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*Total number of authors:*

11

*Publication date:*

2016

*Document Version*

Peer reviewed version

[Link back to DTU Orbit](#)

*Citation (APA):*

Nielsen, L. H., Mazzoni, C., von Halling Laier, C., Tentor, F., Marizza, P., Petersen, R. S., Abid, Z., Keller, S. S., Rades, T., Müllertz, A., & Boisen, A. (2016). *Microcontainers as an Oral Drug Delivery System*. Abstract from 2016 AAPS Annual Meeting and Exposition, Denver, CO, United States.

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## Microcontainers as an Oral Drug Delivery System

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**PURPOSE:** To fabricate microcontainers in either SU-8 or biodegradable poly-L-lactic acid (PLLA), and fill the microcontainers with either poorly soluble drugs or vaccine formulations. Furthermore, the application of the microcontainers as an oral drug delivery system was investigated in terms of release and oral bioavailability in rats.

**METHODS:** SU-8 microcontainers were fabricated using two steps of photolithography, whereas PLLA microcontainers were prepared by hot embossing. In terms of drug filling, the SU-8 microcontainers were filled with polyvinylpyrrolidone (PVP) by inkjet printing followed by supercritical CO<sub>2</sub> impregnation of ketoprofen into the PVP matrix. As one of the alternative filling methods, the powder of amorphous sodium salt of furosemide, (ASSF) was filled into the SU-8 microcontainers. The PLLA microcontainers were filled with drug formulation by embossing the microcontainers into a polycaprolactone (PCL) and furosemide (4:1 w/w) layer. Furthermore, the embossing method also made it possible to load the SU-8 microcontainers with a mixture of budesonide, Soluplus<sup>®</sup> and polyethylene glycol (PEG) and likewise with powder of cubosomes intended for oral vaccine delivery. For both the ASSF-filled microcontainers and the ketoprofen-loaded microcontainers, an enteric-resistant lid of Eudragit<sup>®</sup> L100 was spray coated onto the cavity of the microcontainers. Release of ASSF or of ketoprofen from the coated microcontainers was investigated in simulated intestinal medium at pH 6.5. For the *in vivo* studies, the rats were dosed orally with capsules containing ASSF-filled microcontainers coated with Eudragit<sup>®</sup> L100. As control, capsules were filled with the powder of ASSF and the capsules were coated with Eudragit<sup>®</sup> L100.

**RESULTS:** The SU-8 microcontainers had an inner diameter of 220 µm and a cavity depth of 270 µm, and for the PLLA microcontainers the inner diameter was found to be 240 µm and with a cavity depth of 65 µm. The microcontainers were successfully filled with either PVP:ketoprofen (Figure 1a), ASSF, PCL:furosemide, budesonide:Soluplus:PEG or cubosomes (Figure 1b). A fast release of ASSF (88% within 3h) or ketoprofen (100% within 6 h) from the microcontainers was observed and the Eudragit coating was shown not to be a hindrance for rapid release at intestinal conditions. The oral bioavailability study demonstrated that the relative oral bioavailability of ASSF in microcontainers was 220±43% when compared to drug-filled capsules coated with Eudragit. This was reflected by a larger area below the curve for the ASSF in microcontainers (Figure 2).

**CONCLUSIONS:** Both SU-8 and biodegradable PLLA microcontainers were successfully fabricated and loaded with poorly soluble drugs or vaccine formulation (cubosomes). A fast release of ASSF was facilitated from the SU-8 microcontainers. Furthermore, using the microcontainers resulted in a higher oral bioavailability when compared to non-confined ASSF. The fabricated microcontainers therefore show considerable future potential as oral drug delivery systems.

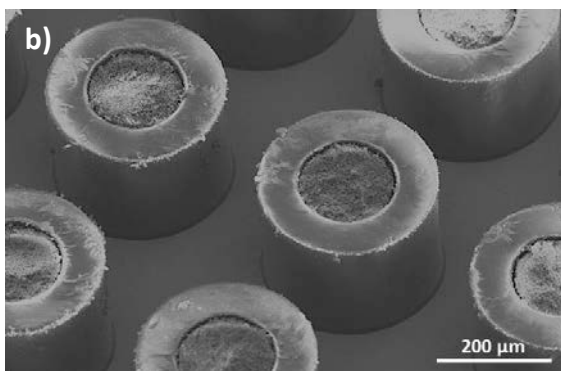
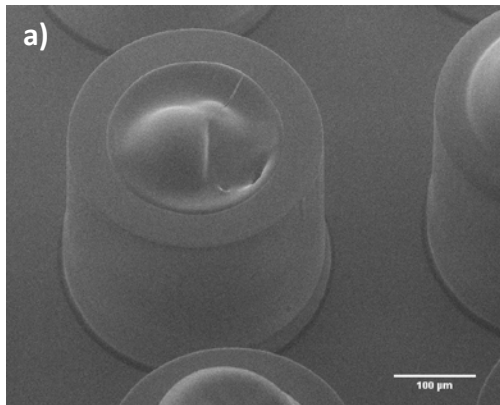


Figure 1: SEM images of microcontainers filled with a) PVP and CO<sub>2</sub> impregnated ketoprofen and b) cubosomes intended for oral vaccine delivery

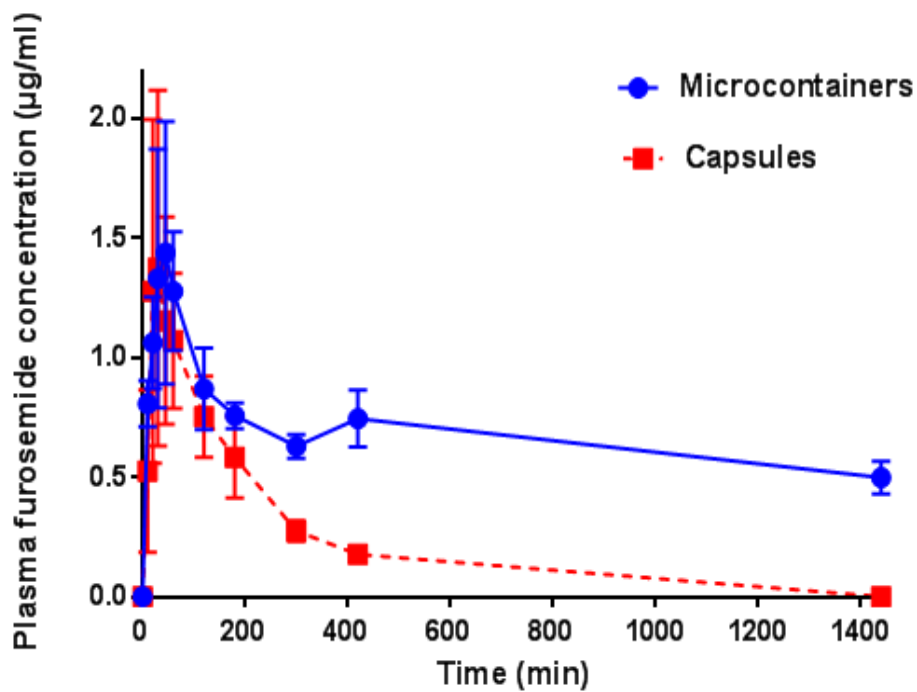


Figure 2: Plasma concentrations of microcontainers filled with ASSF coated with Eudragit® L100 and filled into capsules and ASSF dosed in capsules with Eudragit coating after orally dosing to rats