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## Microcontainers for oral protein delivery

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### Purpose

The aim was to load SU-8 microcontainers with a model protein called lysozyme using an embossing method followed by spray coating polymer lids onto the cavity of the loaded microcontainers. The lids have the function of enhancing protein absorption from the microcontainers. Furthermore, the coated microcontainers were investigated as an oral delivery system for proteins.

### Introduction

Delivery of proteins is often done by injection, but it would be much more convenient for patients, if proteins as e.g. insulin were dosed as a tablet via the oral route. Proteins are degraded by the low pH in the stomach, but also by enzymes found both in the stomach and intestine. Moreover, they have difficulties passing the intestinal membrane due to proteins being large hydrophilic molecules [1].

For being able to deliver proteins by the oral route, micro fabricated drug delivery devices can be used. Of these micro devices, microcontainers are suggested as especially promising [2], [3], [4]. Primarily, this is due to the fact that the size and shape of the microcontainers can be controlled very precisely. Microcontainers are polymeric, cylindrical devices in the micrometer size range (Figs 1). A potential advantage of microcontainers is that these devices allow for unidirectional release, as only one side of the microcontainers is open compared to conventional particles where release occurs from the whole surface [2]. The microcontainers have been suggested as a potential approach to improve oral bioavailability of drugs [2], [3], [4] as they are able to protect the protein through the stomach and bring it to the intestine, where the protein should be released and absorbed.

### Results

The fabrication of microcontainers gave devices with an inner diameter of 260  $\mu\text{m}$  and a cavity depth of 270  $\mu\text{m}$  (Fig 1). Lysozyme was used as a model drug, and the embossing method resulted in filled microcontainers with approximately 3  $\mu\text{g}$  of protein in each microcontainer (Fig 2). An ultrasonic nozzle in a spray coater system was utilized to spray coat lids on the cavity of the protein-loaded microcontainers. After the spray coating, the thickness of each lid was measured using a profilometer. One lid consisted of first 14.0  $\pm$  3.8  $\mu\text{m}$  of poly(lactic-co-glycolic acid) (PLGA) followed by 12.2  $\pm$  2.2  $\mu\text{m}$  of chitosan (Fig 3). This lid should be able to provide a lower local pH and thereby, inhibit enzymes resulting in higher protein absorption through the intestinal membrane. Another lid involved a PLGA lid with the same thickness as before, and on top of this, a poly(ethylene) glycol (PEG) lid was applied in a thickness of 17.0  $\pm$  5.6  $\mu\text{m}$  (Figs 3). The function of this lid was to get the microcontainers physical closer to the absorptive intestinal cells.

After spray coating of the lids, it was determined how fast the lysozyme in the microcontainers was released. This was investigated using *in situ* UV probes, and it was found that within 120 min 100 % of the loaded lysozyme was released from microcontainers with the PLGA/chitosan lid (Fig 4). A similar profile was found for the PLGA/PEG lid. At the moment, we are carrying out cell studies to determine if the lids increase absorption of lysozyme.

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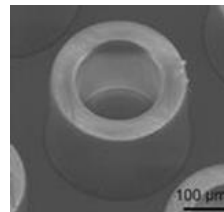


Figure 1: SEM image of a SU-8 microcontainer

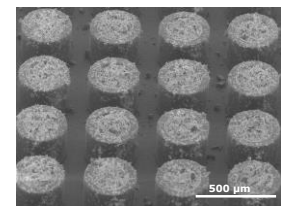


Figure 2: SEM image of microcontainers loaded with lysozyme using an embossing method

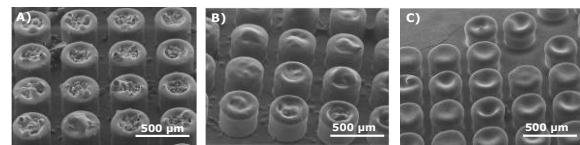


Figure 3: SEM images of coated protein-loaded microcontainers either with a lid of A) PLGA B) PLGA and chitosan or C) PLGA and PEG.

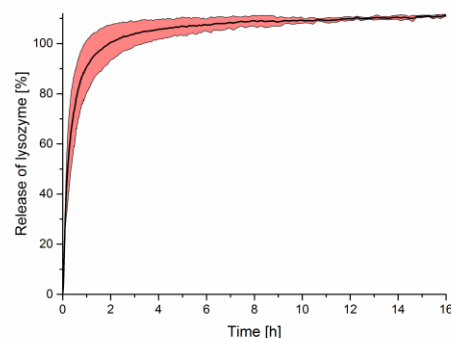


Figure 4: Release profile of lysozyme from microcontainers over time in buffer at pH 7.4. The microcontainers were coated with a lid of PLGA and chitosan. The graph shows the mean  $\pm$  SD, n=3.