Proceedings of the 2021 Design of Medical Devices Conference
DMD2021
April 12-15, 2021, Minneapolis, MN, USA

DMD2021-1063

DESIGN OF A SOFT, SELF-UNCOILING STENT FOR EXTENDED RETENTION OF DRUG DELIVERY IN THE SMALL INTESTINE

Sunandita Sarker
University of Nebraska Lincoln
Lincoln, NE

Ryan Jones
Progenity, Inc
San Diego, CA

Gabriel Chow
Triple Ring Tech.
Newark, CA

Benjamin Terry
University of Nebraska Lincoln
Lincoln, NE

ABSTRACT

Despite being the preferred route of drug administration, the oral formulation of biological drugs is limited due to its intrinsic instability, low permeability, and physical, chemical and immunological barriers. Various innovative swallowable technologies such as drug-loaded, dissolvable microneedles, mucoadhesive patches, and various microdevices present unique drug-carrying capabilities. The current work presents a novel soft stent platform that can facilitate contact between the small intestine tissue and drug carriers to enhance drug absorption and increase residence time. This study aims to prove the concept of this novel platform and determine if the soft stent will retain orally to the ileocecal valve longer than a capsule-shaped bolus. Benchtop studies on an intestinal simulator showed successful retention of the soft stent compared to a control capsule. In vivo studies in pig models also showed that the soft stent was retained longer than the control capsule. Overall, this study shows promise that this novel platform could be used for oral drug delivery of biologics.

Keywords: Oral drug delivery, biological drug, microneedle, tissue contact.

NOMENCLATURE

GIT	gastrointestinal tract
SI	small intestine
ICV	ileocecal valve
GTS	gastrointestinal tract simulator

1. INTRODUCTION

Oral administration has been proven to be the most preferred method of drug delivery universally. Except for some small peptides, most biological drugs or biologics are not suited for oral delivery [1]. Biological drugs are administrated via parenteral routes such as intravenous, intramuscular, or subcutaneous injections. Although the parenteral route ensures a very high drug bioavailability, poor patient compliance and treatment adherence leads to increased complications with chronic diseases such as diabetes mellitus [2]. Biological drugs commonly have large molecules, low membrane permeability, poor water solubility, and are susceptible to rapid degradation in the gastrointestinal tract (GIT) [3]. Even after decades of research, the oral formulation of biological drugs remains a challenge for pharmacologists and engineers alike. Innovative technologies in material formulations and developments of hydrogels, micro, and nanoparticles, silica gel career, etc., have helped with drug solubility and membrane permeability. However, oral bioavailability still remains less than 2% [3].

Drug-device combinations take a holistic approach to protect, transfer, and deliver the drug into the system. Dissolvable microneedles, mucoadhesive patches, scaffolds, and microfabricated devices have been potent in vitro and animal studies [4–7]. For most of these technologies, one prerequisite for drug delivery is the physical contact between the small intestine lumen wall and the drug delivery element, i.e., needle tips or micro patches. A few of these drug-device combinations have active design components to enhance tissue contact [8], but most rely on passive methods. In this study, we propose a drug carrier platform named “soft stent” that can be used to ensure contact between the microdevices and tissue wall. While conventionally, a stent is a metal or plastic tube inserted in a blood vessel to prevent collapsing of the lumen, our soft stent does not serve the same purpose. The soft stent has a self-coiling and uncoiling feature that allows it to collapse and expand with the small intestine’s (SI) peristalsis and segmentation. After placement into the SI, we hypothesize that the soft stent will retain longer in the GI than a standard 000 size plastic capsule and provide more prolonged contact between tissue wall and drug carriers.

The nominal inner diameter of the human SI is 25-30 mm. The ileocecal valve (ICV) is a sphincter muscle valve that separates the small intestine and the large intestine. Its critical

function is to limit the reflux of colonic contents into the ileum. Approximately two liters of fluid pass through the ICV daily in an intermittent flow of jets. It is taper-shaped and thicker and more vascular mucosa folds. Generally, objects greater than 20 mm in diameter will not pass through the ICV [10]. All these properties make the ICV junction a plausible spot for the placement of the soft stent for drug delivery. No study has been done to the author's knowledge that has used the ICV for any medical device retention. Therefore, a proof-of-concept study is needed to examine this novel idea. The objective of this work is to determine if the soft stent will be retained orally to ICV while undergoing peristalsis in vivo.

2. MATERIALS AND METHODS

2.1 Functional requirements and system Design

The soft stent has the following functional requirements. Initially, the soft stent needs to fit inside a traditional capsule shell for easy swallowability. Once in the SI, it needs to expand radially to provide contact between a drug carrier and the SI wall. The soft stent also needs to resist migration by collapsing and expanding with the SI peristalsis and segmentation. These functional requirements were achieved by designing the self-coiling and uncoiling feature similar to a clock spring.

A 0.1 mm thick polyester sheet (Precision Brand Products, Inc.) was laser cut into 75 mm by 20 mm rectangular pieces. The cut pieces were wrapped around a 15 mm diameter aluminum tube and were heated for 15 minutes at 170ºC. This allowed the flat sheet to be plastically deformed into a 15 mm diameter cylinder (FIGURE 1). The Enteric-coated capsule shells used in this study were donated from Lonza Pharma and Biotech. These capsules mechanically disintegrate in a specific pH range of 6-7. While coiled, the soft stent fits into a 00-size enteric-coated capsule shell and is protected in lower pH (less than 2) environment. Once the capsule shells were in the correct pH environment (greater than 6), they disintegrate, and the soft stent expands to full size to contact the inside SI wall.

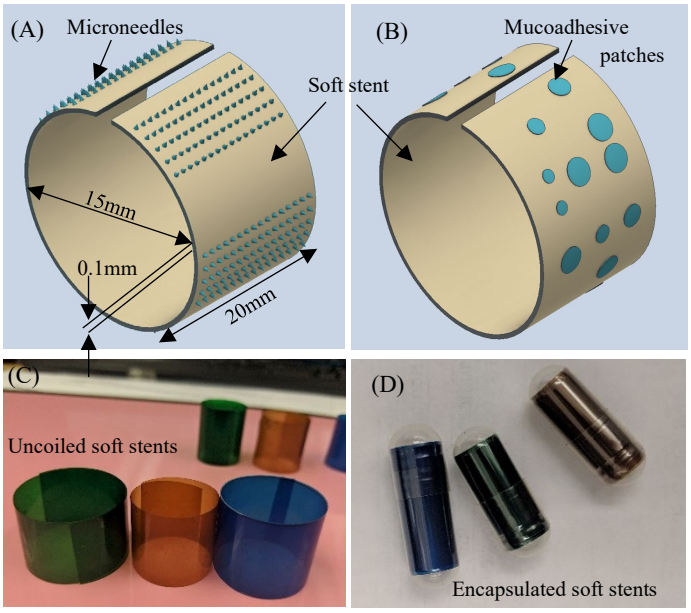

FIGURE 1: Self-uncoiling drug carrier platform- 'soft stent'. Schematic diagram of soft stent with conceptual drug loaded (A) microneedles, and (B) mucoadhesive patches; (C) cylindrical soft stent maintains its shape when no load is applied; (D) soft stent coiled and encapsulated in easily swallowable capsule shells.

2.2 Benchtop experiment

The purpose of this experiment is to determine if the soft platform will be retained orally to the ICV while undergoing simulated peristalsis in a 300 mm long excised porcine tissue sample. The peristaltic simulation was generated by an in-house gastrointestinal tract simulator [11] before performing in vivo testing.

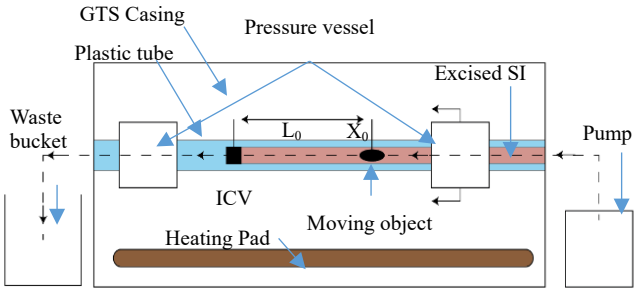

FIGURE 2: Schematic diagram of the bench top experimental setup.

In this experiment, freshly excised porcine SI tissue with the ICV was used in the gastrointestinal tract simulator (GTS). The GTS supports two independently controlled compressive pressure vessels that mimic peristaltic waves and traverse at a speed corresponding to human peristaltic waves (.8 – 20 mm/s). Before the experiment, the GTS was calibrated to operate at the upper end of the physiological range of peristalsis. Thus, the contact force and peristaltic wave speed values were 430 gf and 10 mm/s, respectively, and held constant during all sets of trials.

Nine samples of SI tissue with an intact ICV were collected from donated swine GIT and stored in PBS at 4ºC before testing. All tests were performed within 24 hrs. of euthanization. The experiment had two major steps, the negative control step, and the experimental step. Each step was performed on the same piece of tissue, but the order in which the steps were performed was randomized. A 3D printed (Stratasys Objet 500) capsule with a length of 20 mm and a diameter of 10 mm was used as a negative control to ensure that a capsule shape object will pass naturally. The capsule was placed manually inside the SI loaded into the GTS. The initial position (X_0) was marked by sewing a thread on the exact tissue for measuring migration as well as tissue stretch. The distance between X_0 and the ICV (L_0 = 150 mm) was constant during the whole process. The GTS simulated peristalsis and the number of peristaltic waves (n) required for the capsule to pass the ICV was recorded. A negative control capsule must pass the ICV to be counted as a successful run. In the human SI, one peristalsis wave moves chyme an average of 40 - 50 mm, so if the capsule cannot pass within - 3 peristalsis

waves, it will fail the run. The process was recorded using a camera to indicate any damage or tearing of the tissue.

In the experimental steps, a soft-stent prototype was placed manually at position X_0 inside the same SI. Similarly, the GTS simulated peristalsis and waves were applied. For a large and irregular shape bolus, the chyme can move as slow as 10 mm/wave. So, 5 peristalsis waves were applied to the stent. The stent should be retained orally to the ICV to be counted as a successful run. Migration of the stent after each wave and the total migration, S, were measured. If the stent passes the ICV, the number of peristaltic waves (n) that caused it to pass was recorded. If the tissue was damaged during any steps, the experiment was terminated, and the next sample was used.

2.3 Characterization of retention duration in vivo

The purpose of the first experiment is to evaluate the in vivo retention duration of a surgically placed soft stent orally to the ICV and to identify possible damage on the tissue wall caused by the stent. The study was approved by the University of Nebraska Lincoln's Institutional Animal Care and Use Committee (IACUC, Protocol No. 1866). A 70 kg crossbred, neutered, domestic pig was selected. The pig was fasted overnight before the surgery but had free access to water. An abdominal laparotomy was performed to expose a section of the ileum with the ileocecal valve, and a 15 mm incision was made approximately 450 mm oral to the ICV. To investigate the retention duration a control capsule with a radiopaque marker was inserted through the incision and was pushed aborally to be located approximately 150 mm oral to the ICV. Next, the soft stent encapsulated in a dissolvable capsule was inserted through the incision and pushed aborally to be located approximately 300 mm oral to the ICV. After observing that the capsule shell had dissolved and the soft stent had uncoiled inside the intestine, the enterotomy was sutured closed. Small radiopaque markers were attached to both the control capsule and the soft stent, and a long radiopaque marker was sutured on the intestinal mesentery along the ilium from the soft- sent position to the ICV. This marker enabled tracking the migration of the soft stent.

Radiographs were taken before recovery from anesthesia to record the initial locations of the soft stent. Then the pig was returned to the stall after recovery, following which radiographic images were acquired four hrs. after recovery, and then every twelve hrs. until the devices appear to pass ICV. The pigs had free access to food and water for the experiment's duration, and veterinary staff monitored the behavior and body temperature of the pig to detect signs of discomfort or sepsis. Once the devices passed through the ICV, the pig was euthanized, and the tissue from the attachment position and ICV were collected for a gross histological survey.

2.4 Relative migration vs. thickness

The second in vivo experiment was designed to determine the relative migration of the soft stent with varying thickness and rigidity. We assumed that very thin and less rigid soft stent will be more compliant with the SI wall and collapse and expand easily. As a result, we hypothesize that migration will be minimum for the least rigid and thinnest soft stent. To test the hypothesis, three stents of the same size (15 mm in diameter and 20 mm in length), including the designed soft stent, prototype A (0.1 mm thickness), a thinner one, prototype B (0.05 mm thickness), and a 3D printed rigid ring (thickness 0.5 mm), prototype C, were surgically placed 300 mm apart in the SI. A control capsule was placed 300 mm away from the ICV as well to monitor any obstruction in the GIT. All devices were marked with radiopaque markers, and as before, radiographs were taken before and after surgery. Once the devices passed through the ICV, the pig was euthanized, and the tissue from the attachment position and ICV were collected for a gross histological survey.

3. RESULTS AND DISCUSSION

3.1 Benchtop experiment

Results from nine tissue samples are presented in Table 2. In eight of the nine trials, the control capsule passed the ileocecal junction indicating a successful negative control step. The stent was retained inside the small intestine for all nine samples. For seven samples, stent migration was between 0-3.6% of the migration of the control capsule. For two samples, higher migration was observed (30.7 mm and 27 mm). However, in both cases, sections of the tissue where the stent was placed were stretched by 10 mm and 22 mm, respectively. The total migration length includes the stretch.

TABLE 1: Bench top retention experiments results

Sample	Total stretch (mm)	Section stretch (mm)	Control capsule		Soft stent	
			Waves	Migration (mm)	Waves	Migration (mm)
1	10	0	1	150	15	5.5
2	15	0	1	150	15	3
3	30	0	1	150	15	4
4	35	0	1	150	15	0
5	42	10	3	150	15	30.7
6	26	0	1	150	15	0
7	24	0	3	150	15	0
8	13	0	1	150	15	0
9	50	22	1	150	15	27

After testing with both the control capsule and the soft stent prototype, the tissue was inspected for damage. Samples were collected from the location where the soft stent was placed and from downstream to compare side by side. No visual damage or difference was observed (FIGURE 3).

3.2 Characterization of retention duration in vivo

A control capsule and a soft stent prototype were surgically placed in vivo to measure the retention duration. Representative lateral abdominal radiographs are presented in FIGURE 4. The green mark is indicating the soft stent, and the red mark is indicating the control capsule. A long radiopaque string was attached along the mesentery in the ileum to indicate the end of SI. Once the markers of the devices are further away from the string, assumptions were made that the device passed the ICV.

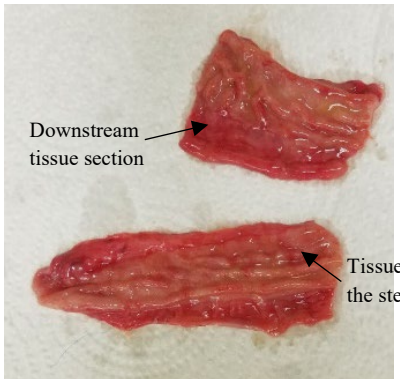

FIGURE 3: Collected tissue samples from the section where the soft stent was placed and downstream from sample 8. No visible damage on the tissue surface was observed.

From the radiographs, it can be observed that the control capsule moved to the large intestine through ICV within 12 hrs. after surgery (FIGURE 4D), while the clock-spring stent was still inside the small intestine 36 hrs. after surgery. Body temperature and behavior remained normal according to the observations by the veterinary staff during the test during this time. Feces of the animal were checked frequently to see any sign of internal bleeding and was not found; however, the control capsule was found in the feces after 24 hrs. After 48 hrs., the pig was euthanized, and the soft stent was collected from the large intestine. Tissue samples from the small intestine were taken from the initial location and near the ICV for gross histology, but no sign of inflammation or damage was found.

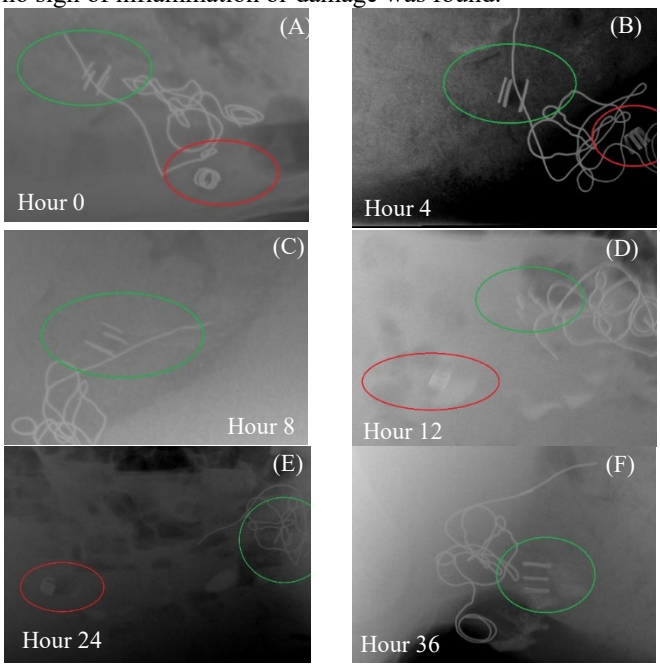

FIGURE 4: X-ray of the retention duration experiment. Green marks indicate the soft stent while the red marks indicate the control capsule. The control capsule moved to the large intestine within 12 hrs. after the surgery while the soft stent stayed for 36 hrs.

3.3 Relative migration vs. thickness

In this experiment, the two soft stents with different thicknesses prototype A (0.1 mm), prototype B (0.05 mm), a 3D printed rigid ring, prototype C, and the control capsule were placed surgically. After recovery, the pig was observed for three days. After the first 8 hrs, only the control capsule moved further from its respective marker while other devices were retained near respective markers (FIGURE 5B). At 20 hrs, both the control capsule and rigid stent/prototype C moved farther away from the markers and assumed to be moved into the large intestine while the two soft stents were held close to their markers (FIGURE 5C). After 32 hrs., the control capsule and the rigid stent were not visible in the radiographs. The less stiff soft stent, prototype B moved from its marker and superimposed with prototype A near the second stent marker (FIGURE 5D). After 44 hrs., the two soft stents were still superimposed; however, they moved away from the markers and were assumed to be passed to the large intestine (FIGURE 5E). The next day no device was seen near any of the markers, and the pig was euthanized. Both soft stents were collected from the large intestine along with the rigid stent and the control capsule. The gross examination of the SI indicated no visible damage in the tissue. Tissue samples were taken from the initial locations and near the ICV for gross histology, but no sign of inflammation or damage was found.

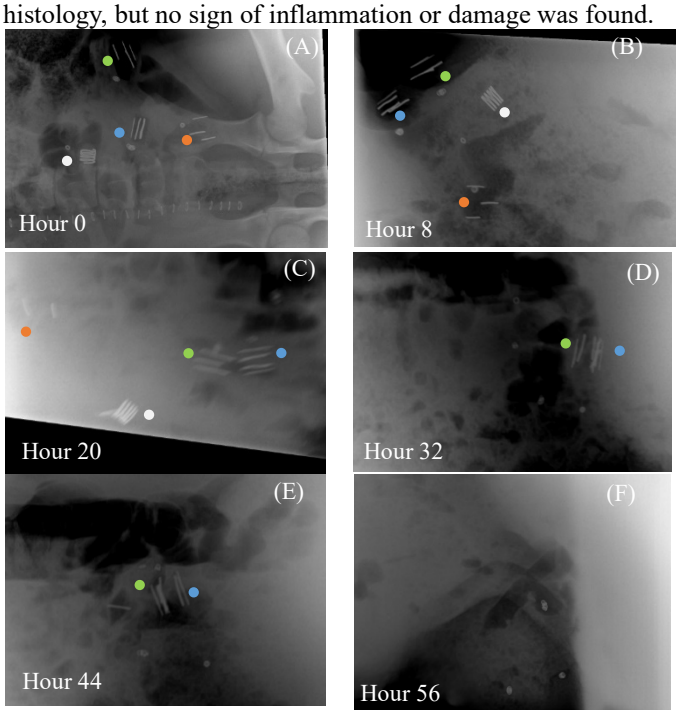

FIGURE 5: X-ray of the migration vs. thickness experiment. White, orange, blue, and green dots indicate the control capsule, the rigid stent, the thicker soft stent, and the thin soft stent. The control capsule and the rigid stent both moved further away from their markers 20 hrs. after the surgery.

3.4 Discussion and limitations

In the benchtop studies the soft stents were retained inside the SI for each of the trials with the limited number of peristalsis simulated using the GTS. More than 3000 peristalsis wave can be present in a healthy individual. Since such a large number of

peristalsis cannot be simulated without damaging the tissue sample, only 15 waves were simulated to observe relative retention and damage only. As observed from the benchtop result, the control capsule passed the ICV 8 out of the 9 times (except sample 7) while the soft stents were retained in all trials. With a large number of peristalsis cycles the soft stent would eventually migrate and pass the ICV which was observed in the in vivo tests.

The retention duration in vivo study showed that the soft stent retains longer than a solid capsule; however, there are some limitations. The true migration rate was not found in this method. Also, the exact time when the devices passed the ICV was not found as X-rays were taken in approximately every 12 hrs. The last time when the devices were near the marker string was used as the retention duration. A real-time localization method could be a possible solution to track the control capsule and the soft stent in future experiments.

In the migration vs. thickness experiment, we observed that a rigid stent with similar dimensions moved faster than any soft stent. However, the individual migration rate of the two soft stents was not found. The total retention for both stents was more than 36 hrs. However, because the soft stents were superimposed with each other, it confounded the result. Also, the thinnest soft stent moved faster than the thicker one. We assumed that the less stiff soft stent collapsed due to the radial forces acting by the SI wall and did not expand to its original diameter after peristaltic force were removed. As a result, it traversed while the stiffer stent expanded instantly once the forces were removed and held its position longer. Hence, an optimized thickness may result in the most prolonged retention. Further experiments are needed to support this hypothesis.

One limitation of this study is the small sample size. Only two pigs were used in total, which is not sufficient to conclude statistical significance. However, the experiments served the purpose of proof of concept for this novel design. Again, only the external dimensions and thickness of the soft stent were considered here. Surface and bulk material properties were not considered. The outer surface coated with mucoadhesive or other binding agents may extend the retention period. Although all devices safely passed with the feces, there might be chances of obstruction in the GIT. Using biodegradable material that dissolves within a predesigned period would eliminate the possibility of obstruction.

Finally, the soft stent platform was used without any drug delivery carrier. Assumptions were made that drug delivery patches, microneedles, or osmotic pumps will not affect the retention duration due to their insignificant mechanical profile. Further study is needed to support hypothesis.

4. CONCLUSION

This study introduces a novel design of a drug carrying platform that can provide extended contact between the SI wall and drug carrying microneedles, patches, or microdevices. The design is less complicated and could be easy to implement with many existing drug carriers. Success in benchtop studies and limited success in vivo showed potential and were sufficient for proof of concept. Further study with a larger sample size and pharmacokinetics is needed to show statistical significance.

ACKNOWLEDGEMENTS

This research was funded by Progenity, Inc. who has intellectual property rights to the inventions. We would also like to acknowledge Craig Kreikemeier-Bower and his staff from the Institutional Animal Care Program of University of Nebraska Lincoln for their animal surgical assistance the life science.

REFERENCES

[1] Zelikin, A. N., Ehrhardt, C., and Healy, A. M., 2016, "Materials and Methods for Delivery of Biological Drugs," Nature Chem, **8**(11), pp. 997–1007.

[2] García-Pérez, L.-E., Alvarez, M., Dilla, T., Gil-Guillén, V., and Orozco-Beltrán, D., 2013, "Adherence to Therapies in Patients with Type 2 Diabetes," Diabetes Ther, **4**(2), pp. 175–194.

[3] Brown, T. D., Whitehead, K. A., and Mitragotri, S., 2020, "Materials for Oral Delivery of Proteins and Peptides," Nature Reviews Materials, **5**(2), pp. 127–148.

[4] Rzhevskiy, A. S., Singh, T. R. R., Donnelly, R. F., and Anissimov, Y. G., 2018, "Microneedles as the Technique of Drug Delivery Enhancement in Diverse Organs and Tissues," Journal of Controlled Release, **270**, pp. 184–202.

[5] Banerjee, A., Lee, J., and Mitragotri, S., 2016, "Intestinal Mucoadhesive Devices for Oral Delivery of Insulin," Bioengineering & Translational Medicine, **1**(3), pp. 338–346.

[6] Huang, H. W., Petruska, A. J., Sakar, M. S., Skoura, M., Ullrich, F., Zhang·, Q., Pané, S., and Nelson, B. J., 2016, "Self-Folding Hydrogel Bilayer for Enhanced Drug Loading, Encapsulation, and Transport," *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 2103–2106.

[7] Hagner Nielsen, L., Sylvest Keller, S., and Boisen, A., 2018, "Microfabricated Devices for Oral Drug Delivery," Lab on a Chip, **18**(16), pp. 2348–2358.

[8] Abramson, A., Caffarel-Salvador, E., Soares, V., Minahan, D., Tian, R. Y., Lu, X., Dellal, D., Gao, Y., Kim, S., Wainer, J., Collins, J., Tamang, S., Hayward, A., Yoshitake, T., Lee, H.-C., Fujimoto, J., Fels, J., Frederiksen, M. R., Rahbek, U., Roxhed, N., Langer, R., and Traverso, G., 2019, "A Luminal Unfolding Microneedle Injector for Oral Delivery of Macromolecules," Nature Medicine, **25**(10), pp. 1512–1518.

[9] Abramson, A., Caffarel-Salvador, E., Khang, M., Dellal, D., Silverstein, D., Gao, Y., Frederiksen, M. R., Vegge, A., Hubálek, F., Water, J. J., Friderichsen, A. V., Fels, J., Kirk, R. K., Cleveland, C., Collins, J., Tamang, S., Hayward, A., Landh, T., Buckley, S. T., Roxhed, N., Rahbek, U., Langer, R., and Traverso, G., 2019, "An Ingestible Self-Orienting System for Oral Delivery of Macromolecules," Science, **363**(6427), pp. 611–615.

[10] Pavlidis, T. E., Marakis, G. N., Triantafyllou, A., Psarras, K., Kontoulis, T. M., and Sakantamis, A. K., 2006,

"Management Of Ingested Foreign Bodies: How Justifiable Is A Waiting Policy?," The Internet Journal of Surgery, **9**(1).
[11] Slawinski, P. R., Oleynikov, D., and Terry, B. S., 2015, "Intestinal Biomechanics Simulator for Robotic Capsule Endoscope Validation," J Med Eng Technol, **39**(1), pp. 54–59.