REGION-TARGETED BILAYER COATING TECHNOLOGY FOR INGESTIBLE DEVICES AND SYSTEMS

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ABSTRACT

We present a pH-responsive bilayer packaging strategy to protect capsule components intended for actuation in the small intestine from stomach acid. The bilayer is resistant to stomach acid but is removed in the small intestine (neutral pH). This structure consists of a water-soluble support layer, polyethylene glycol (PEG), and a pH-responsive polymer coating, Eudragit. We also demonstrate a realistic intestinal simulation apparatus to test physical bilayer removal against intestinal tissue with physiologically relevant forces. Using this simulator, bilayer removal was accomplished in approximately 15.6 min. This technology represents a low-complexity, versatile, and reliable approach to protect ingestible capsule components.

KEYWORDS

Packaging, Ingestible Device, Enteric Coatings, GI tract.

INTRODUCTION

Ingestible capsules offer a promising alternative to enable diagnostics and treatment in the small intestine when compared to traditional methods like endoscopy. Sensors and actuators in these devices for small intestinal targeting require simple and versatile packaging to protect from harsh acidic conditions in the stomach. Using a passive packaging strategy to shield internal components until their time of release without additional active mechanisms conserves valuable capsule space and energy. pH-responsive coatings are used extensively for tablet-based drug delivery [1] and as release triggers for ingestible devices [2]. Our lab has previously demonstrated this technique for the protection of small sensor openings (~250 µm) for biomarker detection in the small intestine [3]. However, fabricating a robust protective layer over a large open cavity (mm-scale) for actuator release using pH-responsive coatings is challenging using traditional coating methods alone.

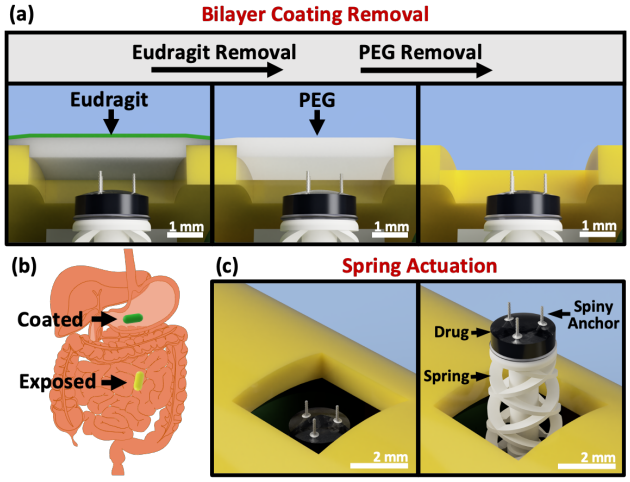

Figure 1: Overview of the packaging system in application. (a) The pH-sensitive polymer coating (green) remains intact and impermeable while in the stomach (pH 1.5-3). (b) In the small intestine, the pH rises (pH 6-7.4) causing polymer swelling and swift removal. The water-soluble PEG layer is then dissolved by the hydrated intestinal environment, thus revealing the capsule actuator cavity. (c) Spring actuator and drug delivery structure from [4].

In this work, we present a novel **f**reestanding **r**egion **r**esponsive **b**ilayer (FRRB) system (Fig. 1) capable of withstanding gastric acid toward the use of a mm-scale actuated drug delivery mechanism in the small intestine. This is accomplished utilizing a novel bilayer composed of a **rigid polyethylene glycol (PEG) support layer** and a flexible **pH-responsive Eudragit layer** that is removed in the small intestine. We also demonstrate the first evaluation of this type of protective system with *ex-vivo* gastrointestinal (GI) tissue, accounting for the blend of **chemical changes** and **mechanical abrasion** contributing to the degradation of the bilayer where beaker experiments fail to adequately approximate these GI conditions.

EX-VIVO INTESTINAL SIMULATOR

pH-responsive coatings swell and soften when the ambient pH exceeds the designed threshold value, however, complete dissolution does not proceed rapidly [1]. Hence, mechanical abrasion plays a critical role in removal of this protective outer coating once swelled. To approximate the abrasive characteristics of the GI tract most closely, a translational motion system was developed – allowing for the evaluation of bilayer removal against *ex-vivo* porcine small intestine tissue. The GI simulator (Fig. 2) is composed of four main components: (*i*) a rail and screw lead system that translates a (*ii*) capsule holder capable of mass loading to control force application on a test capsule, and (*iii*) a polydimethylsiloxane (PDMS) semi-cylindrical tissue holder channel (D=25 mm). This system enables control over the force and translation speed on real intestinal tissue to closely emulate the *in-vivo* interfacial conditions between a capsule and GI tissue.

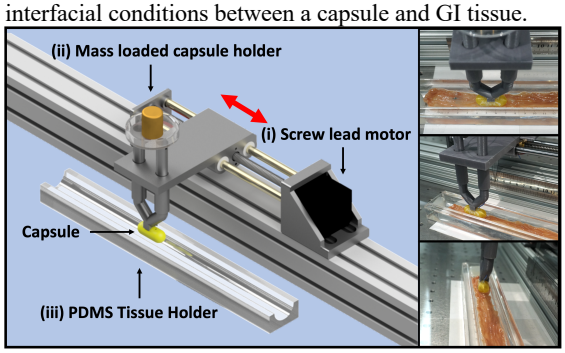

Figure 2: CAD rendering and images of the ex-vivo intestinal simulator system. Translation is facilitated by the screw lead motor which moves the rail-mounted platform attached to the capsule holder. A dish holding a 50g mass is attached to the top of two-pronged mass loaded capsule holder while a coated test capsule is fastened to the bottom. This applies a total of ~70g of mass from the top of the capsule to the tissue placed in the PDMS tissue holder to approximate circumferential peristaltic forces in the GI tract [5].

MATERIALS AND METHODS

Test capsules (∅=13 mm, L=32 mm) were 3D Printed with fused filament fabrication (FFF) of Polyethylene Terephthalate Glycol (PETG) using a Prusa i3 MK3S+ (Prusa). Test capsules contain openings of 4 x 4 x 5 mm (L,W,H). Approximately 0.17 g of PEG was melted on a 1 mil polyimide film, then transferred to the capsule surface to cover the capsule opening. The PEG was

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allowed to solidify then the polyimide film was removed.

Eudragit® FL 30 D-55 (Evonik), a 30 %w/v dispersion of pH-sensitive polymer and plasticizer in water, was diluted to 1 and 10 %w/v formulations for dip coating. Samples were dip coated at a constant entrance and exit speed of 5.5 mm/sec with a submergence time of 1 sec via a custom fabricated dipping apparatus, then allowed to dry at room temperature for 30 min. Film thicknesses were measured in the constant thickness zone using a digital micrometer (Mitutoyo).

FRRB removal was first evaluated in simulated gastric fluid, submerging in a stirred 0.1 M acetate bath (pH=3) for a standard gastric emptying time of 3 h [1, 5]. FRRB permeation by simulated gastric fluid was observed using electrical probes inserted into the capsule cavity that become shorted after fluid enters the capsule.

FRRB mechanical removal was then assessed using the *ex-vivo* intestinal motion simulator. Porcine small intestine tissue (Animal Biotech Industries) was segmented into 20 cm portions and cut in half lengthwise. Tissue samples were laid into the PDMS tissue holder. Upon lowering the test capsule onto the tissue sample, the simulator moved it laterally at 1.4 cm/min, the mean longitudinal translation velocity in the small intestine [5]. FRRB removal was determined upon inspection.

RESULTS AND DISCUSSION

Dip-coated film thickness was found to be 0.3±0.2 µm, 2.0±0.3 µm, and 5.5±0.3 µm for 1, 10, and 30 %w/v Eudragit® FL 30 D-55 solutions, respectively, showing linear correlation (R^2=0.973) with a proportionality constant of 0.18 µm/(%w/v) (Fig. 3). Acid bath dissolution experiments showed that capsules coated with the PEG-Eudragit® FL 30 D-55 bilayer were not permeable after 3 hours, while capsules coated in PEG alone were permeated within 3 min.

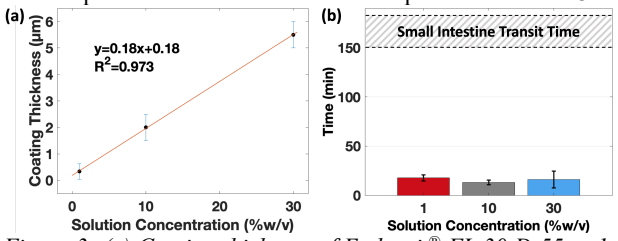

Figure 3: (a) Coating thickness of Eudragit® FL 30 D-55 at 1, 10, and 30% w/v. (b) FRRB removal time in the ex-vivo intestinal simulator fabricated with PEG and 1, 10, and 30% w/v Eudragit® formulations. Gray bar represents expected transit time.

Mechanical removal of FRRB coatings with 1%, 10%, and 30% Eudragit layers showed mean removal times of 17.7±1.8 min, 13.1±1.3 min, and 16.0±4.9 min, respectively (Fig. 3(b)), with an average of 15.6 min. This is approximately 1/10th of the range of small intestine transit times previously demonstrated for a capsule [4], labeled as a gray band. Thus, this system can protect capsule systems (actuators, sensors, openings) in transit through the low-pH stomach region and then rapidly reveal active subcomponents shortly after entering the small intestine target region.

Fig 3(b) showed that Eudragit coating thickness has negligible effect on the removal time of the bilayer, suggesting that the thicker PEG support layer is mostly responsible for removal time, and the Eudragit is only a protective coating to inhibit dissolution of the PEG layer. The Eudragit material showed rapid swelling and softening once placed on the neutral intestinal tissue, followed by rapid removal after the start of translational motion. The underlying PEG layer remained robust for ~15 min after Eudragit removal, followed by PEG disintegration, as can be seen in the image of a capsule sample after translation across *ex-vivo* tissue in Fig. 4.

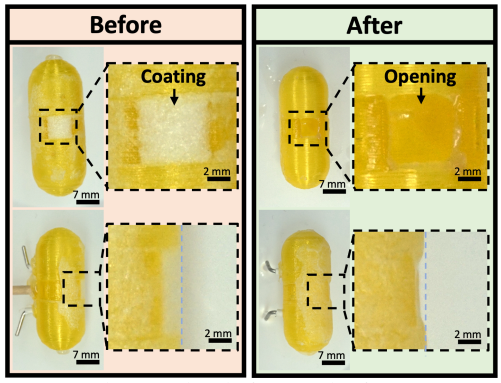

Figure 4: Capsule samples before and after ex-vivo intestinal simulator testing. Before testing, capsules have uniform surface coatings over actuation cavity. After testing, images show complete removal of the FRRB. Blue dashed line indicates capsule perimeter.

CONCLUSION

This work demonstrates an easily translatable strategy for supporting open cavities for actuators and sensors in ingestible devices, along with a novel *ex-vivo* intestinal simulation approach. Eudragit® FL 30 D-55 enteric coating at thicknesses of 0.3–6 µm resisted permeation in simulated gastric fluid, followed by rapid (~30 s) removal in a simulated small intestine environment. The PEG support layer remained intact throughout Eudragit removal, and dissolved within ~15 min, revealing the open cavity. The prompt removal of this support provides timely access of sensors and actuators to the small intestine for monitoring and intervention.

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REFERENCES

[1] S. Hua, "Advances in Oral Drug Delivery for Regional Targeting in the Gastrointestinal Tract - Influence of Physiological, Pathophysiological and Pharmaceutical Factors", *Front. Pharmacol.*, 11 (2020).

[2] A. Abramson, E. Caffarel-Salvador, V. Soares, D. Minahan, R.Y. Tian, X. Lu, D. Dellal, Y. Gao, S. Kim, J. Wainer, J. Collins, S. Tamang, A. Hayward, T. Yoshitake, H.C. Lee, J. Fujimoto, J. Fels, M. R. Frederiksen, U. Rahbek, N. Roxhed, R. Langer, and G. Traverso, "A luminal unfolding microneedle injector for oral delivery of macromolecules", *Nat. Med.*, 25 (2019).

[3] G.E. Banis, L.A. Beardslee, J.M. Stine, R.M. Sathyam, and R. Ghodssi, "Gastrointestinal Targeted Sampling and Sensing via Embedded Packaging of Integrated Capsule System", *J. Microelectromech. Syst.*, 28, 2 (2019).

[4] J.A. Levy, M.A. Straker, L.A. Beardslee, R. Ghodssi, "Biomimetic Anchoring System for Sustained and Localized Gastrointestinal Drug Delivery", Hilton Head Workshop 2022: A Solid-State Sensors, Actuators, and Microsystems Workshop, Hilton Head, SC, June 5-9, (2022)

[5] L. Barducci, J.C. Norton, S. Sarker, S. Mohammed, R. Jones, P. Valdastri, B.S. Terry, "Fundamentals of the gut for capsule engineers", Prog. Biomed. Eng., 2 (2020).

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