ARTIFICIAL GUT-ON-A-DISC PLATFORM TO EVALUATE PH SENSITIVE COATINGS OF ORAL DRUG DELIVERY DEVICES

Sriram Thoppe Rajendran[1,2], Khorshid Kamguyan[1], David Kinahan[2], En-Te Hwu[1], Line Hagner Nielsen[1], Kinga Zór[1], and Anja Boisen[1]

[1]Center for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN), Department of Health Technology, Technical University of Denmark, Kgs. Lyngby, DENMARK

[2]School of Mechanical and Manufacturing Engineering, Dublin City University, Dublin, IRELAND

ABSTRACT

Rapid testing of pH coatings of oral drug delivery (ODD) devices is often complex and time consuming. A lab-on-a-disc (LoD) platform was developed which enables detection of integrity of pH coatings for up to four different pHs. The platform was designed to perfuse ODD devices through different pH in a sequential manner, mimicking the pH variations in the gastrointestinal (GI) tract. The disintegration of pH coatings causes release of drugs, which in turn is used to monitor integrity of pH coatings. Combining 'event-triggered' flow control, based on dissolvable film with electrochemical detection, enables accelerated, real-time characterization of ODD devices.

KEYWORDS: Lab-on-a-Disc, Oral drug delivery devices, Microcontainers, Event-triggered valves

INTRODUCTION

Oral delivery is the most preferred route of administration of drugs and pH-sensitive coatings are widely used to enable pH dependent delivery in different section of the GI. To manage the trivial challenges such as bioavailability, drug stability associated with ODD, micro fabricated devices have become the forefront of advanced ODD systems [1]. Microcontainers (Figure 1B) have been proposed as one of the strategies for ODD [1]. There is a growing need for monitoring the drug release from microcontainers, considering the wide variations of pH in the gut. The manufacturing process of ODD devices is expensive and time consuming while for the conventional drug release studies a large quantity of these devices are required [2]. There is a need for fast and cost efficient methods for evaluation of pH coatings, preferably in microliter volumes to be able to use few tens of ODD devices.

EXPERIMENTAL

We have developed a LoD platform which combines event-triggered DF valves with a centrifugo-pneumatic siphon valve (CPSV) as shown in Fig. 1. The event-triggered valves are sealed by two DFs and function akin to an electrical relay; when the 'control film' is wetted/dissolved, an air pocket is vented, and liquid is released through the 'Load Film '. Combining event-triggered valves with a CPSV provides flexible and well-defined flow-control; the CPSV permits active mixing of a reagent (of a given pH) with the microcontainers. By reducing the disc spin-rate at defined times we can transfer liquid into waste and replace it with a reagent of different pH; thus simulating the pH profile encountered by microcontainers travelling through gut.

The microcontainers in the present study were loaded with paracetamol by powder embossing and later coated with pH-sensitive coating of Eudragit® L100 (sensitive to pH 7.4) by spray coating (Fig. 2A). The rupture of pH coatings was electrochemically monitored directly by measuring the release of paracetamol from the microcontainers in real-time. The electrodes were fabricated in the bottom layer of LoD using stencil-lithography and electron beam evaporation. A custom made potentiostat also called as potentiostat-on-a-disc (PoD) was used for electrochemical detection on the LoD device [4], enabling real-time detection during spin. The drug release was monitored using amperometry at an applied potential of + 0.7 V vs. pseudo-Au-RE.

RESULTS AND DISCUSSION

Interfacing PoD with the designed LoD platform enabled real-time electrochemical detection of drugs from microcontainers. Figure 2B shows the signal from a model drug, paracetamol: after dissolution of the pH-sensitive coating of Eudragit® L100 in comparison with PBS as control. The released drug could be quantified using a calibration curve as shown in the inset of Figure 2. The integrity of pH coatings were tested by consuming few

ODD devices at a faster rate in comparison to conventional methods such as a µDiss profiler. Therefore the developed LoD could be used for optimizing the pH coatings of ODD devices rapidly.

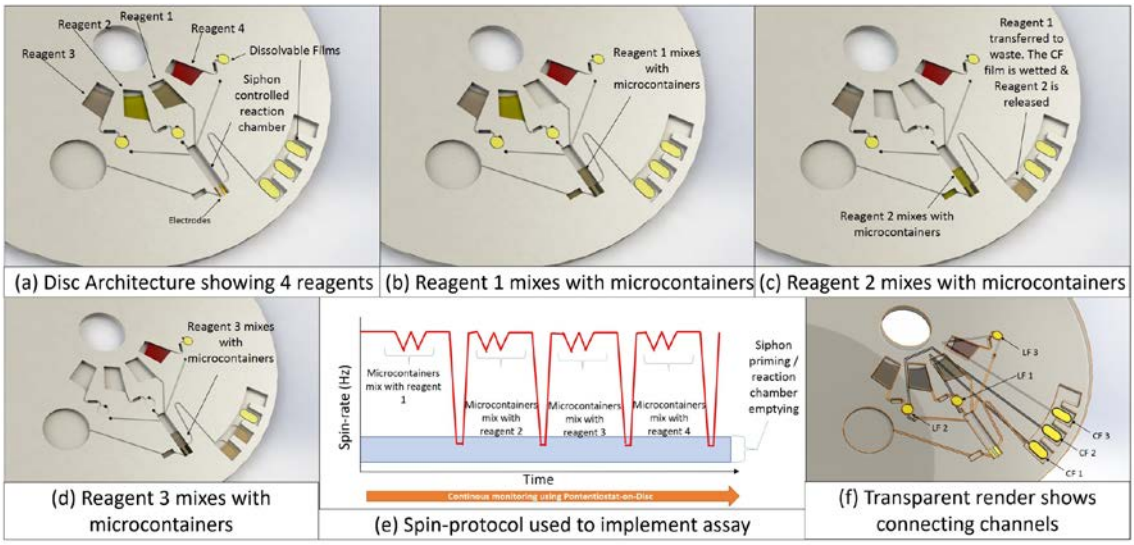

***Figure 1**: A) Fluidic operation of the Lab-on-a-Disc*

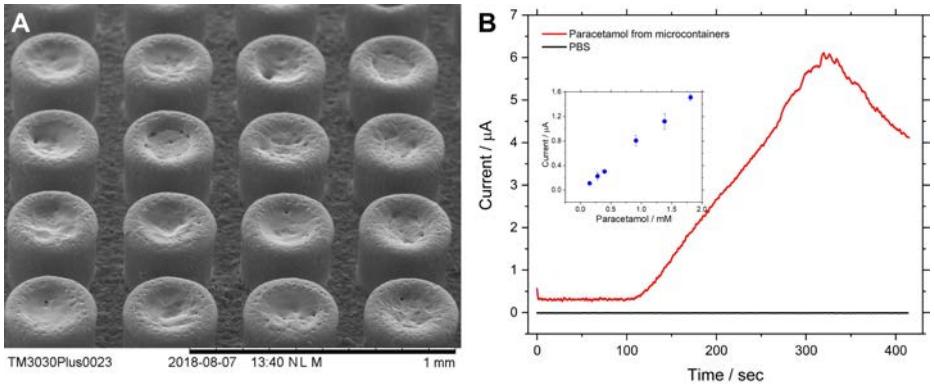

***Figure 2:** A) A SEM micrograph displaying arrays of SU-8 microcontainers of approximately 300 µm outer diameter and 300 µm height. The microcontainers are filled with paracetamol and coated with Eudragit®-L100; B)Amperometric current showing the release of the model electrochemical analyte paracetamol from 50 microcontainers in comparison to PBS as control at pH 7.4 at an applied potential of -0.4 V vs. Au pseudo-RE during spin at 2 Hz. The release of the model analyte is triggered at pH 7.4. The inset shows an example calibration curve for quantifying the paracetamol release, also at low concentrations.*

ACKNOWLEDGEMENTS

This work was supported by the Danish Nation-al Research Foundation (DNRF122) and Villum Fonden (Grant No. 9301) for Intelligent Drug delivery and sensing Using micro-containers and Nanomechanics (IDUN).

REFERENCES

[1] L. H. Nielsen, S. S. Keller, and A. Boisen, "Microfabricated devices for oral drug delivery," *Lab Chip*, vol. 18, no. 16, pp. 2348–2358, 2018.

[2] H. D. Chirra and T. A. Desai, "Emerging microtechnologies for the development of oral drug delivery devices," *Adv. Drug Deliv. Rev.*, vol. 64, no. 14, pp. 1569–1578, 2012.

[3] B. H. Saraí M. Torres Delgado, David J. Kinahan, Niamh A. Kilcawley, Lourdes AN Julius *et al.*, "A fully automated wirelessly powered centrifugal platform towards a sample-to-answer chemiluminescent ELISA assay for CVD detection," in *20th International Conference on Miniaturized Systems for Chemistry and Life Sciences*, 2016, pp. 1348–1349.

[4] S. Thoppe Rajendran *et al.*, "Lab-on-a-disc platform with an integrated potentiostat for real-time drug release monitoring," in *44th International conference on Micro and Nano Engineering*, 2018.