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Towards Combinational Drug Therapy

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Sequential Drug Release in the Gut Achieved with Dual-compartment Microcontainers: Towards Combinational Drug Therapy

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Introduction: Combinational drug therapy is commonly used to treat various diseases such as cancer, diabetes, cardiovascular conditions and infections [1]. However, these treatments face challenges associated to patient compliance (challenging to take several drugs, maybe even at different time points) and toxicology. Microdevices have progressively emerged as a promising platform for oral delivery, with the potential of tuning drug release and lowering the needed drug dose. However, one of the major requirements is promising *in vivo* data quantifying the potential benefits of using said microdevices for oral administration of drugs [2,3]. This study aimed to develop monodisperse dual-compartment microcontainers (DCMCs) to physically separate two model drugs and achieve sequential release *in vitro* and, for the first time, also *in vivo*.
Methods: DCMCs (Figures 1 and 2A) were fabricated in a biocompatible negative photoresist (SU-8) [4] by maskless UV lithography. Using nickel and PDMS shadow masks (Figure 2B, E and F), the drug furosemide was manually loaded in the inner compartment (Figure 2C) and propranolol was subsequently loaded in the outer compartment (DCMC-A) (Figure 2G), and vice versa (DCMC-B). Eudragit® S100 was used to seal the inner compartment (Figure 2D), whereas Eudragit® L100 was subsequently coated on both compartments (Figure 2H) using an ultrasonic spray coating system (ExactaCoat system, Sono-Tek, Milton, NY, USA). The release of the two drugs was evaluated *in vitro* in a µDiss Profiler™ (Pion Inc., Billerica, MA, USA) in phosphate buffered saline (PBS, pH 7.5), and in fasted state simulated gastric fluid (FASSGF, pH 2.4) followed by fasted state simulated intestinal fluid (FASSIF, pH 7.5). *In vivo* studies were performed in rats where DCMC-A and a 1:1 powder mixture of the two drugs were filled into capsules and orally administrated to the rats followed by temporal blood sampling. The analysis of plasma concentrations of furosemide and propranolol was performed using a Shimadzu HPLC system (Shimadzu, Kyoto, Japan) and a Shimadzu Nexera X2/Prominence HPLC (Shimadzu, Duisburg, Germany), respectively.
Results: Nine chips containing 324 DCMCs were successfully fabricated with the dimensions shown in Figure 1. DCMC-A was loaded with 1.1 ± 0.1 mg of furosemide and 1.1 ± 0.1 mg of propranolol and DCMC-B was loaded with 1.3 ± 0.1 mg of furosemide and 1.6 ± 0.1 mg of propranolol (mean ± SD, n = 10). Uniform coatings of Eudragits® were applied as lids. *In vitro* studies revealed that it is possible to produce a sequential co-delivery of furosemide (inner compartment) and propranolol (outer compartment) from DCMC-A in both PBS and in FASSGF followed by FASSIF media with a time gap of 30 min (Figures 3A and B). DCMC-B provided a slightly different release profile, where furosemide (outer compartment) and propranolol (inner compartment) were released at the same time, but with different rates due to intrinsic differences in solubilities (Figures 3C and D). *In vitro* results correlate well with *in vivo* observations, where dosage of DCMC-A resulted in a propranolol (outer compartment) peak concentration measured at t=1.50 ± 0.22 h whereas for furosemide (inner compartment) was measured at t=3.67 ± 0.67 h. In contrast, the peak concentration times were more similar for the control group (1.67 ± 0.46 h for furosemide and 2.50 h for propranolol) (mean ± SE, n= 3-5).
Conclusion: Compared to previous works in this field, we demonstrated that with the DCMCs we can achieve sequential release secured by selective coatings both *in vitro* and *in vivo*, and a 1000-fold increase in drug loading capacity. These findings are highly relevant, since we showed for the first time *in vivo* results for combinational therapy. Future perspectives will focus on the development of biodegradable microdevices for sequential drug delivery.
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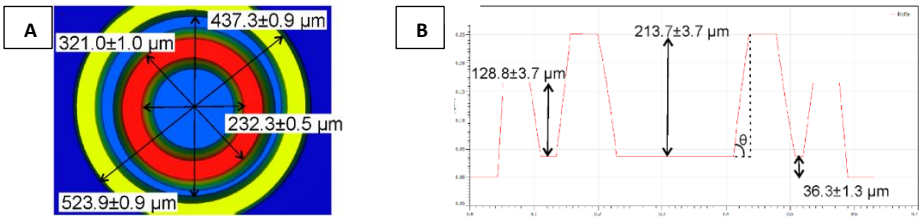

Figure 1. (A) Top-down contour image of a DCMC illustrating the horizontal dimensions and **(B)** Cross-sectional profile through the center of a single DCMC showing the vertical dimensions.

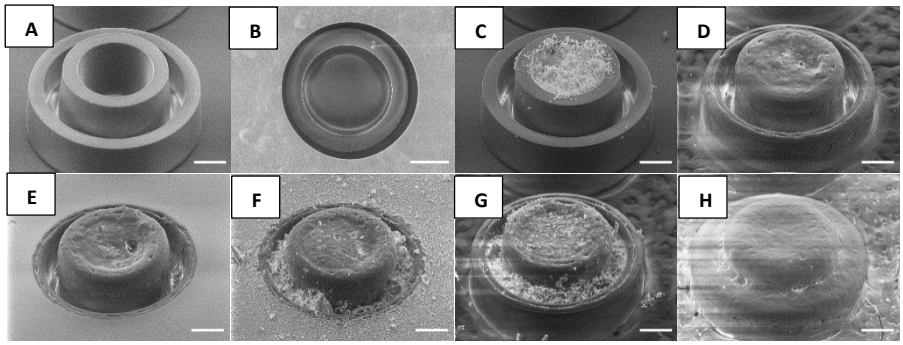

Figure 2. Scanning electron microscopy (SEM) images of **(A)** one DCMC with **(B)** metal shadow mask covering everything but the inner compartment, **(C)** the inner compartment loaded with furosemide, **(D)** coated with Eudragit® S100, **(E)** PDMS shadow mask covering the space around the microcontainer, **(F)** and **(G)** the outer compartment loaded with propranolol before and after removal of PDMS mask and **(H)** coated with Eudragit® L100. All scale bars represent 100 µm.

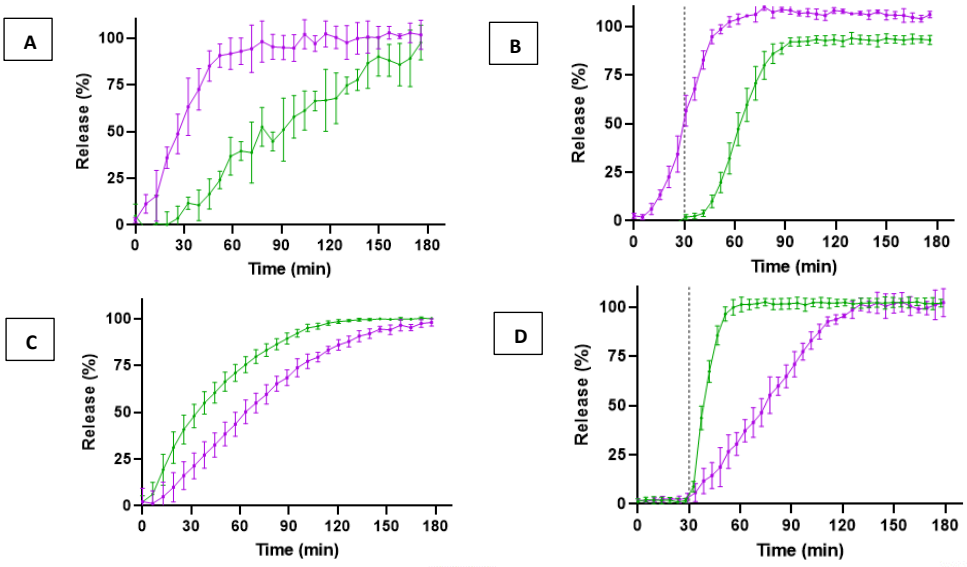

Figure 3. Sequential *in vitro* release of **(A)** propranolol (outer compartment) and furosemide (inner compartment) from DCMC-A in PBS and **(B)** FASSGF and FASSIF media over time. Sequential *in vitro* release of **(C)** furosemide (outer compartment) and propranolol (inner compartment) from DCMC-B in PBS and **(D)** FASSGF and FASSGIF media over time. All data represents mean ± SD (n= 3-4).