INTRODUCTION
One of the key challenges in oral drug delivery is to increase the dissolution rate and solubility of poorly water-soluble drugs and thereby, improve the oral bioavailability of the drugs. One solution is to modify the actual drug formulation, but recently micro fabricated drug delivery devices have been proposed as alternative oral drug delivery systems [1,2]. Microcontainers are small polymeric devices consisting of a flat base with a walled reservoir and have been suggested as a potential approach to increase the oral drug bioavailability [3,4]. The microcontainers are characterised by enabling unidirectional release directly to the intestinal mucosa, as only one side of the microcontainers is open. The cavity of the microcontainers is filled with drug and subsequently coated with a lid of a pH-sensitive polymer to protect the drug from degradation and premature release in the stomach. After emptying into the duodenum the polymer lid will dissolve at the higher pH in the small intestine and the drug is released and absorbed through the intestinal wall (Fig. 1). A challenge that has not been addressed so far is to fabricate the microcontainers using a biodegradable polymer. Here, we demonstrate the fabrication of the microcontainers with Poly-L-lactic acid (PLLA), a polymer approved by the US Food and Drug administration (FDA) for drug delivery purposes and categorised as a biopolymer with long biodegradation time [5] and therefore, suitable to use for fabrication of the microcontainers for oral drug delivery.

The purpose was to fabricate microcontainers in PLLA polymer films using hot embossing, and to identify a method to fill powders into the microcontainers. Moreover, the application of fabricated microcontainers as an oral drug delivery system for a poorly soluble drug was studied (Fig. 1).

EXPERIMENTAL METHODS
For fabrication of the PLLA microcontainers, a film of PLLA was deposited by spin coating on a silicon wafer. The film was heated above the glass transition temperature ($T_g$) of the polymer, and a Nickel stamp was pressed into the film. Following cooling of the film, the stamp was removed, exposing the formed microcontainers.

The microcontainers were filled with amorphous furosemide salt (produced by spray drying) [6] using a simplified version of a screen printing technique (Fig. 2).

![Fig. 1. Illustrations of the experimental methods. A) Fabrication of PLLA microcontainers. B) Filling with amorphous furosemide salt. C) Spray coating of a lid of Eudragit L100. D) Dissolution of coating and release of drug.](image_url)

![Fig. 2. Graphics showing the powder filling process of PLLA microcontainers using screen printing modifications. 1. The stencil was aligned to the microcontainers. 2-3. Furosemide was pressed into the microcontainers. 4. The stencil was removed resulting in filled PLLA microcontainers.](image_url)
A gastric-resistant lid of Eudragit L100 was subsequently spray coated onto the cavity of the microcontainers. Release of amorphous furosemide salt from the coated microcontainers was investigated using a µ-Diss profiler (Plon Inc). Release experiments were carried out in biorelevant gastric medium (pH 1.6) for 2 h, followed by 3 h in a biorelevant intestinal medium (pH 6.5). Moreover, biorelevant flow through dissolution was also carried out in conjunction with UV imaging (Sirius Analytical) to visualise the release of amorphous furosemide salt from the coated microcontainers.

RESULTS AND DISCUSSION
The Nickel stamp, utilised for the hot embossing process, made the fabrication of the microcontainers very robust, resulting in PLLA microcontainers with an inner diameter of 240 µm and a height of 100 µm (Fig 3).

Fig. 3: SEM image of a single microcontainer in polylactic acid (PLLA) after hot embossing. Outer diameter of 300 µm, inner diameter of 240 µm, and height of 100 µm.

The filling of amorphous furosemide salt into the microcontainers using the screen printing technique was shown to be a very useful method for quickly filling the microcontainers while avoiding deposition of drug powder in between the microcontainers (Fig 4a). Moreover, the method can be utilised for all type of powders. The lid of Eudragit L100 on the microcontainers can be seen in Fig. 4b.

Fig. 4: a) An optical microscope image of a PLLA microcontainers filled with furosemide. b) A SEM image of drug-filled PLLA microcontainers spray coated with Eudragit L100.

From both release experiments (in the µ-Diss profiler and UV imaging system) it was observed that the Eudragit layer prevented drug release in biorelevant gastric medium, while an immediate release of the amorphous furosemide salt was seen in the biorelevant intestinal medium (Fig. 5).

Fig 5: Release profiles obtained in µ-Diss profiler from PLLA microcontainers filled with furosemide and coated with Eudragit L100 in gastric medium pH 1.6 (from 0-120 min) and intestinal medium pH 6.5 (120-300 min). Data shown represent the mean of 3 replicates±SD.

CONCLUSION
Biodegradable microcontainers in PLLA were successfully fabricated and loaded with drug powder. Coating with Eudragit L100 proved to be useful for protecting drug release from microcontainers in gastric medium, and facilitated an immediate release in the intestinal medium. The fabricated microcontainers therefore show considerable potential as new oral drug delivery systems.

REFERENCES