolayer was established. Since confluence was achieved at day 2 flow was initiated to remove waste products of the cell metabolism.

CONCLUSION

The membrane- and electrode-integrated cell-based lab-on-a-chip system is established and an experiment over 7 days with BeWo b30 cells is carried out. By using pressure sensitive double-sided adhesive tapes the concept-to-chip time is under 3h. This rapid prototyping represents a very easy and fast adaption and manufacturing of the membrane- and electrode-integrated cell-based lab-on-a-chip system. There is no clean room needed and only a low investment in the manufacturing infrastructure is necessary. The adhesive tape ARcare 90445 shows suitable properties which withstand the experimental set up. ARcare 90445 was chosen to build up the membrane- and electrode-integrated cell-based lab-on-a-chip system.

The valid lab-on-a-chip system can be used to study the influence of the barrier properties through nanoparticles and drugs. Beside the TEER measurement the integrated electrodes can be used to new applications as short circuit current, action potentials of electrically active cells for electrophysiology studies, which are currently lacking in the majority of micro physiological systems.

REFERENCES

[1] Odijk, M. et al. Measuring direct current trans-epithelial electrical resistance in organ-on-a-chip microsystems. Lab Chip 15, 745–52 (2015).