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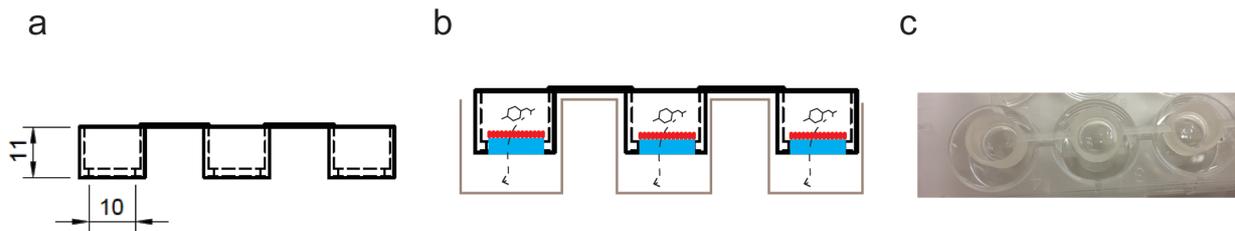
# 3D printed system based on hydrogels for drug transport

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## Introduction

When investigating permeability of orally administrated drugs *in vitro*, Caco-2 cells grown on filter membranes are normally utilized<sup>1</sup>. 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.



**Figure 1. (a) Drawing of 3D printed insert design. Numbers in mm. (b) Illustration of transport principle for 3D printed inserts with a hydrogel matrix. (c) Image of casted hydrogel in 3D printed inserts.**

## 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 ( $3 \times 10^5$  cells) in 500  $\mu$ L 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 % CO<sub>2</sub> and the medium was changed every other day. For comparison, Caco-2 cells were seeded on a Corning<sup>®</sup> 12 transwell plate. Transepithelial electrical resistance (TEER) values were measured at room temperature with a Millicell<sup>®</sup> 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  $\Omega \times \text{cm}^2$ )<sup>2</sup>. However, the hydrogel itself also raises the resistance.

**Table 1. Characteristics of hydrogels in 3D printed inserts compared to commercial inserts with filters.**

	Hydrogel	Polyester membrane
<b>TEER (<math>\Omega \times \text{cm}^2</math>)</b>	310.7 $\pm$ 43.5 (day 28) (n=3, $\pm$ SD)	983.6 $\pm$ 84.1 (day 22) (n=9, $\pm$ SD)
<b>Young's modulus (Pa)</b>	1080	N.A.

## 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

1. Hubatsch, I et al. . *Nat. Protoc.* **2**, 2111–2119 (2007).
2. Tavelin, S et al. *Epithelial Cell Culture Protocols* 233–272 (2002).