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INTRODUCTION

Oral delivery is the preferred administration route for drugs. Sometimes it can be necessary to employ advanced drug delivery systems to achieve targeted and/or sustained delivery in the gastro-intestinal (GI) tract after oral administration. Micro fabricated drug delivery devices have been proposed as an advanced drug delivery systems being able to increase the oral bioavailability of drugs [Chirra et al., 2012]. Of these micro devices, microcontainers are suggested as especially promising [Chirra et al., 2014]. Primarily, this is due to the fact that the size and shape of the microcontainers can be controlled very precisely and therefore, polydispersity as seen example for micro- and nanoparticles is avoided [Randall et al., 2007]. Microcontainers are polymeric, cylindrical devices in the micrometer size range (Figure 1). A major advantage is that these devices allow for unidirectional release, as only one side of the microcontainers is open compared to microparticles where release can occur over the whole area of the particle [Nielsen et al., 2012], [Nielsen et al., 2014].

EXPERIMENTAL

SU-8 microcontainers were fabricated using lithography, 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 CO2 impregnation of ketoprofen into the PVP matrix. As an alternative filling method, the powder of amorphous sodium salt of furosemide (ASSF) or cubosomes with ovalbumin were 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. For the ASSF-filled microcontainers, an enteric-resistant lid of Eudragit L100 was spray coated onto the cavity of the microcontainers. Release of ASSF from the coated microcontainers was investigated using a µ-Diss profiler in simulated intestinal medium at pH 6.5. Closed loop in situ intestinal perfusions were performed in rats of the Eudragit-coated ASSF-filled microcontainers and compared to a furosemide solution. The microcontainers were dosed to the small intestine, and at the end of the study, the small intestine was harvested from the rat and imaged under a light microscope. For the in vivo studies, the rats were dosed orally with capsules containing ASSF-filled microcontainers coated with Eudragit L100. As control, capsules were filled with the powder of ASSF and the capsules were coated with Eudragit L100.

RESULTS

The SU-8 microcontainers had an inner diameter of 220 µm and a cavity depth of 270 µm (Figure 1), and for the PLLA microcontainers the inner diameter was found to be 240 µm and with a cavity depth of 65 µm (Figure 2).
The microcontainers were successfully filled with either PVP:ketoprofen, PCL:furosemide, cubosomes or ASSF (Figure 3A), and the ASSF-filled microcontainers were coated with a lid of Eudragit L100 (Figure 3B).

A fast release of ASSF from the microcontainers was observed and the Eudragit coating was shown not to be a hindrance for rapid release at intestinal conditions. For the intestinal perfusion studies, the absorption rate constant of ASSF was 1.5 fold higher, when ASSF was confined in the microcontainers compared to a furosemide solution. Micrographs of the small intestine after the perfusion studies showed that the microcontainers interacted with the mucus in the small intestine, and the microcontainers were engulfed by the intestinal mucus (Figure 4). This was also observed for empty microcontainers without drug and coating (Figure 4C).

The oral bioavailability study showed that the relative oral bioavailability of ASSF in microcontainers was 220±43% when compared to drug-filled capsules coated with Eudragit (Figure 5).

CONCLUSION
Both SU-8 and biodegradable PLLA microcontainers were successfully fabricated and loaded with drug/formulation. A fast release of ASSF was facilitated from the SU-8 microcontainers. Furthermore, the microcontainers were found to interact with the intestinal mucus resulting in a higher oral bioavailability when compared to non-confined ASSF. The fabricated microcontainers therefore show considerable future potential as oral drug delivery systems.

REFERENCES
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