3D Printed Microdecives for Oral Drug Delivery

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3D Printed Microdevices for Oral Drug Delivery

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INTRODUCTION

In the past years, microcontainers for oral drug delivery were validated for increasing the absorption and thereby, the oral bioavailability of *e.g.* poorly water-soluble drugs. [1][2] Traditionally, microcontainers are polymeric and cylindrical drug delivery microdevices with an outer diameter of approximately 300 µm. A pH-sensitive polymeric lid coated on the cavity of the drug-loaded microcontainers isolates the drug from the harsh gastric environment and offers a fast release in the small intestine.

When the microcontainers reach the small intestine, the drug absorption often depends on the adhesion of the microcontainers to the intestinal epithelium. The longer the adhesion, the more drug will have the possibility to be absorbed. Although, the microcontainers offer unidirectional drug release directly to the intestinal epithelium, the symmetrical cylindrical shape makes the microcontainers randomly spread and release the drug in all directions. The microcontainers with spikes on the cavity were proposed for assisting the devices in sticking onto the mucus layer, as the increased contact area of the spikes led to a stronger mucus adhesion. [3] To realize this complicated feature, 3D printing is the most suitable method for fabricating the microcontainers. Nevertheless, limited by printing resolution, the size of 3D printed containers until now was on the millimeter scale. [3]

In this study, we utilized an HD-DVD optical pickup unit to custom build a micro-scale stereolithography 3D printer for manufacturing microcontainers in the micrometer size and in four different shapes. The fabricated microcontainers were tested on an *ex vivo* open perfusion model to investigate the influence of shape on mucus adhesion force. Moreover, the microcontainers were loaded with the model drug, furosemide followed by coating a pH-sensitive polymer on the cavity of the drug-loaded microcontainers.

METHODS

3D Printing of the Microcontainers

The custom-built 3D printer (Fig. 1a) utilies a 405 nm wavelength laser to crosslink photo-resin for manufacturing the microcontainers. [4] Four different kinds of micro-containers were designed (Fig. 1b) and printed.

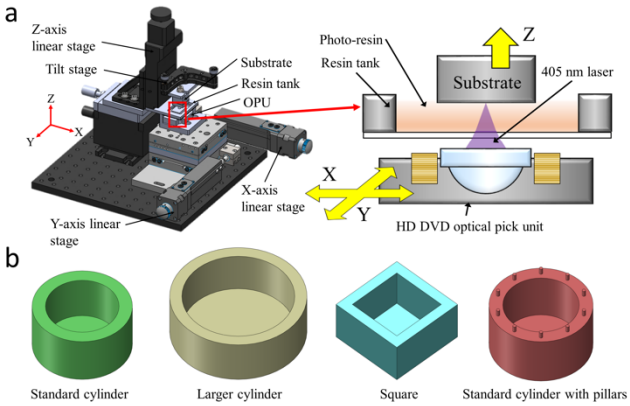

Figure 1. a) Drawings of the custom-built 3D printer with submicron printing resolution b) schematics of the four designs of the microcontainers

Mucoadhesion Testing Using an *ex vivo* Open Perfusion Model

For testing the adhesion between the intestinal mucus layer and the devices, the 3D printed microcontainers were randomly distributed on top of an inclined open porcine small intestinal tissue. [5] An angled holder tilted the intestinal tissue to 30˚ followed by perfusing the tissue with 10 mL/min of phosphate buffer for 10 min. The whole set-up was in a controlled environment to maintain the temperature at 37°C and the relative humidity at 80%.

Drug Loading and Lid Coating

Furosemide powder was loaded into the 3D printed microcontainers by using a manual brush method. After loading, Eudragit® L100 was spray coated on the cavity of the microcontainers.

RESULT AND DISCUSSION

Fabrication of the Microcontainers

100 microcontainers of the four designs were 3D printed. After the 3D printing process, a 99 % ethanol solution was utilized to wash the residual photo-resin. The size of the standard and larger cylinders was 297 µm and 420 µm in outer diameter, respectively, and the length of the square microcontainers was 260 µm (Fig 2). In Fig 2d, 10 pillars of 10 µm in diameter and 20 µm in height can be seen printed on standard cylinder microcontainers.

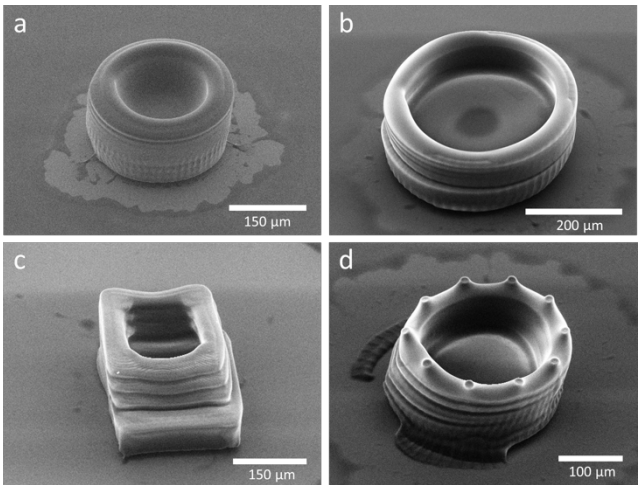

Figure 2. SEM images of 3D printed microcontainers in the design of a a) standard cylinder b) larger cylinder c) square d) standard cylinder with pillars

Mucoadhesion Testing Using an ex vivo Open Perfusion Method

After perfusing phosphate buffer for 10 min onto the microcontainers placed on the intestinal tissue, the standard cylinders, larger cylinders and squares had 23 %, 0 % and 6 % microcontainers, respectively staying at their original location. The standard cylinder with pillars had the strongest adhesion force, as it had the highest non-moving amount of microcontainers of 24 %. This study showed that the standard cylinder shape has better adhesion force than square and larger cylinder shapes, and the micro pillar could slightly increase the adhesion force. For a better mucoadhesion, the micro pillars on the cylinder should be optimized in diameter, length and shape.

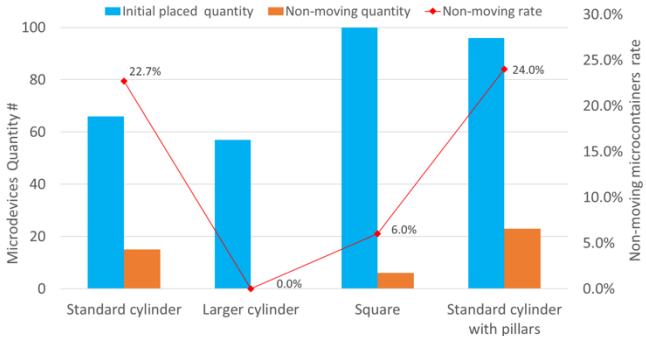

Figure 3. The comparison of initial placed and non-moving quantity, and non-moving rate of four microcontainers designs in *ex vivo* open perfusion method

Drug Loaded and Lid Coated Microcontainers

Here, the square microcontainers were loaded with furosemide powder (Fig 3a). The spray coating process perfectly generated a Eudragit® L100 lid on the cavity of the microcontainers (Fig 3b).

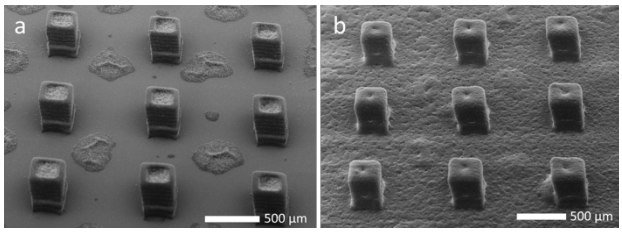

Figure 3. SEM images of square microcontainers a) loaded with furosemide powder followed by b) coating a lid with Eudragit® L100

CONCLUSION

In this study, we 3D printed micron-scale containers for oral drug delivery. The loading and coating process facilitate controlled drug release in the future. An *ex vivo* intestinal perfusion test showed that the standard cylinders had the strongest mucoadhesion. Micropillars on the edge of the cylinder were found to improve mucoadhesion to intestinal tissue.

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