Rapid development of microfluidic device using additive manufacturing

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Abstract

The aim of our project is to create a biological cell model by microfluidics device. The current methods for production of microfluidic devices are complex and time-demanding. Therefore, we have proposed, tested and verified a specific technology for the development of microfluidic device using stereo-lithography. We have produced several types of microfluidic devices: from simple one to devices with complex geometry. We have proved that it is possible to produce uniform unilamellar liposomes with controlled size and shape. The liposomes will serve as biological cell models to test mechanical properties living cells of various phenotypes.

Keywords: additive manufacturing, liposomes, microfluidic device, mechanical properties

1. Introduction

Microfluidics is both the science which studies the behaviour of fluids through micro-channels, and the technology of manufacturing micro miniaturized devices containing chambers and tunnels through which fluids flow or are confined [1]. At micrometrics scale, the fluids behave very differently than they do in everyday life: these unique features may be used either for controlled synthesis or detection using a minimum of sample. Fluids in the microfluidic channels could be directed, mixed, separated or manipulated by external field.

In biology, the microfluidics allows to modify the environment of a sample at the scale of the cell itself. The possible applications range from proteins crystallization, performing the polymerase chain reaction, sequencing DNA, study protein expression of single cells, perturbation of embryonic development in flies, or culturing the cells [2]. An important application of microfluidics in medicine is the liposome production. Liposomes are composed of lipid bilayer membranes that encapsulate an aqueous volume [3]. Liposome structures have a wide range of applications in biology, biochemistry, and biophysics. In conventional methods, lipids are spontaneously assembled into heterogeneous bilayers in a bulk phase. Microfluidics enables precise control of the lipid hydration process and thereby production of liposomes with controlled size and composition.

A microfluidic chip is a pattern of microchannels, molded or engraved. The current methods for production of microfluidic devices are complex and time-demanding and involve soft lithography (REM – replica molding, Injection molding, Hot embossing, Micro-contact printing, Micro-molding in capillaries).

High-precision additive manufacturing has potential to engineer of functional microfluidics devices at lower higher and higher speed. This contribution aims on overview of methods that were used to produce microfluidics devices at CTU in Prague.

1.1 Methods

Two methods have been adopted for microfluidic devices production: stereo-lithography and polyjet additive manufacturing. In the former, the model is produced by curing layers by layers of photopolymer resin by ultraviolet (UV) laser beam. Stereo-lithography (SLA) is suitable for creating very fine surfaces. Common used materials for SLA are PDMS, FEP, glass and resin. For microfluidics applications, the materials must be biocompatible, because microfluidic devices are in contact with living material.

Polyjet is the only technology, that is able to print multiple materials simultaneously. Operation principle is similarly to inject printing. Polyjet 3D printers use softly print head nozzles, which are filled photo curable liquid material. The material is simultaneously cured as it is deposited via UV light. Uses polyjet technology, it is possible to produce complex geometries and thin walls thanks to accuracy down to 0.1 mm and microscopic layer resolution. Layer thickness is down to 14 microns and its accuracy is up to 200 microns for full model size [4].

All of CAD models were designed in 3D CAD design software SolidWorks, (SolidWorks Corporation, Santa Monica, CA, USA). A variety on models were prepared with subsequent sizes of channel and connection angles ranging from 30° to 180°. Choosing the right angle has high impact on flow rate where the Reynolds number with

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viscosity of the liquid needs to be evaluated. The smallest size was 0.3 mm and the biggest 1 mm.

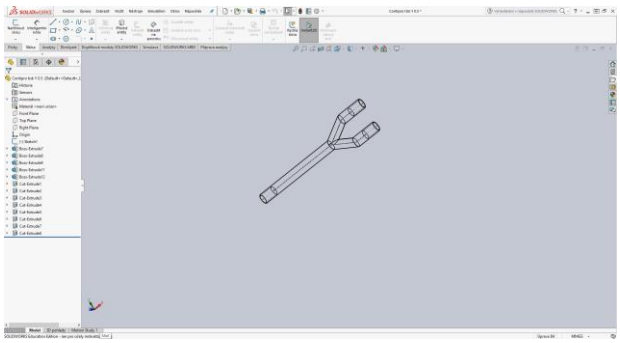

Figure 1"SolidWorks"Y type of microfluidic device

Microfluidic devices were in the first case manufactured by 3D printer Projet 1200, which uses Stereo-lithography (SLA) and the Digital Light Processing (DLP) 3D printing technology. Projet 1200 uses a DLP LED projector to solidify liquid resin. Later, we have utilized 3D printer Stratasys 750 that is based on Polyjet technology.

Table 1 Basic specifications of AM process using Projet 1200.

Technology	SLA, DLP
Material	Liquid resin
Min. layer thickness	0.03 mm
Max. build size	43x27x150 mm

Table 2 Basic specifications of AM process using Stratasys 750

Technology	Polyjet
Material	Acrylate
Min. layer thickness	14 µm
Max. build size	490 x 390 x 200 mm

Results

We have tested production of the following microfluidics devices. The first model resembled a microfluidic device manufactured by CNC machine was produced by SLA method. The range of angle was 30° and size of channels: outlet channel - 0.4 mm and two inputs channels - 0.5 mm.

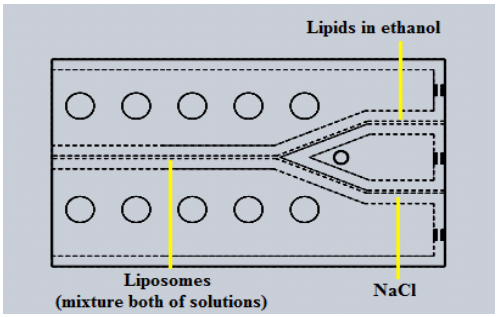

Figure 2 CAD model of "Y" type in the block,

The second type of microfluidic device was type "T" which we wanted to expand to other input channel. In the place of the crossing of the channels there was an accumulation of individual layers of material resulted in channels block.

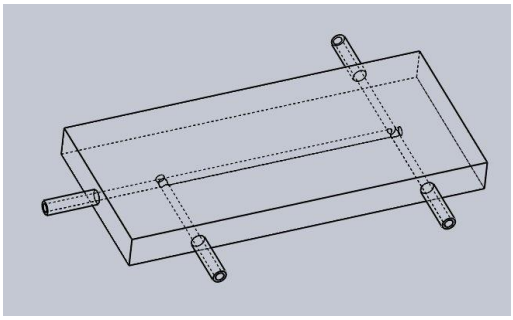

Figure 3 CAD model of "T" type in the block

Following, the simple model of microfluidic device ("Y" type) was printed without block, as the AM allows to reduce supporting material. To verify the accuracy of the printer we printed this simplest type of microfluidic device in 4 different size (0.4., 0.5., 0.75., 1 mm).

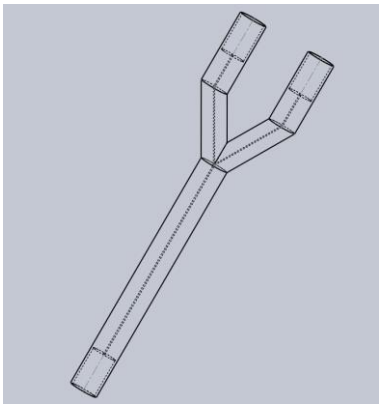

Figure 4 CAD model of "Y" type

If we want to create of liposomes using different solutions, we need to introduce additional channels. The last type looks like "2Y" type. We are intended to use on our next research are phospholipids dissolved in ethanol, hyaluronic acid and physiologic solution.

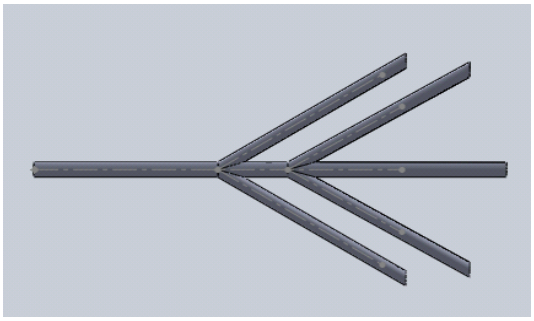

Figure 5 CAD model of "2xY" type

Since we had a problem when we were printing "T" type of MD in the block. We used to print "T" type without block, unfortunately the problem was repeated. The channels were blocked also in this case.

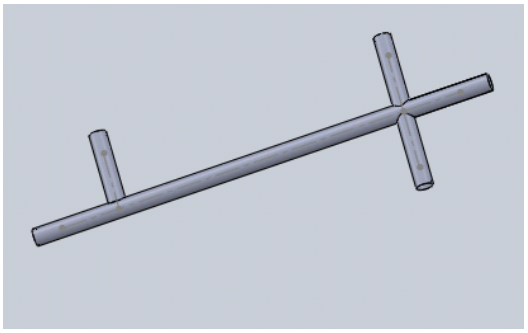

Figure 6 CAD model of "T" type

By Stratasys 3D printer, the final prototypes manufactured more precisely. It has better resolution than Projet 1200, also as better accuracy. We suggested and manufactured three types of microfluidic devices with different ranges of angle (30º-120º). These different ranges of angle are important to us regarding the study of flow rate and in creation of liposomes.

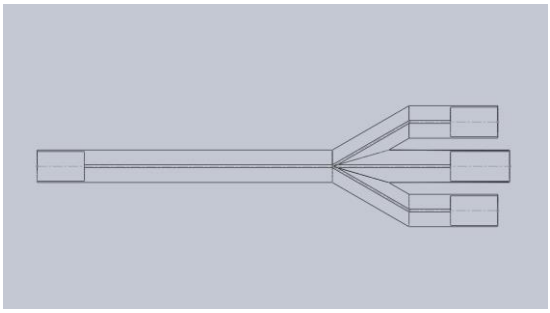

Figure 7 CAD model of MD with 60° range of angle

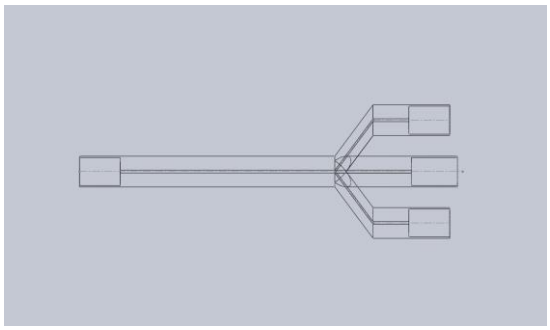

Figure 8 CAD model of MD with 120° range of angle

This type utilizes three inlet channels, through which a delivery compound stream flows and one outlet channel. This method rests in mixing both of solutions dosed by injected syringes. One of the solutions is phosphate buffer and second one (middle channel) are dissolved phospholipids in ethanol. Microfluidic device maintains laminar flow allowing for liposomes production by mixing of solutions. The flow rate of phosphate buffer is 1 ml/h and dissolved phospholipids in ethanol is 0.1 ml/h. In crossing of two channels happens to tearing off one mixture from the other. To create stable liposomes occurs, when the mixture of solutions reaches equilibrium. These liposomes have different sizes, from 300 to 650 nm. Dimensional analysis of dispersions was performed using a DLS Zetasizer Nano-ZS.

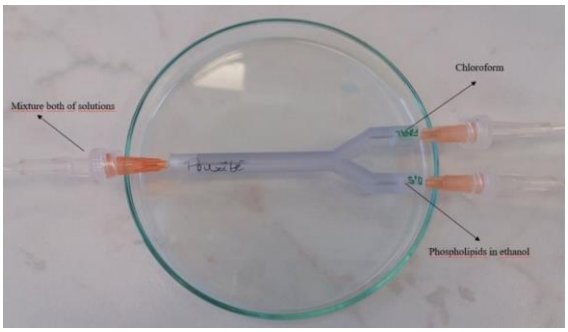

Figure 9 Microfluidic device

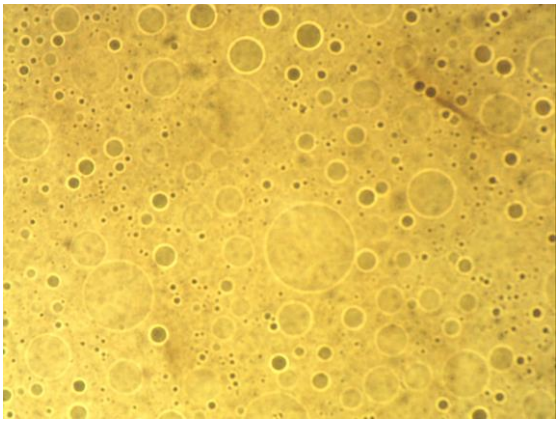

Figure 10 Liposomes created by "Y type microfluidic device"

Discussion

Additive manufacturing (3D printing) has many advantages in microfluidic chip manufacturing. In comparison with a common used method, AM is the fastest. The fabrication of our microfluidic devices, from their design in the CAD system to the finish prototype (microfluidic device), lasted in first case about 8 hours and in the second case only 1 hour. Development MD by 3D printer Projet 1200, which used SLA technology is more time consuming as 3D printer Stratasys J750 uses Polyjet technology. Post processing of 3D printer Projet 1200 in comparison with 3D printer Stratasys J750 takes also more time.

The results obtained by MHF method demonstrate that, liposomes created by MHF method have smaller size and uniform size distribution than liposomes created by bulk method. To reach the required size is necessary used to mini extruder, which is capable to create large unilamellar vesicles by extrusion in an efficient manner

Although microfluidics is a new method for creation liposomes, the characteristics of laminar flow and tenable mixing in microfluidics channels have a lots of advantages in comparison to conventional methods, such as sonification, lipid film preparation or bulk method. Just by changing the flow rates, liposomes with smaller size could easily be formed. MHF method provides a new platform to optimization and development of liposomes in biomedical fields.

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