

Improving Cell-to-Cell and Cell-to-Matrix Contact inside Microphysiological Systems

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Abstract

Innovative microfluidic technology aims to create more realistic *in vitro* simulations of human tissues. Organ-on-a-chip (OoC) devices within microfluidic chips mimic *in vivo* environments but face limitations due to inert material between compartments, hindering cell interaction. Current membranes made of PDMS or plastic impede proper cell-nutrient exchange and induce unexpected cell responses. This work focuses on minimizing inert materials while maximizing cell-matrix and cell-cell interactions in microfluidic chips.

Introduction

Efforts to enhance *in vitro* tissue simulation led to Microphysiological systems (MPS) with low fabrication costs and micrometric dimensions [1]. Organ-on-a-chip (OoC) models aim to mimic native tissue environments, utilizing membranes for compartmentalization [2,3]. However, these structures may impact cell responses due to their mechanical properties. This study aims to minimize inert materials in microfluidic devices to preserve proper cellular distribution. Two designs were developed: the Mesh device with a nylon mesh for increased cell-cell interactions, and the Macropore device with inert COC-Flex membrane for enhanced cell-matrix contact. Biological validation includes cell migration assays and epithelial development, contributing to more biomimetic *in vitro* models.

Theory and experimental procedure

Both devices were designed using AutoCAD for 2D drawings and SolidEdge for 3D rendering. They are made from cyclic olefin polymers (COP) and copolymers (COC), and the primary manufacturing method used is thermocompression molding.

The Mesh device (Figure 1a) is composed of a COP injection-molded part, a 150 μm nylon membrane for compartmentalizing the chip and replacing standard membranes, and COC layers that include the channel and well profiles along with a COP base. The fabrication process starts with creating the base of the device using a cutting plotter. The next step is thermocompression bonding: first, the channels are bonded to the base. Then, the mesh is carefully positioned in the injection-molded part, and finally, the final bonding is performed. The completed device features two distinct wells, separated from the lower channels by a nylon mesh.

The Macropore chip (Figure 1b) is made from cyclic olefin polymers (COP) and copolymers (COC). It includes a COP injection-molded piece that forms the inlets, outlets, and wells of the device. The subsequent layers, made from COC, constitute the lower part of the wells, the membrane, and the channels. The base of the device is also made of a COP layer. A plotter cutting machine is used to create the geometries for all the layers: the bottom part of the wells (4 mm diameter and 388 μm height), membrane holes (1 mm diameter and 100 μm height), and channels (1.5 mm width and 300 μm height). Afterward, a two-step thermocompression process using hot embossing assembles the pieces. First, the layers are bonded together, then these layers are bonded to the injection-molded part. Finally, the 3D printed wells are bonded to the injection-molded piece. The resulting device features two separate wells, each with a base containing holes that connect to the lower channels.

Conclusions

The goal of creating experimental models that mimic biology better is to minimize the use of materials that don't interact with cells. Two new microfluidic devices have been made for this purpose. One, called Mesh, has a nylon membrane with small pores. The

other, called Macropore, has a flexible COC membrane with larger pores. Both devices have been tested to see how well cells move, how epithelial cells grow, and how different types of cells interact in three dimensions.

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Figures

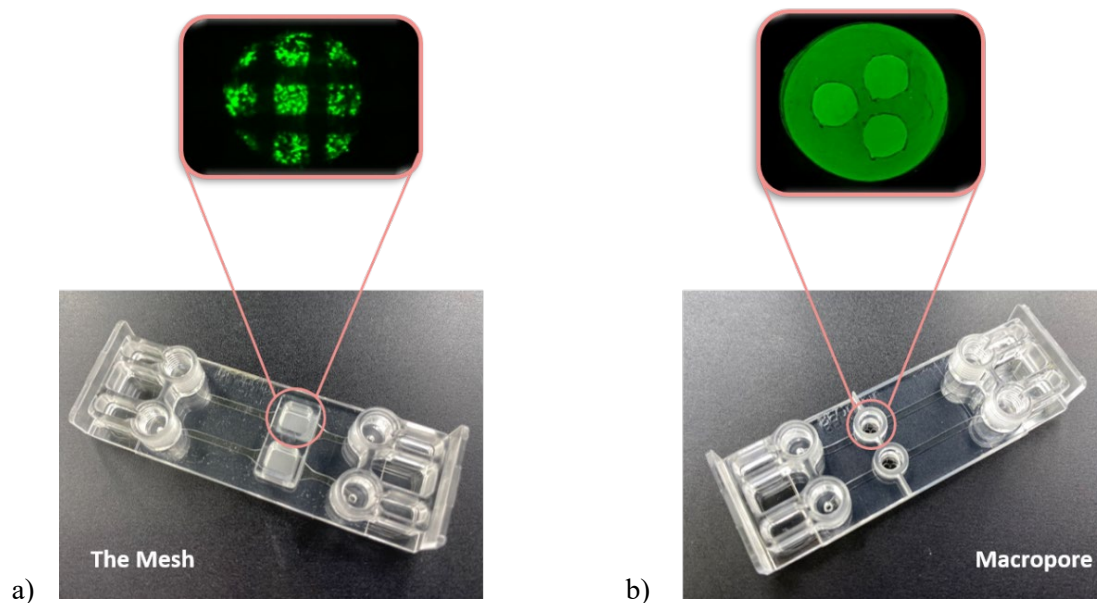


Figure 1: a) The Mesh device with a magnification of the membrane by confocal microscopy showing a spheroid on the mesh. b) The Macropore device with a magnification of the well under the confocal microscope showing collagen gel with green fluorospheres.

References

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