ENTERIC & 3D-PRINTED HYBRID PACKAGE FOR SAMPLING IN DIGESTIVE REGIONS

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ABSTRACT

We present a packaging concept for an ingestible sensing capsule, which utilizes biodegradable polymers to target the sensors to specific areas of the gut. Interdigitated electrodes (IDE) are inserted into 3D-printed capsules with embedded gratings that are filled with pharmaceutical polymers tuned to dissolve at a specific pH threshold. Sensors, housed within a 3D-printed package accessible only by the gratings, are connected to a microcontroller capable of transmitting data to a smartphone via Bluetooth Low-Energy (BLE). The system is tested with varying amounts and types of enteric coatings over the gratings, used toward optimizing control over timed polymer dissolution. This represents a minimally-invasive strategy toward *in situ* sampling and analysis at pH-targeted locations in the gastrointestinal (GI) tract.

INTRODUCTION

Integrated capsule systems are widely gaining momentum for analysis or drug delivery in GI regions where traditional techniques are expensive, highly invasive, or inadequate [1], [2]. Depending on the region, there are numerous physiological considerations that must be addressed for fluid sampling and sensing with minimal human intervention [3]. Previous passive approaches to GI sampling lack a means of knowing whether a sample has been retrieved in real-time, while active approaches suffer due to cost and complex assembly [4]. In this work, a breadboard level circuit representative of the electronics, ultimately for integration within the device, is used to monitor the removal of polymer material from grids within a 3D printed capsule. The goal is to use the polymers to protect sensors within the capsule, only exposing them when the device has reached the GI region of interest [5]. Different Eudragit polymers are used to target different GI regions, depicted in Figure 1: E PO, S 100, and L 100 dissolve respectively at the stomach, ileum, and duodenum.

Figure 1: Depiction of system outlook and application (Image credits: NIH). Polymer coatings are intended to dissolve at either the stomach (pH 1.5-3) or the duodenum (pH 7-8.5). At the duodenum, gastric acid-neutralizing bicarbonate is secreted from the pancreas via the sphincter of Oddi.

WORKING PRINCIPLE AND RESULTS

Figure 2 presents a 3D representation of the capsule (left) and a schematic overview of the electronics. Each die, containing four sensors, is inserted into a slot designed in one end of the 3D-printed capsule. Once inserted, the capsule was fastened using built-in threads and sealed with epoxy, then dip-coated into a 30 w/v% solution of each polymer in methanol, each for 1-5 coats with removal for 20 min intervals between each coating. The circuit setup is depicted in Figure 2, characterized in Figure 3a, and transmission protocols are compared in Figure 3b.

Figure 2: System overview, including the packaging design with the inserted IDEs and the circuit design. The capsule is made from MED610 using a Connex 3 Objet500 (Stratasys). Capacitor electrodes consisting of Cr(20nm)/Au(200nm) IDEs with 75μm width and spacing were fabricated using photolithography and lift-off over a pyrex wafer. Circuit design includes a multiplexer (MUX) integrated circuit (IC), a capacitance-voltage-converter (CVC) IC, a 1.5 MHz step-up DC-DC converter, and a BLE System-in-Package (SIP) microcontroller unit (MCU).

Figure 3: (a) Circuit calibration with standard capacitors across four multiplexed inputs. The resulting system senses capacitive changes in the 0.8-220 pF dynamic range with a sensitivity of 3.2×10^{-3} pF/mV and operated using a 3.3 V source. (b) Comparison of data obtained through Bluetooth versus serial (UART) communication, where the capsule (open gratings) was measured in air, inserted into buffer, then removed ($n=4$).

Capsule coating thicknesses for S 100 were analyzed, shown in Figure 4, over gratings and non-grating regions. Gratings resulted in a slower increase (Figure 4d) with each coating due to polymer infill. Capsules were then immersed in 0.1 M acetic acid (pH 3) and progressively adjusted at 30 min intervals to increasing pH levels. Figure 5 presents the sensor output and corresponding change in capacitance over the course of pH adjustments for the S 100 polymers, indicating the expected length of time for chamber filling and sampling dynamics for each coating thickness.

Figure 4: Cross-sectional optical images of the sampling gratings (a) uncoated and (b) with 1 coating of red-dyed polymer, where yellow markers indicate the grating locations. (c) Top-view optical image of uncoated gratings. (d) Characterization of polymer coating thickness vs. number of dipping steps from both non-grating and grating regions over the 3D-printed capsule surface ($n=3$).

Figure 5: Sensor responses inserted (at 5 min) into capsules with different numbers of S 100 coatings (0, 2, 3, and 4, respectively) with increasing pH using titers of 1 M NaOH ($n=4$). Chamber filling is characterized by a capacitance change of ~ 50 pF from the initial capacitance in air. For each formulation, it was determined that 3 coatings was optimal for the w/v% used.

After coating optimization was performed for each polymer, combined coatings were tested to determine ability to tailor sampling for more complex pH sequences. Figure 6 presents representative sequences of L 100 and E PO formulations (a and b, respectively), as well as a combined coating of both polymers. As expected, the capacitance increase did not occur until $\sim$ pH 5, indicative that this combined coating strategy can be used to protect the sensing chambers until the characteristic pH-targeted regions are reached.

Figure 6: Sensor responses inserted into capsules with different types of coatings (3 dip-coatings each) compared to uncoated controls: (a) L 100, (b) E PO, and (c) combined coatings, where E PO is outer-most and L 100 is between the 3D-printed capsule and the E PO layers ($n=4$).

CONCLUSION

This work is the first demonstration of a passive pH-dependent packaging strategy for ingestible capsule technology that offers information on the package integrity at any given time, while simultaneously providing a real-time active microelectronics-based system capable of wireless retrieval of sensor data for use in GI sampling and analysis.

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