Ingestible Medical Device for Controlled Drug Delivery to the Small Intestine

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Oripill

Introduction

- Crohn's disease affects 5 million people worldwide and approximately 75% of those people will undergo surgery at some point.
- Crohn's causes inflammation of the gastrointestinal (GI) tract
  a. Ulceration, swelling, and scarring of the intestinal walls
  b.

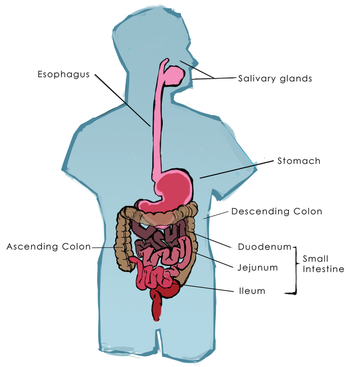

Figure 1: Anatomy of the Gastrointestinal Tract

- Crohn's promotes accelerated GI transit, so treatment time is reduced
- Treatment options are limited, non-site specific, and induce unwanted side-effects
- Current alternative site specific oral treatments:
  a. pH-sensitive enteric coatings
  b. Delayed release systems

Manufacturing

Outer Capsule:

1. Synthesize eudragit polymer
2. Spray coat gel capsules with eudragit

Inner Capsule:

1. Dissolve PLGA and antibodies in dichloromethane
2. Homogeneously mix in salt (porogen)
3. Evaporate Solvent
4. Leach Salt Particles

Arms:

1. Polymerize PAA from AA monomer
2. Cure the polymer inside the 3D printed PLA mold

Acknowledgements
This project was sponsored by Dr. Christopher Bettinger
Additional financial support from Department of Biomedical Engineering CMU
Special Thanks to Dr. Zapanta and Angela Lai

Production

Figure 2: Methodology of creating porous PLGA scaffolds used as the inner capsule3

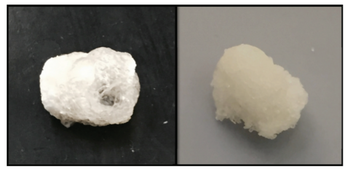

Figure 3: Porous PLGA scaffolds for the only PLGA (left) and PLGA loaded with Anti-TNF Receptor II (right) scaffolds scaffolds used as the inner capsule3

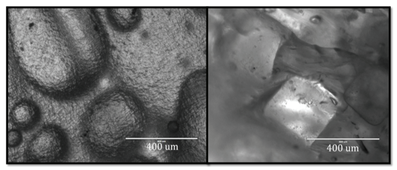

Figure 4: Representative images taken at 10x of the PLGA surface for the only PLGA (left) and PLGA loaded with Anti-TNF Receptor II (right) scaffolds scaffolds used as the inner capsule3

Our Device

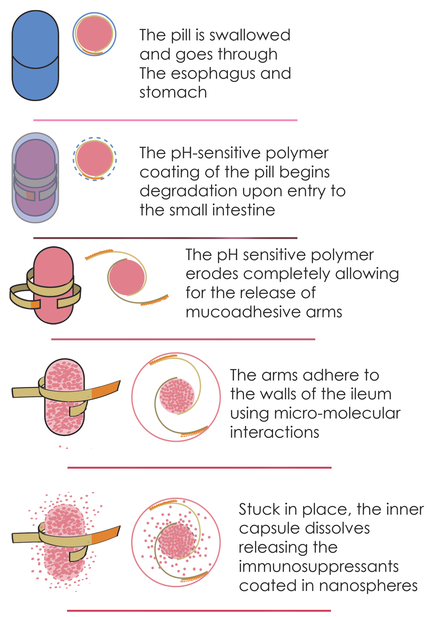

Figure 5: Pill Release mechanism with reference.

Goal

To directly target the inflammation within the small intestine, our group has designed an orally administered device which uses a multi-layered pill system and deployable adhesive arms to encourage retarded motion of the device in the small intestine.

Outer Capsule
- pH sensitive polymer Eudragit L 100
- Degrades at pH > 6

Arms
- Synthesized from PAA,a mucoadhesive polymer
- Released once outer capsule degrades

Inner Capsule
- PLGA and the drug (Antibody: Anti-TNF Receptor II)

Proof of Functionality

-Modelling of the drug release from the inner capsule done in MATLAB
-Drug diffusion based on random walk
-Able to achieve different drug release profiles based on different drug and polymer parameters

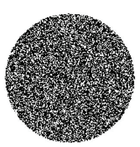

Figure 6: A cross section of the drug matrix at t=0 hours with 30% porosity and a 0.23 probability of polymer erosion.

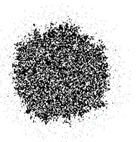

Figure 7: A cross-section of the drug matrix at t=48 hours with 30% porosity and a 0.23 probability of polymer erosion.

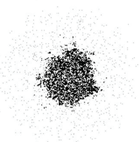

Figure 8: A cross-section of the drug matrix at t=96 hours with 30% porosity and a 0.23 probability of polymer erosion.

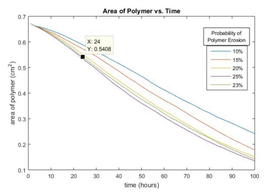

Figure 9: Plot of area of the matrix versus time with different probabilities of polymer erosion. This method was used to determine the appropriate probability that aligned with the data.

References

1. "Inflammatory Bowel Disease." Crohn's And Colitis Foundation of America, Nov. 2014.
2. Ogbru, Annette G. "What Are the Side Effects of NSAIDs? - RxList." The Internet Drug Index. RxList, 26 Apr. 2016.
3. Pan, Z., and J. Ding. "Poly(lactide-co-glycolide) Porous Scaffolds for Tissue Engineering and Regenerative Medicine." Interface Focus 2.3 (2012): 366-77
4. Johannes Laaksonen, Timo et al. "Cellular Automata Model for Drug Release from Binary Matrix and Reservoir Polymeric Devices." Biomaterials 30.10 (2009): 1978–1987. Web.
5.Kang, Jichao, and Steven P. Schwendeman. "Determination of Diffusion Coefficient of a Small Hydrophobic Probe in Poly(lactide- c O -Glycolide) Microparticles by Laser Scanning Confocal Microscopy." Macromolecules 36.4 (2003): 1324–1330. Web.

Conclusion

-Demonstrated degradation through a 2D model
-Began to characterize drug release from PLGA drug loaded pill
- Results are inclusive due to the cumulative fraction for shaken capsule decreasing over time.

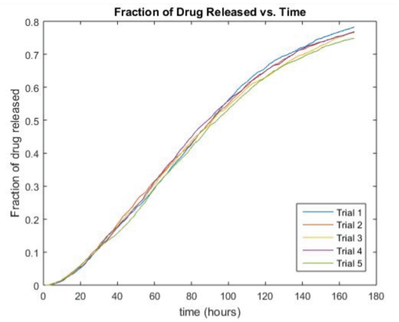

Figure 10: Multiple iterations of the final drug release profile over a week-long timeframe.

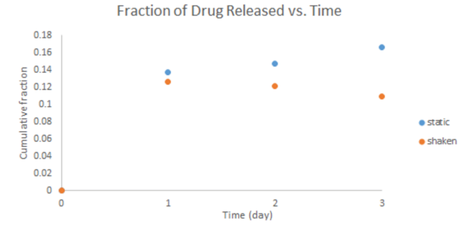

Figure 11: Drug release profile over 3 days for two capsules, one kept static and one kept on a shaker, created using an UV-Vis detector.

Future Work:

Micropillars technology:

Making arms out of a micropatterned surface will further increase the gastro-retentive capabilities of the device. This will keep the device in the small intestine for more time and further increase drug delivery to the inflamed area.

In vivo studies looking at drug release using dog or pig models

Goals:
- Prove dose-dependent effects of the drug loaded in the device
- Establish a timeline for the device moving through the GI tract
- Compare efficacy with pre-existing treatments for Crohn's