3D printed system for based on hydrogels for drug transport

Jepsen, Morten Leth; Nielsen, Line Hagner; Almdal, Kristoffer; Boisen, Anja; Dufva, Martin

Publication date:
2018

Document Version
Peer reviewed version

Citation (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
3D printed system based on hydrogels for drug transport

Morten Leth Jepsen; Line Hagner Nielsen; Kristoffer Almdal; Anja Boisen; Martin Dufva
The Danish National Research Foundation and Villum Foundation’s Center for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN), Department of Micro- and Nanotechnology, Technical University of Denmark, Ørsteds plads 345C, 2800 Kgs. Lyngby, Denmark, *mojep@dtu.dk

Introduction
When investigating permeability of orally administered drugs in vitro, Caco-2 cells grown on filter membranes are normally utilized. However, these filters are far from the in vivo growth matrix for intestinal cells. We here present a method for casting a soft gelatin hydrogel in a 3D printed holder as growth matrix for intestinal cells. The method is easy to use and relies on the use of a commercially available Form 2 3D printer.

Methods and materials
The design of the 3D print was drawn in Fusion 360 and exported as a STL file for preparation for 3D printing in PreForm. The 3D printed inserts were printed in Dental SG resin and cleaned with isopropanol and UV cross-linked for 1 hr at 60°C and autoclaved. A 5 % (w/v) gelatin hydrogel in PBS was cross-linked into the 3D printed holder with 5 U/mL mTransglutaminase for 30 min. Followed by seeding of Caco-2 cells (3 x 10⁵ cells) in 500 µL medium (DMEM with 10 % FBS, 1 % P/S, 1 % NEAA) apically and 3 mL medium was added basolaterally. The cells were grown for 28 days at 37°C and 5 % CO₂, and the medium was changed every other day. For comparison, Caco-2 cells were seeded on a Corning® 12 transwell plate. Transepithelial electrical resistance (TEER) values were measured at room temperature with a Millicell® ERS-2 Voltohmmeter. Moreover, Young’s modulus was measured at 37°C using a Discovery Hybrid Rheometer 2 with a 40 mm parallel plate and a steel Peltier plate. Mineral oil was added around the sample to ensure no evaporation of water from the hydrogel.

Results
3D printed biocompatible inserts have been designed (Figure 1a) with a size of 11 mm in height and 10 mm in diameter for culturing Caco-2 cells for testing permeability of drugs. A gelatin hydrogel was casted into the 3D printed inserts and Caco-2 cells were seeded on top of the hydrogel (Figure 1b). The 3D printed inserts were inserted into a commercially available 12-well culturing plate (Figure 1c). Once the cells have proliferated and differentiated to a tight monolayer (after 28 days), drug transport and permeability will be investigated as with a commercially available Transwell system (Figure 1b). This makes the method easy applicable in ordinary laboratory settings. Caco-2 cells grown on a gelatin hydrogel have a softer matrix to grow on (Table 1), thus, the growth is closer to the in vivo situation. Growing Caco-2 cells on hydrogel resulted in lower TEER values (Table 1), however, the value of Caco-2 on the hydrogel is within the range reported for Caco-2 cells (62 to 1290 Ω·cm²). However, the hydrogel itself also raises the resistance.

Conclusion
The presented system is easy applicable for transport studies over a monolayer of Caco-2 cells. Moreover, the gelatin hydrogel is transparent and suited for microscopy and can be cut out of the insert for fluorescent staining. The presented permeability test system also has the capability of being used for growth of cells on the underside of the hydrogel. Furthermore, the cells can be casted into the gel for advanced co-cultures.

References