Gastric resident systems for large dose drug delivery

by

Malvika Verma

B.S. Bioengineering (2014),
California Institute of Technology

Submitted to the Department of Biological Engineering
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Biological Engineering

at the

Massachusetts Institute of Technology

June 2019

Signature of Author: Signature redacted

Malvika Verma
Department of Biological Engineering
May 14th, 2019

Certified by: Signature redacted

Robert Samuel Langer, Sc.D.
Institute Professor, MIT
Thesis Supervisor

Accepted by: Signature redacted

Forest White, Ph.D.
Professor of Biological Engineering, MIT
Chair, Graduate Program Committee of Biological Engineering

The following committee has evaluated this doctoral thesis:

Professor Robert Samuel Langer, Sc.D.
Thesis Supervisor
Institute Professor, MIT

Professor Angela Koehler, Ph.D.
Chair, Thesis Committee
Assistant Professor of Biological Engineering, MIT

Professor James Collins, Ph.D.
Member, Thesis Committee
Professor of Biological Engineering, MIT

Professor Yonatan Hagai Grad, M.D., Ph.D.
Member, Thesis Committee
Assistant Professor in Department of Immunology and Infectious Diseases, Harvard TH Chan School of Public Health
Attending Physician in Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School

Professor Carlo Giovanni Traverso, M.B., B.Chir., Ph.D.
Member, Thesis Committee
Assistant Professor of Medicine and Associate Physician in the Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School
Assistant Professor of Mechanical Engineering (Starting Fall 2019), MIT

Gastric resident systems for large dose drug delivery

by

Malvika Verma

Submitted to the Department of Biological Engineering on
May 24, 2019, in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Biological Engineering

Abstract

Lack of medication adherence is a worldwide problem. As many as 50-70% of patients have trouble following treatment recommendations. Whereas adherence is driven by many factors including the socioeconomic status of a patient and the quality of the health care team, drug regimen complexity also affects treatment outcomes. For example, adherence decreases as the number of pills per dose and the number of doses per day increases. For diseases where potent medications are available, depot formulations provide sustained drug release to simplify dosing. For diseases lacking potent compounds for treatment, there remains an unmet need for depot systems that could transform medication adherence.

Tuberculosis (TB) is one such disease with a high pill burden, where poor patient adherence to the treatment regimen is a major cause of treatment failure and contributes to the emergence of drug-resistant TB strains. For example, an average 60-kg patient with TB needs to take 3.3 g of antibiotics per day, which is a dose that exceeds the largest swallowable capsule and current depot systems. According to the World Health Organization (WHO), 10 million people developed TB in 2017 with a global economic burden amounting to $12 billion annually.

This thesis presents a solution to the challenge of prolonged dosing for regimens such as TB that require multigram drug dosing. First, a gastric resident system (GRS) compatible with transesophageal administration was designed using biocompatible materials. The GRS consists of a series of drug pills on a coiled superelastic nitinol wire; the ends are protected with a retainer and tubing. Safe administration, gastric retention for 1 month, and retrieval of the GRS were demonstrated in a swine model. Next, sustained release formulations for 6 TB antibiotics were formulated into drug-polymer pills, and first-order drug release kinetics were achieved *in vitro*. Then, the GRS was demonstrated to be capable of safely encapsulating and releasing 10 grams of an antibiotic over the period of weeks in a swine model. Lastly, end-user assessment was evaluated with a field questionnaire in India and an economic model to estimate the impact of the GRS on the health care system. There are multiple applications of the GRS in the field of infectious diseases, as well as for other indications where multigram depots could impart meaningful benefits to patients, helping maximize adherence to their medication

Thesis Supervisor: Robert Samuel Langer
Title: Institute Professor, MIT

This page is intentionally left blank.

Acknowledgements

"If I have seen further than other, it is by standing upon the shoulders of giants" – Sir Isaac Newton

This work has been enabled by so many, and I am grateful to of all of you for being part of my journey. Also, this section was my favorite to write.

Project Advising

- Professor Robert Samuel Langer, Sc.D. for teaching, advising, and inspiring me to work on impactful problems
- Professor Carlo Giovanni Traverso, M.B., B.Chir., Ph.D. for teaching me how to communicate, focus, and mentor students
- Professor Angela Koehler, Ph.D. for advising me from the start and always making time to guide me on PhD life in and out of the lab
- Professor James Collins, Ph.D. for asking hard questions and advising me to focus whenever we meet
- Professor Yonatan Hagai Grad, M.D., Ph.D. for constantly encouraging me to push the project forward and advising on the clinical impact

Thank you for taking out time to guide me.

Colleagues, Collaborators, and Students

- Langer Lab members (past and present) for your friendship, guidance, and positive spirit
- Professor Niclas Roxhed for brainstorming new ideas and teaching me how to setup experiments during my early years of graduate school
- Professor Michael Cima and his lab for guidance on a variety of drug delivery techniques
- Professor Alexander Slocum and his lab, especially Dalia Leibowitz for her input on mechanical engineering aspects and laying the groundwork for the field questionnaire
- Professor Jennifer Furin for encouraging me and providing constant guidance on the impact of our work for patients with tuberculosis
- Mr. David Collins for picking up a random phone call from me for a class project and turning it into a productive collaboration on our economic model
- Tata Trusts for believing in our project and providing constant feedback
- Operation ASHA for your continued support and faith in our work
- Government of India for collaborating with us on our field questionnaire
- My students for teaching me to be a better scientist, communicator, and mentor: Karan Vishwanath, Feyisope Eweje, Macy Castaneda, John A F Salama, Dan J Fulop, Chinonyelum Ikeanyi, Gal Zeidman, Elizabeth Mule, Sooraj Boominathan, Ellena Popova, Ryan Koeppen, Talha Faiz

Thank you for all your contributions to this body of work.

Funding and Resources

- Bill and Melinda Gates Foundation
- National Institutes of Health
- National Science Foundation Graduate Research Fellowship
- MIT Tata Center and leadership team for believing in and guiding our project

Thank you for supporting this work.

Research Advisors Before MIT

- Professor Eleanor Stride and Dr. Paul Rademeyer at the University of Oxford
- Professor Scott Fraser and Dr. Jeffrey Fingler at Caltech
- Professor Chin-Lin Guo and Dr. Jiun-Yann Yu at Caltech

Thank you for being patient as a teacher and giving me the tools and confidence to pursue a PhD.

Around my Life

- MIT Biological Engineering friends and faculty
- Graduate Student Council friends
- Ashdown House friends and staff
- Mem Miller and Jonathan B Miller
- Family in India for making me feel at home on every work and social trip
- My brother Rishab, grandparents, and parents

Thank you for your love and motivating me every day.

Conflicts of Interest

Malvika Verma is a co-inventor on multiple patent applications describing large dose gastric drug delivery systems: US Patent Applications #62/678,439, #62/678,471 and #62/678,492.

This page is intentionally left blank.

Table of Contents

List of Figures

Number: Figure Title Page

List of Tables

Number: Table Title Page

List of Abbreviations

TB	Tuberculosis
GRS	Gastric resident system
WHO	World Health Organization
SD	Standard deviation
DDS	Drug delivery system
IVIVC	*In Vitro-In Vivo* correlation
GI	Gastrointestinal
MTB	*Mycobacterium tuberculosis*
AM	Alveolar macrophage
AMR	Antimicrobial resistance
SDI	Socio-demographic index
DOTS	Directly Observed Treatment Short Course
NG	Nasogastric
PCL	Poly(Ɛ-caprolactone)
THV	Tetrafluoroethylene hexafluoropropylene vinylidene fluoride
3D	Three-dimensional
SGF	Simulated gastric fluid
PETG	Polyethylene terephthalate
VPS	Vinylpolysiloxane
PEG	Poly(ethylene glycol)
HPLC	High-performance liquid chromatography
UPLC-MS/MS	Ultra-performance liquid chromatography–tandem mass spectrometry
AUC	Area under the curve
PES	Pill ejector system
DSTB	Drug-susceptible tuberculosis
NTP	National tuberculosis control program
LTFU	Loss-to-follow-up
MDR-TB	Multi-drug resistant tuberculosis
HCV	Hepatitis C virus
DAA	Direct-acting antivirals

Chapter 1: Introduction

1.1 Medication adherence

"Drugs don't work in patients who don't take them." – Charles Everett Koop, M.D.

1.1.1 Problem

Lack of medication adherence is a worldwide problem. As many as 50% of patients have trouble following treatment recommendations (*1*). Participants at the World Health Organization (WHO) Adherence meeting in June 2001 defined adherence as "the extent to which the patient follows medical instructions (*2*)." However, they acknowledged that this was just a helpful starting point, and the term "medical" may be too restrictive of the range of interventions used to treat disease (*2*). The modified definition of adherence is more fitting: "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider (*1*)."

The terms "compliance" and "adherence" are often used interchangeably, but they are not synonyms. (*3*). The word "compliance" comes from the Latin word "complire", meaning to fill up and hence to complete an action, transaction, or process and to fulfill a promise (*4*). The word "adherence" comes from the Latin word "adhaerere", which means to cling to, keep close, or remain constant (*4*). Therefore, "compliance" implies patient passivity, whereas "adherence" presumes patient's agreement with recommendations and is more reflective of the tenacity required to complete treatment regimen (*3–5*). For the remainder of this work, "adherence" will be used to reflect the health care community's view of patient centeredness and activation (*6*).

Medication nonadherence has important health consequences, ranging from decreased quality of life to even death (*1*). It has been estimated that better adherence to antihypertensive treatment alone could prevent 89,000 premature deaths in the United States annually (*7*). Poor health outcomes increase health care service utilization and overall health care costs **(Figure 1.1)**

(*6*). Often, the financial pressure is passed to patients by payers through higher copayments or via higher costs to employers for coverage (*6*). Increased patient costs further increase nonadherence. Over $300 billion of avoidable health care costs have been attributed to nonadherence in the United States annually, representing 10% of total health care costs (*6*).

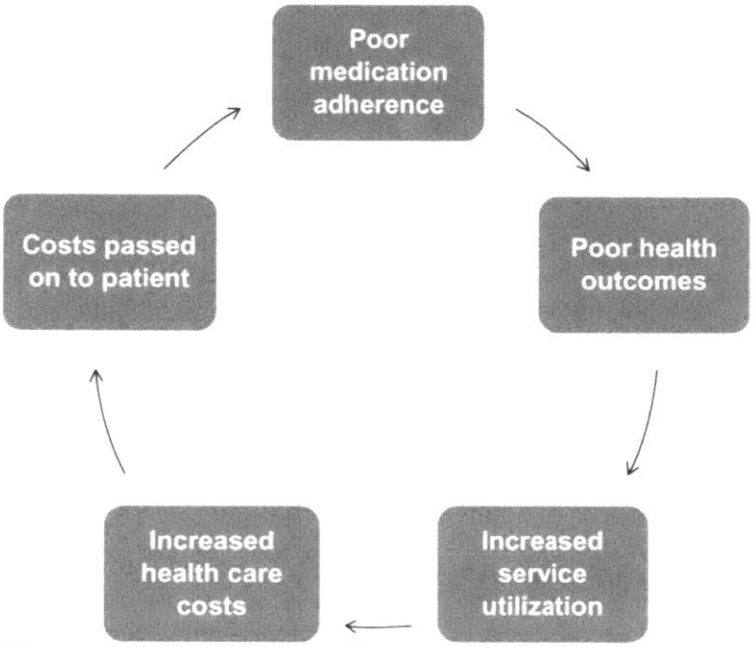


Figure 1.1: Conceptual diagram displaying the consequences of medication nonadherence.
Poor medication adherence results in poor health outcomes, which ultimately increases health care costs for society and the patient, continuing nonadherence. Reproduced with permission from (*6*).

Accurate assessment of adherence behavior ensures that changes in health outcomes can be attributed to the recommended regimen, enabling effective and efficient treatment planning (*1*). As early as the time of Hippocrates during 5th century BCE, adherence was monitored to understand the effects of various potions using notations of whether the patient had taken them (*5*, *8*). Even today, patients' self-reports are the most common method for assessing adherence, although they tend to overestimate adherence behavior (*5*, *9*). Current methods measuring adherence can be broken down into direct and indirect methods, with each having advantages and disadvantages **(Table 1.1)** (*5*). No method is considered the "gold standard (*1*, *5*)."

Table 1.1: Methods of measuring adherence.
Reproduced with permission from (*5*), Copyright Massachusetts Medical Society.

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

1.1.2 Problem

Adherence is a multidimensional phenomenon determined by the interplay of five factors or "dimensions": 1) social & economic, 2) health care system, 3) condition-related, 4) therapy-related, and 5) patient-related **(Figure 1.2)** (*1*). Social and economic factors include poverty, level of education, and cultural beliefs about medication. Health care system factors include insurance plans and distribution networks for medicine. Condition-related factors include symptoms of the disease itself. Therapy-related factors include complexity of the medication regimen and side effects. Patient-related factors include impairments, knowledge about the disease, and motivations to cure the disease.

Diagram Outlining the Factors Related to Non-Adherence.

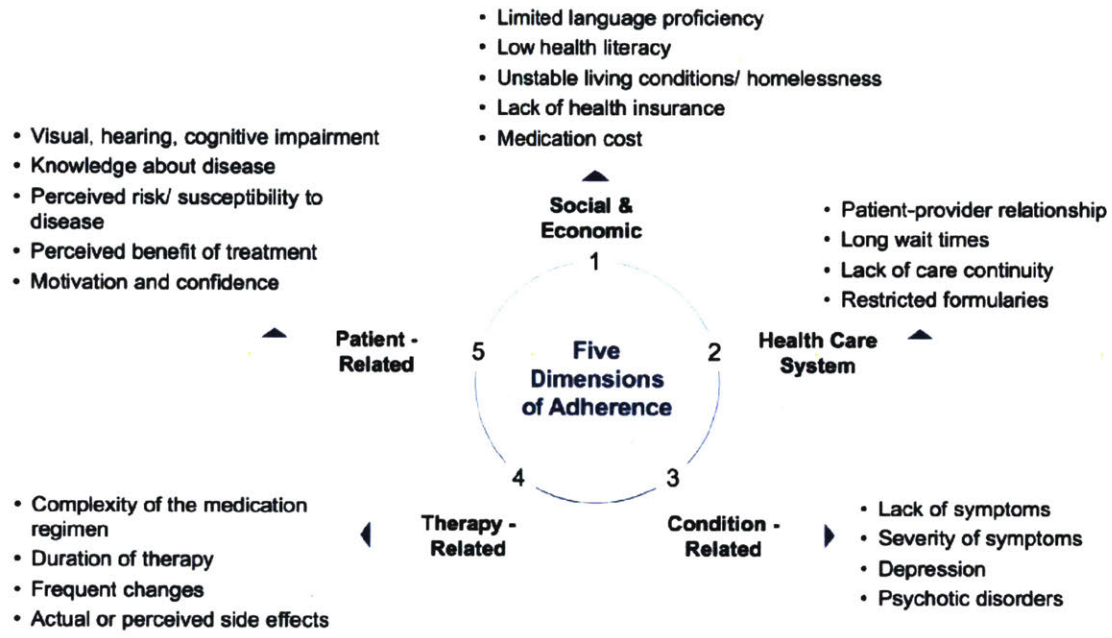


Figure 1.2: Five dimensions of adherence.
Medication adherence is influenced by many factors including: 1) social and economic, 2) health care system, 3) condition-related, 4) therapy-related, and 5) patient-related. Reproduced with permission from (*10*), Copyright Massachusetts Medical Society.

1.1.3 Interventions

Growing evidence suggests that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments (*1*)." Numerous factors contribute to nonadherence, and therefore combining interventions that are tailored to address a patient will ultimately lead to successful health outcomes (*1*, *11*). Strategies to improve medication nonadherence can be seen as targeting the patient, provider, and external factors **(Table 1.2)** (*6*).

Table 1.2: Strategies for improving medication nonadherence.
Reproduced with permission from (*6*).

Strategies	Examples
Patient	
Education	Patient counseling by physicians or other health care personnel[58]
Engage social network	Family members can provide reminders and feedback. This is particularly helpful for patients with psychiatric disease[85]
Reminders	Automated alerts, telemonitoring[86]
Provider	
Improve relationship with patients	Training physicians to improve their communication skills, patient activation by improving patient–physician communication[87]
External factors	
Simpler regimen	Medications with long half-life or extended release[9]
Auto-delivery systems	Eg, auto-injectors, pumps[89]
EMR based	Electronic prescribing[81]
Team based care, care coordination	Patient centered medical homes; case management; engagement of nursing staff, pharmacists[58]
Value based insurance designs	Lowering copayments can improve adherence[34]

Abbreviation: EMR, electronic medical records.

Often, it is difficult to change the patient and provider during the timeframe of treatment. Scientists and engineers can impact adherence by designing solutions to enable simpler regimens (*12*). Simple dosing helps to maximize adherence, as supported by numerous studies and reviews (*1*, *5*, *13–15*). Claxton and colleagues analyzed 76 studies and found that adherence was inversely proportional to frequency of dose **(Figure 1.3)** (*5*, *15*). Patients taking medication on a schedule of four times daily achieved average adherence rates of about 50 percent; patients taking medication on a once daily schedule achieved average adherence rates of about 80 percent (*15*). Kishimoto and Maehara studied the data of 9,326 patients taking oral bisphosphonates (BP) for treatment of osteoporosis (*13*). BP products include those for daily,

weekly, and monthly oral dosing. Their study measured the persistence rate over time for all the patients on each kind of oral BP. At each time point, persistence was calculated as the ratio of patients receiving BP therapy to patients prescribed with BPs. The analysis indicated that a monthly regimen had better adherence to treatment as compared with the weekly and daily regimens.

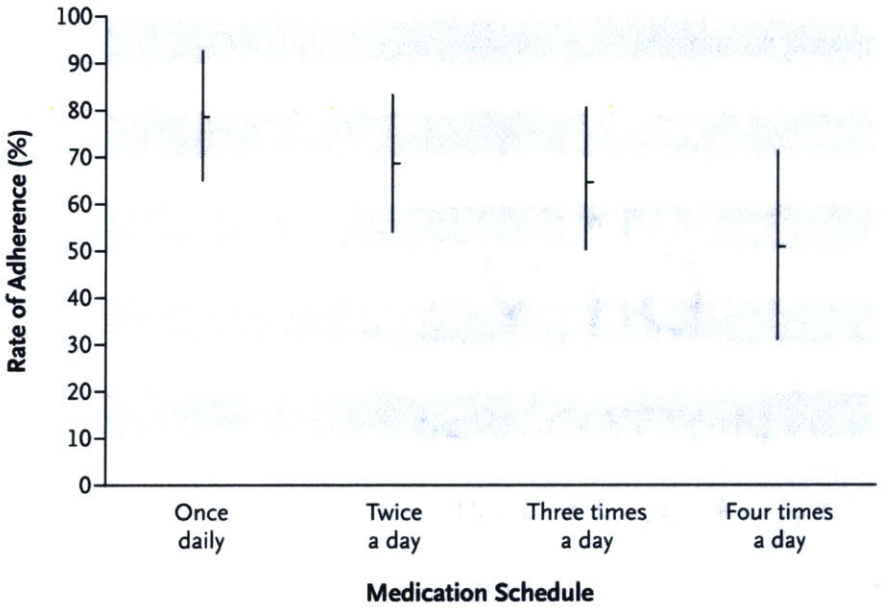
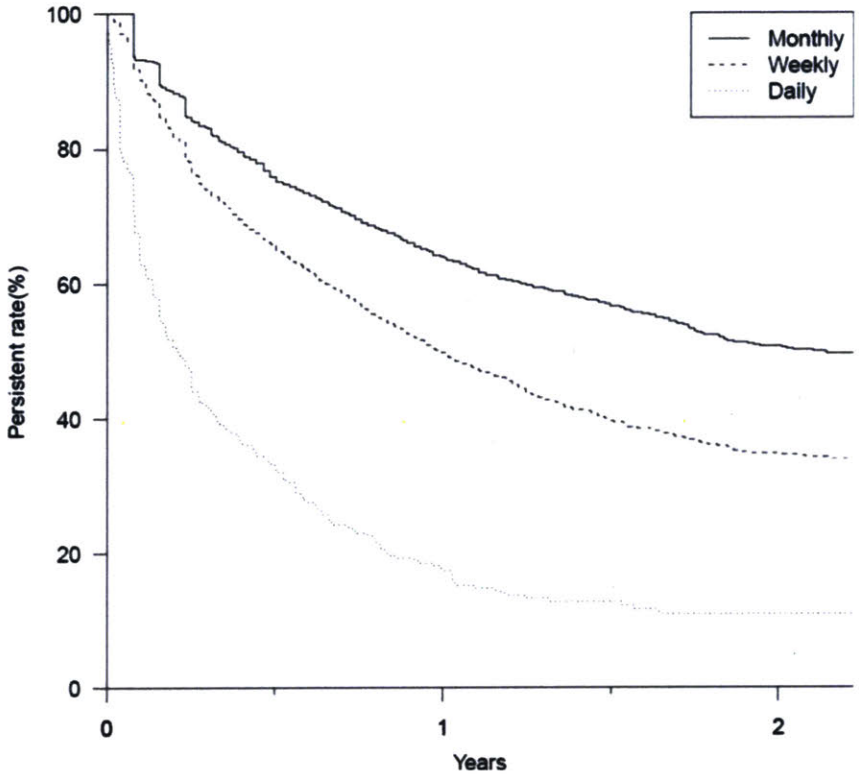


Figure 1.3: Rate of adherence according to medication schedule.
Adherence rate increases when medication schedules are less frequent. Vertical lines represent 1 standard deviation (SD) on either side of the mean rate of adherence (horizontal bars). Reproduced with permission from (*5*), Copyright Massachusetts Medical Society.



No. at risk

Monthly	4,538	2,837	1,730	720	397
Weekly	4,392	2,404	1,345	714	270
Daily	396	116	45	26	18

Figure 1.4: Persistence rate over time for various dosing frequencies of oral bisphosphonates (BPs).
A monthly regimen had higher persistence rates to treatment as compared with the weekly and daily regimens. Reproduced with permission from (*13*).

1.2 Controlled Release Drug Delivery Systems

The release of an active ingredient from a controlled release drug delivery system (DDS) proceeds at a rate that it predictable kinetically and reproducible from one unit to another (*16*, *17*). To develop a controlled release DDS, one must understand the physicochemical properties of the drug, which will then determine the type of delivery material and drug release mechanism. Numerous parameters must be considered while designing *in vitro* release experiments followed by *in vivo* pharmacokinetic studies **(Figure 1.5)** (*16*). The route of administration is also important, as that will affect patient adherence and requirements for additional health care personnel (*1*, *17*, *18*). There are many advantages to developing a controlled release DDS: 1) improve patient adherence by decreasing frequency of dosing, 2) reduce fluctuation in drug levels, 3) reducing the total dose by enabling localized delivery of the drug to a particular body compartment (*19*, *20*). On the other hand, several disadvantages include: 1) risk for dose dumping, which can cause toxicity, 2) poor *in vitro-in vivo* correlation (IVIVC), and 3) the high cost of developing formulations or devices (*19*).

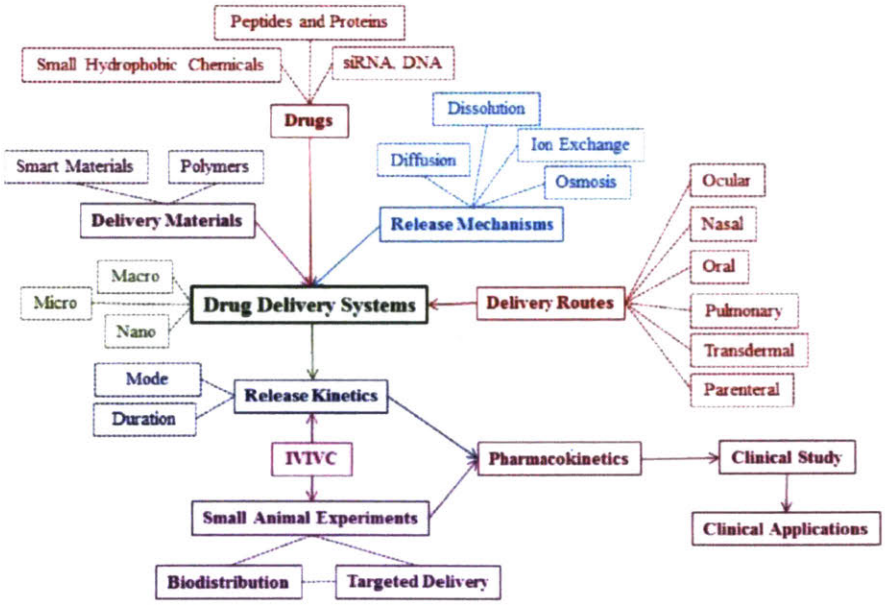


Figure 1.5: Components and processes of drug delivery systems (DDS).
The main components of DDS and processes are shown in bold face with a solid box, and subsections of each component are shown in a dotted box. Reproduced with permission from (*16*).

Most drugs have an optimum range of concentrations within which the maximum therapeutic benefit is derived (*21*). Drug concentrations above the range can result in toxicity, and drug concentrations below the range may have no therapeutic effect. Conventional DDS from tablets or injections typically have a concentration-time profile initially marked by a sharp increase in concentration to a peak followed by a rapid decrease in concentration. Controlled release DDS initially focused on development of sustained (or continuous) DDS over an extended period of time (*20*, *22*). These have concentration-time profiles initially marked by a rise to a concentration in the therapeutic range that is steady over time **(Figure 1.6)** (*22*). In numerous cases, however, sustained release profiles are not optimal for drugs such as hormones. Instead, pulsatile DDS are ideal to release these drugs at specific time intervals **(Figure 1.6B)** (*22–26*). The next generation of DDS are "smart" and responsive to stimuli. They can release drugs at the proper site at the proper rate using either exogenous or endogenous triggers **(Figure 1.7)** (*27*, *28*).

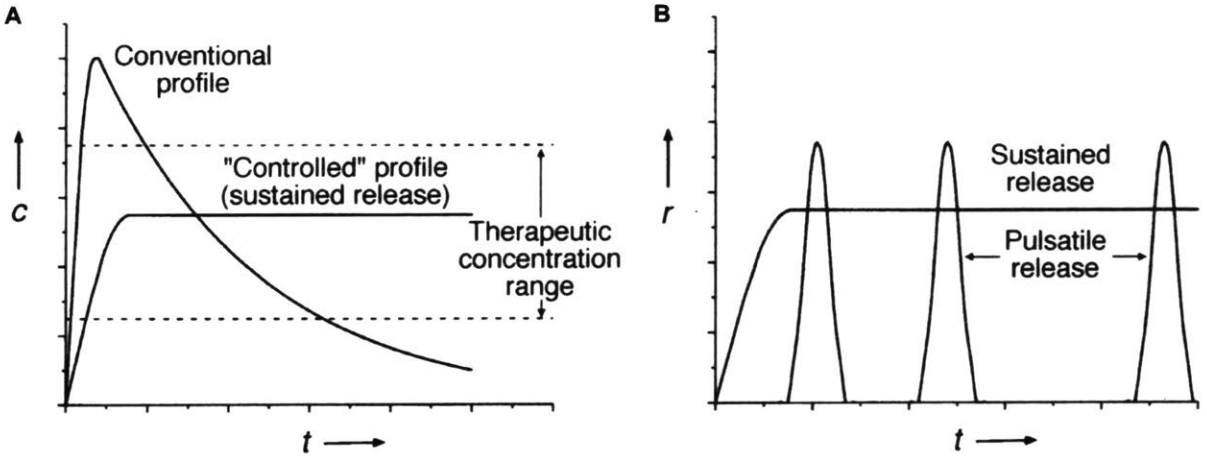


Figure 1.6: Release profiles from controlled release DDS.
(A) Representative concentration *c* vs. time *t* profiles for conventional and controlled release DDS. **(B)** Representative release rate *r* vs. time *t* profiles for sustained release DDS and pulsatile DDS. Reproduced with permission from (*22*).

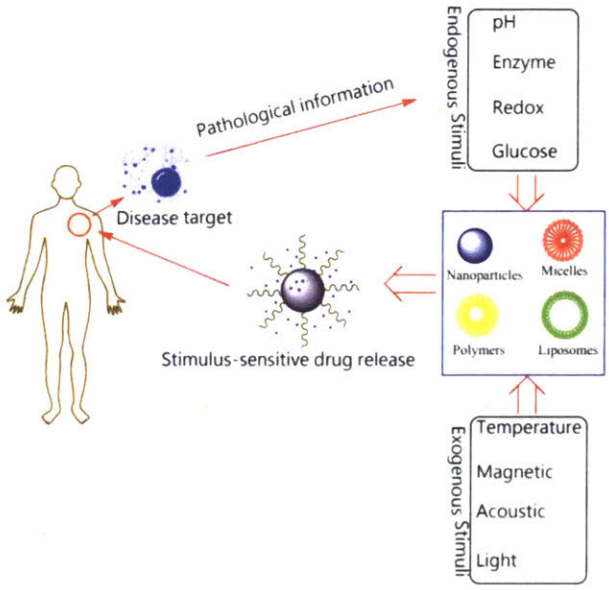


Figure 1.7: Schematic for "smart" DDS.
"Smart" DDS can be responsive to endogenous and exogenous triggers to deliver drug at the correct site and time. Reproduced with permission from (*28*).

1.2.1 Sustained Drug Delivery Systems

Research in biomaterials research has contributed to the development and clinical success of sustained DDS on both macroscopic and microscopic scales (*29*, *30*). Controlled diffusion through matrix, reservoir, and hydrogels has been extensively studied and applied to both small and macromolecules **(Figure 1.8)** (*17*, *20*, *29*, *30*). An example of a commercially available polymeric devices for constant drug release is Norplant (now Jadelle) (*31*, *32*). The Norplant system was introduced in the 1980s to provide five years continuous release of levonorgestrel for birth control. The levonorgestrel is incorporated into silicone capsules placed under the skin in a clinic, and drug releases via diffusion through the silicone matrix. Because the silicone does not degrade, the capsules must be retrieved after five years. Another example is the Lupron® Depot system, which uses poly(D,L-lactide-co-glycolide) microspheres to encapsulate and deliver the hormone leuprolide for weeks to months for treatment of prostate cancer (*33*).

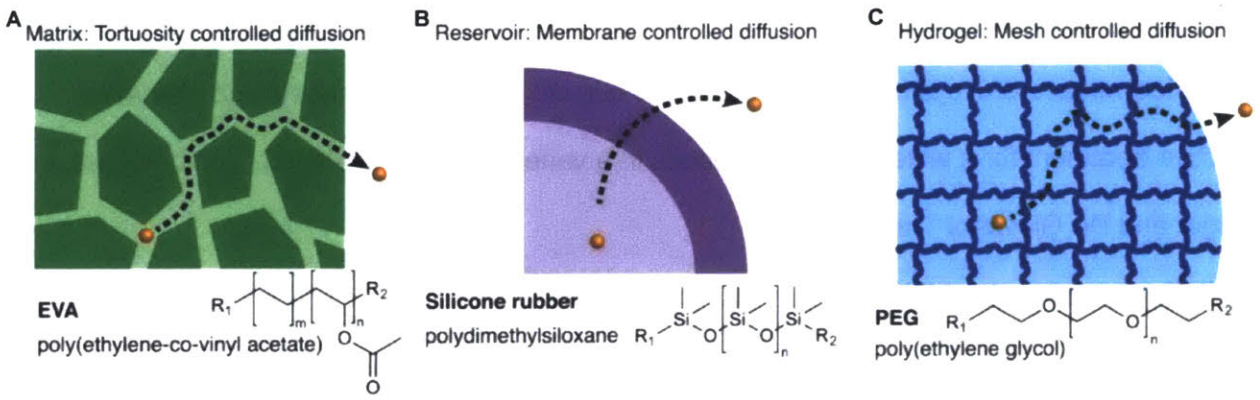


Figure 1.8: Examples of mechanisms of controlled release.
(A) The release of molecules via matrix tortuosity-controlled diffusion. **(B)** The release of molecules through reservoirs with membrane-controlled diffusion. **(C)** The release of molecules through hydrogels with control over mesh size and network swelling. Reproduced with permission from (*30*).

1.2.2 Pulsatile Drug Delivery Systems

The use of pulsatile DDS should be considered for drugs that show chronopharmacological behavior and a high first-pass effect or those that require night-time dosing or site-specific absorption (*23–25*). In recent years, several systems have been developed and commercialized, including the OROS® and Pulsincap™ (*23*, *25*). Pulsatile release systems can be externally regulated (open-loop) or self-regulated (closed-loop) (*22*, *34*). Farra and colleagues have tested an implantable drug delivery device based on microchip reservoir technology and demonstrated the ability to pulse microgram quantities of an anti-osteoporosis drug once daily for up to 3 weeks (*35*). The pharmacokinetic profiles of the drug were similar between implant-mediated release and multiple injections of the drug.

1.3 Gastric Resident Systems

"Extended-release oral systems will revolutionize current clinical-care models and maximize effective treatment for a wide range of diseases in a variety of clinical settings." – Dr. Robert Langer and Dr. Giovanni Traverso

1.3.1 Gastrointestinal Tract

Oral drug delivery remains the most convenient and common for patient treatment, although many of the new millennium drug candidates are becoming increasingly difficult to formulate for good systemic absorption (*36*). The field of oral delivery therefore represents an important area of innovation for both old and new drug candidates. In order to deliver an active pharmaceutical ingredient accurately, one must understand the organization of the gastrointestinal (GI) tract at the organ, tissue, and cell level. This section covers the GI tract on a macroscopic level as well as some of the major factors underlying physiology and function.

The GI tract, a tube that extends from the mouth to the anus, is primarily designed for absorption of nutrients, which are presented in a complex matrix comprising protein, carbohydrate, fat, minerals, and vitamins in different proportions **(Figure 1.9)** (*36*, *37*). The GI tract is composed of multiple different organs and can be divided into the upper and lower GI tract. The upper GI tract includes the mouth, esophagus, stomach duodenum, jejunum, and ileum; the lower GI tract includes the colon, rectum, and anus. The esophagus propels ingested food from the pharynx into the stomach via a wave of highly coordinated esophageal peristalsis. Once in the stomach, the food bolus mixes with gastric acid and digestive enzymes and is broken down to allow digested material, now called chyme, to pass through the pyloric sphincter into the duodenum. Once in the small intestine (duodenum, jejunum, and finally ileum), the digestive process breaks down proteins, fats, and carbohydrates to smaller components to allow for nutrient absorption. Accessory organs that aid in the digestive process include the salivary glands, pancreas, liver, and gallbladder. Once the luminal contents reach the large intestine, the contents

are now called feces and expelled via the rectum and anal canal. The basic plan of the GI tract is a long muscular tube supplied by arteries and drained by veins and a lymphatic trunk, all of which are supported in a mesentery, which are folds of the peritoneum attached to the abdominal wall **(Figure 1.10)**. There is a hollow portion of the tube known as the lumen, a muscular layer in the middle, and a layer of epithelial cells. These layers are responsible for maintaining the mucosal integrity of the tract.

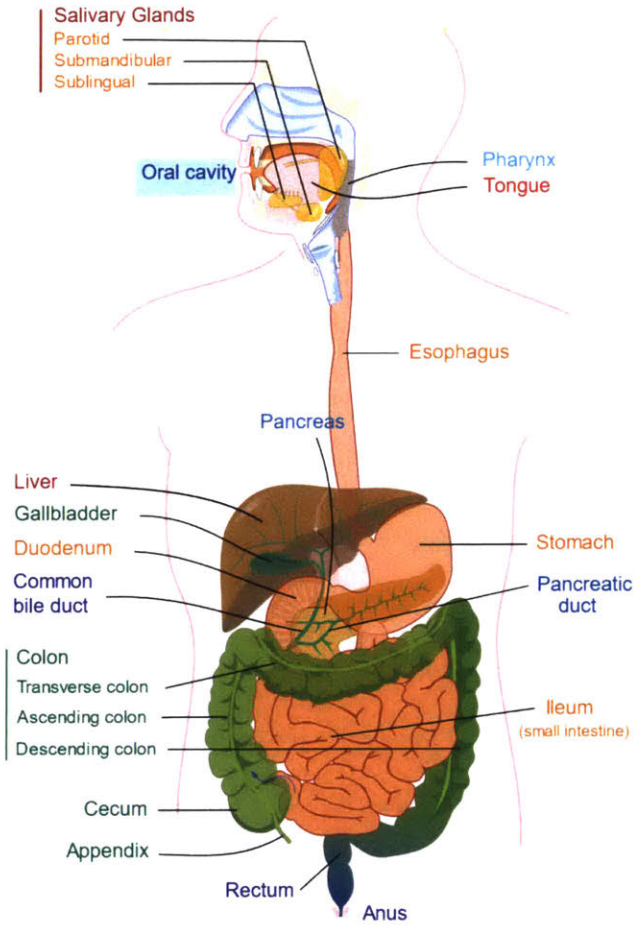


Figure 1.9: Diagram of the human gastrointestinal (GI) tract.
The human GI tract is composed of a series of organs from the mouth to the anus with the responsibility of absorbing nutrients. Reproduced with permission from (*38*).

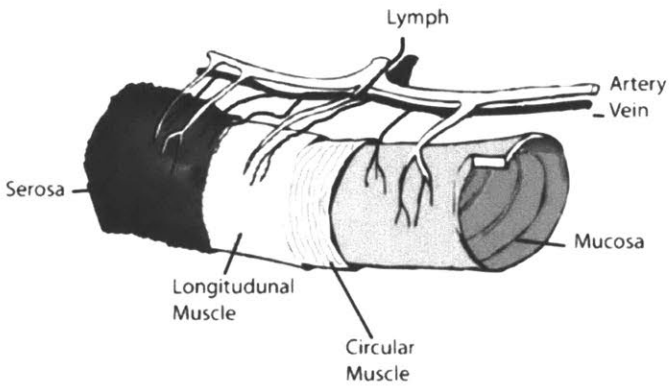


Figure 1.10: Plan of the GI tract with mucosa and muscular layers.
The human GI tract is composed of a series of organs from the mouth to the anus with the responsibility of absorbing nutrients. Reproduced with permission from (*36*).

1.3.2 Mechanisms for Gastric Residence

Technologies that enable extended drug release through the GI tract can help improve delivery of oral therapies (*12*). Observations of patients with bezoars and the use of bariatric balloons for obesity treatment support the ability for the stomach to hold long-lasting medications, also known as GRSs, for weeks or even months without significant adverse effects (*12*, *39–41*). Recently, GRSs for drug delivery have gained immense popularity in the field of oral delivery recently (*42–46*). Several of these have been developed by the Traverso and Langer labs with applications ranging from treating malaria to preventing HIV to veterinary health (*47–52*).

Design of such a GRS platform is constrained by the stomach's anatomy and physiology. The stomach is a J-shaped, hollow, and elastic organ located in the upper left-hand portion of the abdomen, just below the diaphragm (*53*, *54*). Its main function is to store food temporarily, begin digestion, and release the resulting chyme into the small intestine (*43*). The stomach has three anatomical parts: 1) the fundus, which is the proximal part, 2) the body, which is a reservoir for undigested material, and 3) the pylorus, which acts a pump for gastric emptying by propelling actions **(Figure 1.11)** (*53*). The stomach is capable of dilating to accommodate more than a 1-L meal without a significant increase in luminal pressure (*54*). After a typical meal, an average-sized human stomach is about 10 cm wide at its widest point, and its greater curvature is about 30 cm long (*55*). The stomach is always in a state of continuous motility with gastric emptying

characterized by a cycle of electromechanical activity known as the interdigestive migrating myoelectric complex (*43*). Factors affecting the gastric emptying and, hence the gastric retention time of oral dosage forms include (*43*, *44*):

- density, size, and shape of the dosage form
- concomitant ingestion of food and its nature, caloric content, and frequency of intake
- simultaneous administration of drugs acting as anticholinergic agents, opiates, and prokinetic agents
- biological factors, such as gender, posture, age, sleep, body mass index, physical activity and disease states

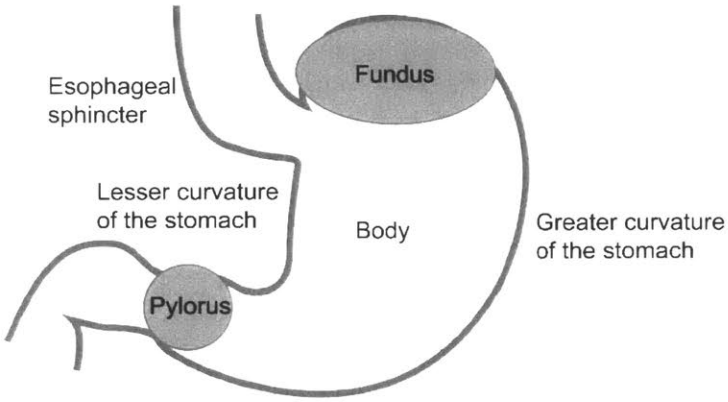


Figure 1.11: Anatomy of the stomach.
The stomach is composed of 1) the fundus at the proximal end connected to the esophagus, 2) the body as a reservoir for food, and 3) the pylorus to pump out food to the small intestine. Adapted with permission from (*53*).

The pH gradients within the stomach can vary by at least a pH unit **(Figure 1.12)** (*36*). The volume of the stomach swells by relaxation of the fundus to accommodate a meal and food layers without significant mixing if the viscosity is high enough. The resting volume is very low – around 50–100 mL but intake of food causes it to relax to accommodate between 1 and 1.5 L. The maximum volumes recorded are around 4 L in man. Researchers have also studied forces associated with GI motility and contractility using Hall array sensor technology on a magnetic pill (*56*). These forces are important to understand as they inform the design of mechanical structures for GRS platforms.

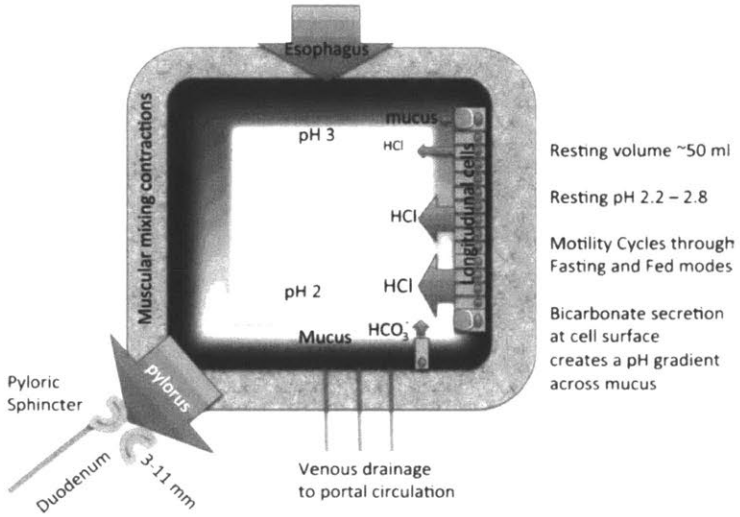


Figure 1.12: Features of the stomach.
The stomach between the esophagus and duodenum varies with respect to pH reflective of the amount of bicarbonate secretion across the mucus. Motility cycles through fasting and fed modes, creating ranges of contraction forces. Reproduced with permission from (*36*).

Over the last few decades, several GRS approaches have been designed or developed including the following: high density systems retained in the bottom of the stomach, low density systems that float in gastric fluid, mucoadhesive systems that cause bioadhesion to the stomach mucosa, unfoldable or swellable systems which withstand transit through the pylorus based on their size, superporous hydrogel systems, and magnetic systems (*44*, *57*, *58*). The Traverso and Langer labs have focused on achieving prolonged retention in the stomach using systems that expand to greater than 2 cm in the stomach health (*12*, *47–52*). This expansion avoids passage through the pylorus, which can be as large as 1.3 cm in diameter (*59*). Size-increasing systems potentially present the hazard of permanent retention and obstruction of the pylorus (*43*). Consequently, these systems should consist of biodegradable materials or lose integrity after a desired time period. A major advantage of size-increasing systems is the independence of their performance on the filling state of the stomach (*43*).

One of the gastric resident vehicles that has been successful in large animal models and now in humans is a star-shaped dosage form, which is being translated by Lyndra Therapeutics

Inc. **(Figure 1.13)** (*48*, *49*, *51*, *60*, *61*). An oral, ultra-long acting capsule can be swallowed and deployed as a star-shaped dosage form when reaching the stomach. The geometry of the dosage form prevents passage through the pylorus, while allowing passage of food, enabling prolonged gastric residence. To allow tunable and safe dissolution of the macrostructure, pH-dependent linkers can be triggered so they system can dissociate into small pieces through the intestine. Clinical, radiographic, and endoscopic evaluation of the star-shaped dosage forms in a swine large animal model showed safety and 2-week long drug release.

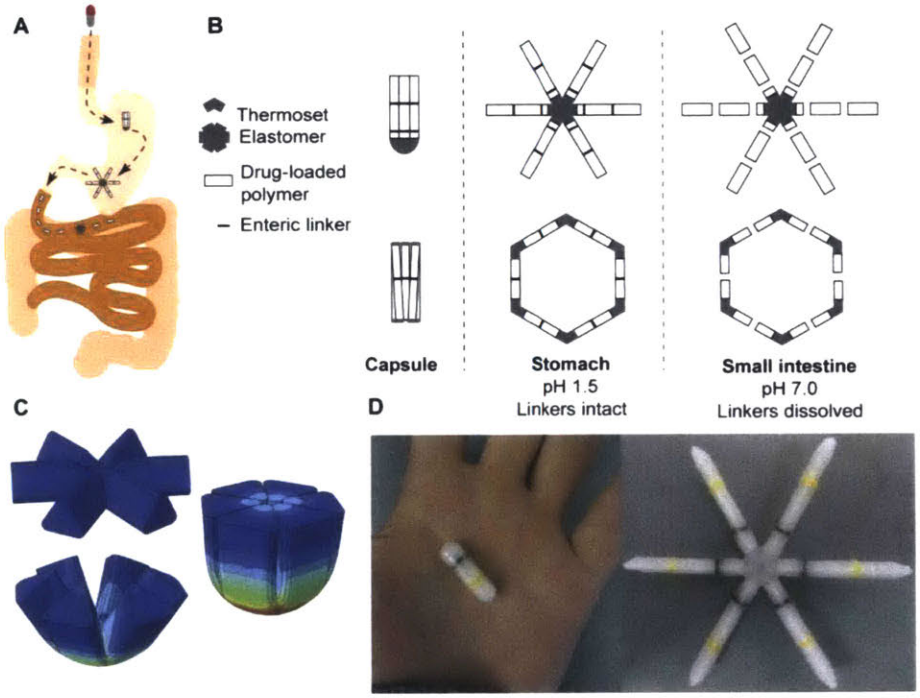


Figure 1.13: Design of a star-shaped gastric resident dosage form.
(A) The ingestible capsule is swallowed and deploys into a star-shaped dosage form, which can then be triggered to dissociate into smaller pieces to pass through the intestines. **(B)** Two geometric arrangements of flexible and rigid arrangements can fit inside a capsule with pH-dependent linkers. **(C)** Stress distribution of the central flexible component when it is folded into a capsule as determined by finite element modeling. **(D)** Representative dosage form after assembly and loading into a "00el" gelatin capsule. Linkers are yellow and black. Reproduced with permission from (*48*).

1.4 Tuberculosis: A Striking Example of Medication Nonadherence

1.4.1 Historical Background

TB, caused by *Mycobacterium tuberculosis* (MTB), has plagued humankind throughout known history and prehistory and has killed more people than any other microbial pathogen **(Figure 1.14)** (*62–65*). Skeletal abnormalities of TB have been found in Egyptian mummies and documented more than 5000 years ago (*62*). Around 400 BCE, Hippocrates wrote about the clinical symptoms of TB in *Epidemics* (*66*). Finally, in 1882, German physician and microbiologist Robert Koch discovered that MTB causes TB. In 1905, he was awarded the Nobel Prize in Physiology or Medicine.

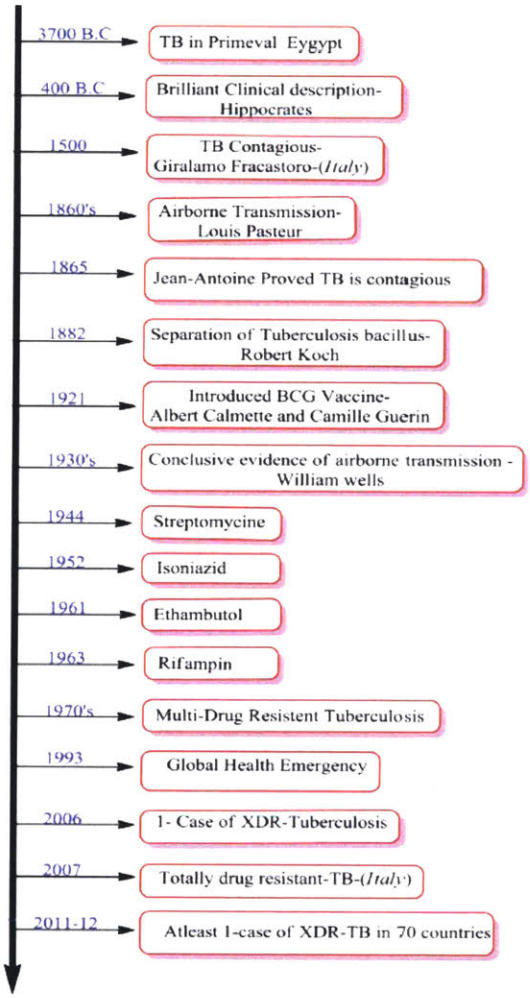


Figure 1.14: History of tuberculosis (TB).
TB has plagued humankind since 3700 BC and continues to be a global health emergency. Reproduced with permission from (*63*).

1.4.2 Pathophysiology

TB is generally caused by inhalation of droplet nuclei containing MTB that enter the respiratory tract and infect the alveoli of the lungs **(Figure 1.15)** (*67–69*). During the first stage, alveolar macrophages (AMs) recognize, engulf, and attempt to destroy the bacilli. The second stage of symbiosis occurs when the bacilli grow logarithmically within infected AMs that are unable to stop the bacilli from growing. Eventually, the infected areas transform into a granuloma, a hallmark of TB characterized by a wall of macrophages and other inflammatory cells and severe chest pain. This third stage of the disease results in a solid caseous center, where the bacteria can survive for years. Most humans infected with TB do not exhibit progression of the disease, as it remains in a latent state and cannot be transmitted to others. It is estimated that 1.7 billion people, or 23% of the world's population, have latent TB (*70*). However, some infected individuals progress to the fourth and final stage of the disease, where the caseous center liquefies and cavitates to fill the lungs with free-floating bacteria, causing pulmonary TB. These bacteria can disseminate to more distant tissues and organs via the lymphatic system or bloodstream to result in extra-pulmonary TB. The cycle is complete when a person who is sick with TB coughs, sneezes, speaks, or sings to release highly transmissible infectious droplet nuclei into the air for a susceptible individual to inhale.

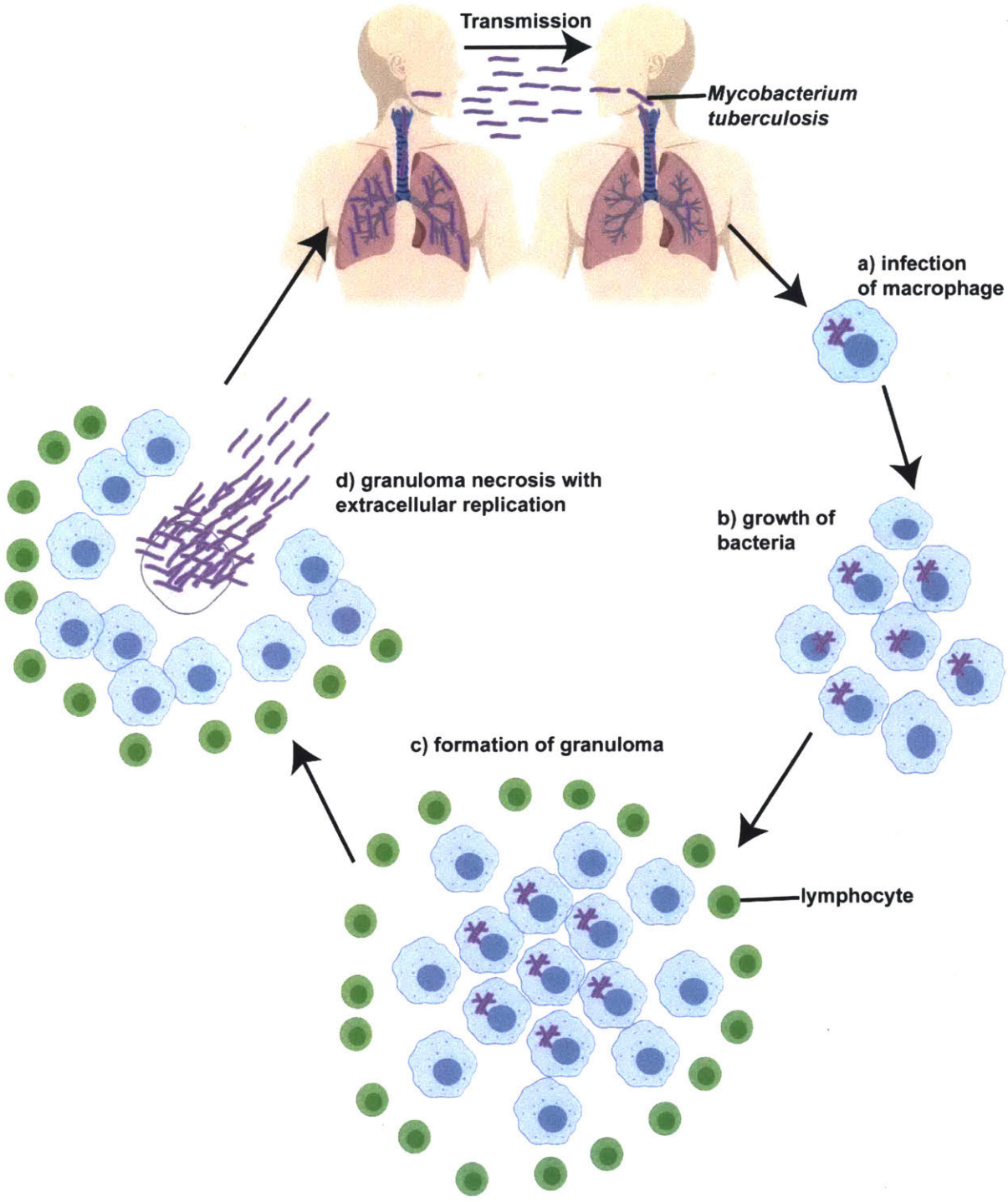


Figure 1.15: Pathogenesis of TB.
TB infection begins with phagocytosis of MTB by AMs followed by formation of a granuloma, as the immune system attempts to fight the disease (*69*).

1.4.3 Global Burden

TB, which claims the lives of over 3,500 people every day, is the world's leading killer among infectious diseases (*71*). According to the WHO, 10 million people developed TB in 2017 with a global economic burden amounting to $12 billion annually (*71*, *72*). The burden of TB is concentrated in Asian and African countries, while only 6% of global cases are in the WHO European Region and WHO Region of the Americas **(Figure 1.16A)** (*71*, *73*). Furthermore, TB is the most significant pathogen in the global antimicrobial resistance (AMR) crisis (*74*). Unless radical action is taken, drug resistant strains of TB will account for 25% of the AMR-related deaths and cost the global economy $16.7 trillion by the year 2050 (*74*, *75*). Currently, drug-susceptible TB strains comprise most cases, but as MTB evolves resistance to current antibiotics, drug-resistant cases are predicted to rise **(Figure 1.16B)** (*73*, *76*). Temporal trends of mortality show that although the overall number of deaths is declining, the gap between deaths in high socio-demographic index (SDI) countries and low SDI countries remains significant **(Figure 1.16C)** (*73*). Unfortunately, clinical trials for TB are also lagging compared to conditions such as cancer and cardiovascular diseases **(Figure 1.17)** (*77*). Hence, there is an urgent need to identify practical and impactful strategies that enable better diagnosis and treatment of TB.

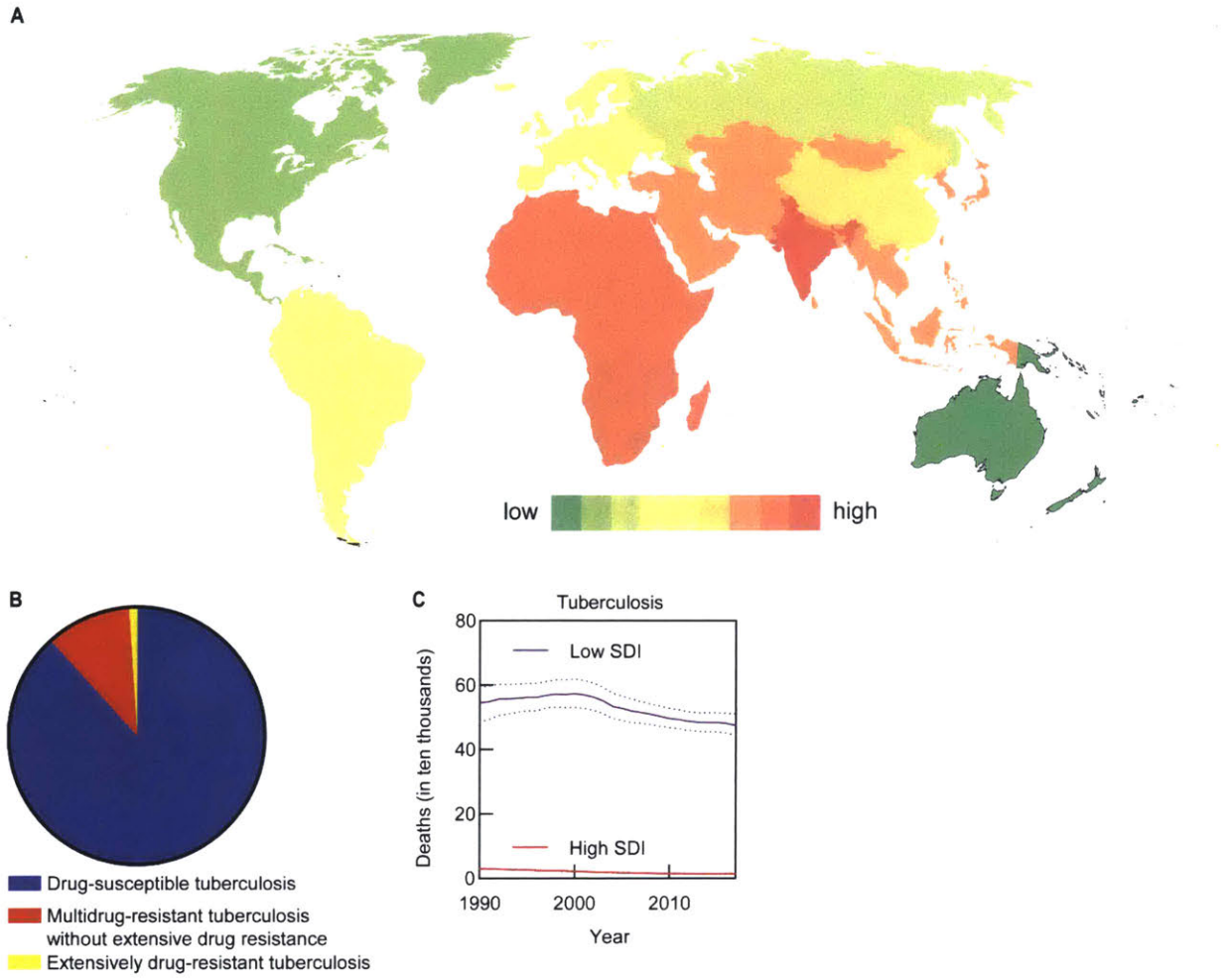


Figure 1.16: Global burden of TB.
A) Deaths of tuberculosis on global map. **(B)** Distribution of TB deaths by susceptible and drug-resistant cases. **(C)** Trend of TB deaths from 1990-2017 in low and high SDI countries (*73*).

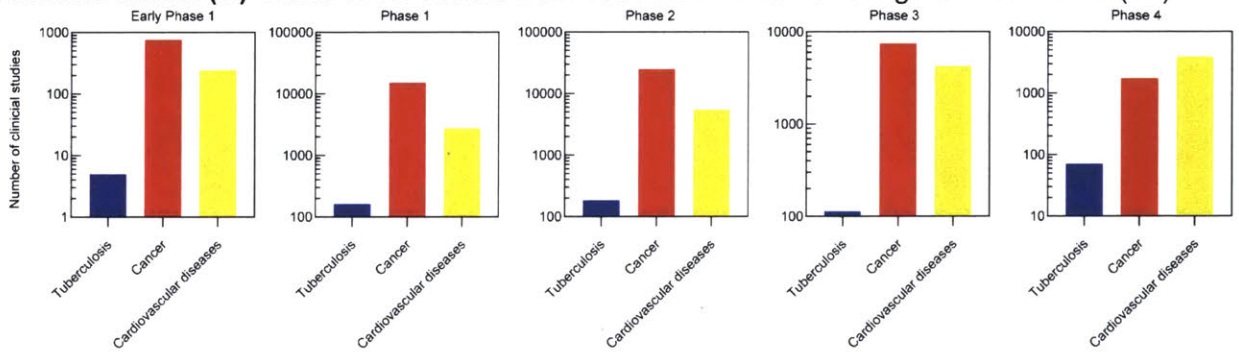


Figure 1.17: Clinical trials for TB, cardiovascular diseases, and cancer.
Number of clinical trials in early Phase 1, Phase 1, Phase 2, Phase 3, and Phase 4 (*77*).

1.4.4 Diagnosis

With timely diagnosis and adherence to the prescribed course of treatment, most TB is treatable and curable (*78*). Sputum smear microscopy, in which bacteria from sputum samples

are examined under a microscope, is the most common method for diagnosing TB worldwide (*79*). However, this test can miss almost half of all people with infectious TB. Currently, TB culture laboratories in resource-poor countries often lack adequate infrastructure and have inadequate or outdated equipment and poor biosafety measures due to a scarcity of human and financial resources (*80*). Developments in TB diagnostics in the last few years have resulted in more sensitive and rapid molecular tests, but most of these cannot be routinely implemented at the point of treatment. If effective treatment is not given, the death rate of TB is extremely high. During the pre-chemotherapy era, 70% of people with sputum smear-positive TB died within 10 years (*81*).

1.4.5 Current Treatment

The goals of antibiotic chemotherapy are to ensure cure without relapse, impede transmission, and to prevent the emergence of drug resistance (*82*). Treatment of TB started in 1946 with the introduction of streptomycin (*83*). During the following two decades, a rapid succession of anti-TB drugs appeared. This was important because resistant mutants to streptomycin were emerging, indicating that monotherapy was not effective against TB (*83*). Rather, a combination of drugs was necessary for maximizing success of treating TB. Following streptomycin, p-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962), and rifampicin (1963) were introduced as anti-TB agents (*83*).

Current WHO guidelines recommend a minimum of 6 months of treatment for drug-susceptible TB with two phases: 1) intensive phase of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months and 2) continuation phase of isoniazid and rifampicin for 4 months **(Table 1.3)** (*84*). TB is one such disease with a high pill burden, where poor patient adherence to the treatment regimen is a major cause of treatment failure and contributes to the emergence of drug-resistant TB strains (*1*). For example, an average 60-kg patient with TB needs to take 3.3 g of antibiotics per day, which is a dose that exceeds the largest swallowable capsule and current depot systems (*30*, *84–86*).

Table 1.3: Recommended WHO treatment regimen for patients infected with TB. Adapted from (*84*).

	Daily		3 times per week	
Drug	**Dose and range (mg/kg body weight)**	**Maximum (mg)**	**Dose and range (mg/kg body weight)**	**Maximum (mg)**
Isoniazid	5 (4-6)	300	10 (8-12)	900
Rifampicin	10 (8-12)	600	10 (8-12)	600
Pyrazinamide	25 (20-30)	-	35 (30-40)	-
Ethambutol	15 (15-20)	-	30 (25-35)	-
Streptomycin	15 (12-18)	-	15 (12-18)	1000

There are multiple factors that influence adherence among people living with TB (*87*). These include a provider-focused system of care delivery, high pill burden, transport difficulties, and other competing daily priorities. In 1994, the WHO endorsed the directly observed treatment short course (DOTS) strategy, which is now accepted worldwide (*88*). DOTS involves administration of oral fixed-dose combination formulations of TB drugs at a designated clinic in the presence of a health care provider either daily or three times per week (*84*, *89*). Although some studies have shown DOTS to be effective, it requires substantial infrastructure with adequately staffed health care personnel to achieve desired results (*87*, *90–96*). Furthermore, a recent study found that patients who fully adhered to a dosing regimen 7 of 7 days per week had more favorable outcomes compared to patients who were fully adherent to a dosing regimen 6 of 7 days per week (*97*). Full adherence may not be easily achieved in resource-constrained environments, where DOTS is costly to provide and time consuming for both patients and caregivers (*98*, *99*).

The WHO End TB strategy has patient-centered care as a central pillar, and achieving such care requires innovative methods of treatment support and drug delivery (*100–102*). Shorter and simplified regimens, electronic reminder systems, and incentive programs are being implemented to improve adherence (*103–105*). Yet, additional interventions will be necessary to eliminate TB. Technologies that enable extended drug release of medication have the potential to overcome patient nonadherence to long and frequent dosing regimens. Long-acting

formulations are being implemented to reduce the frequency of HIV treatment administration, though they require injections, which can be uncomfortable for patients (*106*). Instead, a long-acting oral dosage would be very attractive and improve adherence to treatment, as the oral route of drug delivery is preferred by patients. Novel ingestible gastric resident systems for extended controlled drug release are being developed by several groups (including the Langer and Traverso laboratories) for antimalarials and antiretrovirals (*48*, *49*).

The challenge with designing drug depot systems for TB treatment is to balance the ease and safety of administration with the accommodation of gram-level quantities of TB drugs, which have low potency. One potential area of development which could aid in improved delivery include inhaled or orally delivered nanocarriers which have been designed for extended release of existing TB drugs, although they have yet to be tested in large animal models (*107*, *108*). Considering that bedaquiline is the first new approved TB drug in more than 40 years and the dearth of others in the TB drug development pipeline to overcome challenges of the current drugs, nanotechnology can provide an enormous impact with design of novel and targeted delivery systems for existing drugs (*109*). Ideally, these nanomaterial-based systems would be inexpensive, easy to administer, minimize side effects, and reduce the required dosing frequency to improve patient adherence.

Developments in depot systems and more potent drugs can also improve treatment of children, who comprised 1 million (10%) of the new TB cases in 2017 (*70*). Children face challenges in adhering to their treatments due to the difficulty in swallowing pills, bad taste of crushed tablets, and aversion to needles (*110*). Therefore, it is difficult for caregivers to ensure the child is achieving the correct dosage while minimizing toxic effects. A recent study in Mozambique found that over 30% of children do not adhere to the WHO recommended regimen (*111*). Finally, child-friendly first line TB formulations became available through the Global Drug Facility (*110*). Optimizing second-line drugs for drug resistant TB in children is much further behind, and there are currently few drug depot systems available to simplify treatment and

improve adherence (*112*, *113*). Notably, a pediatric dispersible formulation of delamanid may be promising and is currently being assessed in clinical trials (*114*).

TB treatment adherence challenges contribute to poor health outcomes, prolonged infectiousness, drug resistance, relapse, and death. While most adherence work has focused on changing the behaviors of people taking TB medications, there has been little work done exploring how the medications might be altered to improve the experience of people living with TB. Global health agencies and funding bodies should prioritize patient-friendly interventions that improve adherence by incentivizing more collaborations between clinicians, engineers, and patients (*115*). These include development of technologies to facilitate dose administration with more potent drugs or novel drug depot systems, while addressing the needs of vulnerable populations such as children. Preferences and adoption rates for drug delivery modalities, such as inhalable nanotechnology systems, transdermal patches, liquid formulations, and gastric resident systems vary across patient groups **(Table 1.4)** (*115*). Increased interaction among physicians, engineers, and the TB community stands to facilitate innovative solutions to maximize delivery of medicine to patients and transform the treatment of infectious diseases.

Table 1.4: Advantages and disadvantages of different routes of administration for drug delivery formulations relevant to infectious diseases
Reproduced with permission from (*115*).

Route of administration		Site of absorption	Examples of drug delivery formulations	Advantages	Disadvantages
Enteral	Oral (per os)	Along GI tract	Ingestible gastric resident systems for antimalarials and antiretrovirals (*48*, *49*)	1. Non-invasive 2. Can be self-administered 3. Preferred by patients	1. Non-adherence due to frequent dosing for high pill burden of TB treatment 2. Chemical environment is harsh 3. Degraded by first pass-metabolism
			Solid lipid nanoparticles of TB treatment (*107*)		
			Pediatric dispersible tablets for Coartem and		

			delamanid (*114*, *116*)		
	Sublingual or Buccal	Surfaces in the mouth	Metered sublingual spray of artemether (ArTiMist) for children (*117*)	1. Non-invasive 2. Can be self-administered 3. Rapid absorption 4. Avoids first-pass metabolism	1. Low surface area for absorption, which limits dose and may not be in line with gram-level dosing of TB treatment 2. Bitter taste of drugs 3. Prone to irritation of oral mucosa
	Rectal	Rectal mucosa	Rectal artesunate suppositories for the pre-referral management of severe malaria (*118*)	1. Useful for unconscious patients and children 2. No need to taste-mask drug 3. Partial avoidance of first-pass metabolism	1. Absorption can be slow or erratic 2. Frequent application to match gram-level dosing of TB treatment 3. Prone to irritation of rectal mucosa
Parental	Intravenous	Veins, systemic bioavailable	Artemisinin nanoformulation (*119*)	1. Achieves 100% bioavailability 2. Reproducible	1. Invasive 2. Requires trained personnel 3. Prone to infection 4. Frequent injections to match gram-level dosing of TB treatment
	Intramuscular	skeletal muscle	Nanoparticles of rilpivirine and cabotegravir for HIV treatment (*120*)	1. Rapid absorption 2. Avoids first-pass metabolism	1. Invasive 2. Limited volume for injection, so may not match gram-level dosing of TB treatment 3. Risk of nerve damage
			Atovaquone solid drug nanoparticles for malaria prophylaxis (*121*)		
	Subcutaneous	Into tissue between	Ultra-long-acting dolutegravir	1. Slow absorption	1. Invasive

		dermis and muscle	implant for HIV treatment and prevention (*122*) Nanochannel implant with refillable feature for delivery of tenofovir diphosphate (*123*)	and distribution compared to intramuscular 2. Avoids first-pass metabolism	2. Limited volume for injection, so may not match gram-level dosing of TB treatment 3. Risk of tissue damage
	Intradermal	Into dermis layer	Intradermal injections of HIV DNA vaccines using needle-free injector (*124*)	1. Faster absorption and distribution compared to subcutaneous 2. Avoids first-pass metabolism 3. Higher immune responses for vaccinations	1. Invasive 2. Limited volume for injection, so may not match gram-level dosing of TB treatment 3. Risk of tissue damage
	Intrathecal	Into cerebrospinal fluid	Intrathecal administration of isoniazid for TB meningitis treatment (*125*)	1. Bypass es blood-brain barrier 2. Local effect on meninges or cerebrospinal axis	1. Invasive 2. Limited volume for injection, so may not match gram-level dosing of TB treatment 3. Risk of tissue damage
	Intra-articular	Into joint space	Intra-articular streptomycin in tuberculosis of the knee (*126*)	1. Avoids first-pass metabolism 2. Local effect on joint	1. Invasive 2. Limited volume for injection, so may not match gram-level dosing of TB treatment 3. Risk of tissue damage
	Inhalation	Mucosal surfaces for the lung	Nebulized solid lipid nanoparticles for TB treatment (*108*)	1. Non-invasive 2. Large surface area for absorption	1. Variability in dosing depends on patient technique

			Nano microparticle vaccine formulation for TB (*127*)	3. Avoids first-pass metabolism 4. Targets where TB bacteria reside	2. Requires portable, cheap, and easy to operate devices for administration 3. Frequent inhalation to be compatible with gram-level dosing of TB treatment
	Transdermal	Through skin	Film of HIV inhibitor IQP-0410 (*128*)	1. Non-invasive 2. Can be self-administered 3. Avoids first-pass metabolism	1. Transport barriers for many drugs 2. Slow absorption 3. May require frequent administration or very large patch to match gram-level dosing of TB
			Solid dispersions of artemisinin for malaria treatment (*129*)		
	Topical: Ocular, Nasal, Skin	At site of application	Topical treatment of cutaneous TB using oil nano-emulsions (*130*)	1. Non-invasive 2. Can be self-administered 3. Rapid absorption 4. Local effect, so avoids side effects	1. Transport barriers for many drugs 2. May require frequent administration to match gram-level dosing of TB
	Intravaginal	Mucosal surfaces lining the vagina	Monthly vaginal rings for dapivirine, an HIV drug (*131*)	1. Reduce frequency of dosing 2. Avoids first-pass metabolism 3. Dense network of blood vessels in vagina, so ideal for systemic drug absorption	1. Invasive 2. Requires trained personnel 3. Implants may require frequent dosing to match gram-level dosing of TB treatment

1.5 Thesis Overview

The remainder of this thesis is devoted to a proposed solution to tackle medication adherence for disease such as TB: development and application of the first GRS compatible with transesophageal administration and multigram dosing (*132*). Chapter 2 illuminates the design of the GRS platform with evaluation of safe administration, retention, and retrieval performed both *in vitro* and *in vivo*. Chapter 3 then presents *in vitro* and *in vivo* studies of various approaches to deliver medication from the GRS. Chapter 4 tests end-user assessment and economic benefit of the GRS with another application for treatment of hepatitis C. Finally, this thesis concludes in Chapter 5 with a summary of the findings presented in Chapters 2-4 and proposed potential future directions of research.

Chapter 2: Design of a Gastric Resident System for Multigram Dosing

2.1 Introduction

The challenge with designing drug depot systems for diseases such as TB is to balance the ease and safety of administration with the accommodation of multigram-level quantities of drugs (*115*). Inspired by the recognized capacity of the stomach to hold large objects including bariatric balloons and bezoars, we reasoned that a GRS capable of prolonged gram-level dosing could help patients adhere to TB treatment (*12*, *39*, *40*). Drug delivery via the GI tract offers multiple advantages, including ease of administration, immunotolerance to a broad range of materials, and the ability to accommodate gram-level dosing in line with current regimens for TB. Here, we describe a proof-of-concept study demonstrating the capacity of a device to be administered through the nasogastric (NG) route, to safely reside in the gastric cavity of a large mammal, and to be retrieved via an NG tube.

2.2 Materials and Methods

2.2.1 Manufacturing of the Gastric Resident System Prototypes

The assembled GRS consists of a superelastic nitinol wire as the retention frame upon which drug pills are strung with a retainer and tubing at the ends of the device. Nitinol wire (Fort Wayne Metals), with diameter of 0.59 mm and phase transformation at 37°C, was wrapped around a custom fixture and secured in place using steel screws. The nitinol-fixture assembly was placed in a furnace at 500 °C for 15 minutes and then quenched in water at room temperature for 20 minutes (*133*, *134*). Fixtures made of aluminum for different shapes have been considered: pretzel, toroid, cone, star, and cylindrical **(Figure 2.1)**. The nitinol was unwrapped from the fixture, ready for pills to be added.

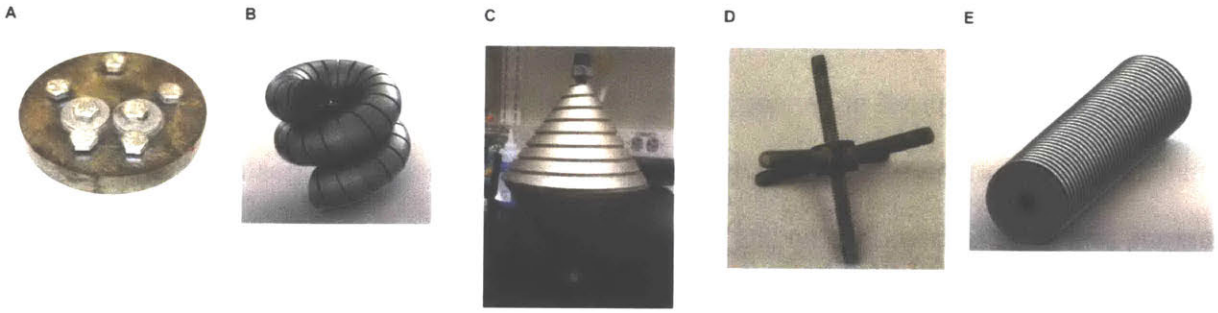


Figure 2.1: Custom fixtures for setting shape of nitinol.
(A) Pretzel. **(B)** Toroid with open ends. **(C)** Sphericon. **(D)** Star. **(E)** Cylindrical.

For devices without pills, the nitinol wire was strung through Tygon® tubing (Inner Diameter X Outer Diameter: 4.76 x 6.35 mm), obtained from McMaster-Carr, with ends crimped using a pair of pliers. The ends were then filled with Med3-4213 silicone adhesive (NuSil), followed by a 6.35 mm stainless steel ball bearing (McMaster-Carr). More silicone adhesive was used to seal the free ends of the tubes at both ends of the device. For device with pills, each end of the nitinol wire was crimped using a pair of pliers. Poly(Ɛ-caprolactone) (PCL) molecular weight 37,000 (Sigma-Aldrich Corporation) pellets were then pressed into two 3- inch (76.2 mm) long pieces of Tygon® tubing (Inner Diameter X Outer Diameter: 4.76 x 6.35 mm). The end of each tube was then filled with Med3- 4213 silicone adhesive, followed by a 6.35 mm stainless steel ball bearing.

Once completely packed with the pellets, the tubes were heated at 100 °C to melt the PCL using a heat gun. Each crimped end of the nitinol was then slowly inserted into the molten PCL and set into place as the PCL cooled at room temperature to solidify around the nitinol wire. More silicone adhesive was used to seal the free ends of the tubes at both ends of the device.

Multi-lumen tubing was designed in SolidWorks (Dassault Systèmes) and then extruded in tetrafluoroethylene hexafluoropropylene vinylidene fluoride (THV) by Zeus Industrial Products, Inc. Single-lumen THV tubing (Inner Diameter X Outer Diameter: 3.97 x 6.35 mm) was obtained from McMaster-Carr and wrapped around a cylindrical fixture at 110°C for 25 minutes and then quenched in water at room temperature for 20 minutes. The retainer and silicone adhesive were applied at each end of the coiled THV tubing.

2.2.2 *In Vitro* Characterization of Administration Forces

The assay involves a three-dimensional (3D) printed fixture to guide the bending of a 200 mm long Tygon® tube (Inner Diameter X Outer Diameter: 6.35 mm x 9.53 mm) from McMaster-Carr, in order to represent the curvature along the entrance of the device into the esophagus from the nasal passage (*135–137*). The fixture is secured to the base of the Instron 5943 (Instron), allowing for the stability of the structure during the insertion of the device **(Figure 2.2)**. A 2-56 screw was secured within a 3D printed part at one end of the device, replacing the steel ball and Nusil. The device was pulled through the fixture by inserting the screw through a tapped 3D printed part. A crimped Nitinol wire was inserted through a hole in this 3D printed part and was clamped within the pneumatic grips of the Instron. A method was generated in the Instron software, Bluehill, to raise the load cell and consequently the device at a rate of 10, 20, or 30 mm/s. Data analysis involved finding the maximum force load after the 3D printed part and screw assembly exited the Tygon® tube, which occurred at an extension of 200 mm.

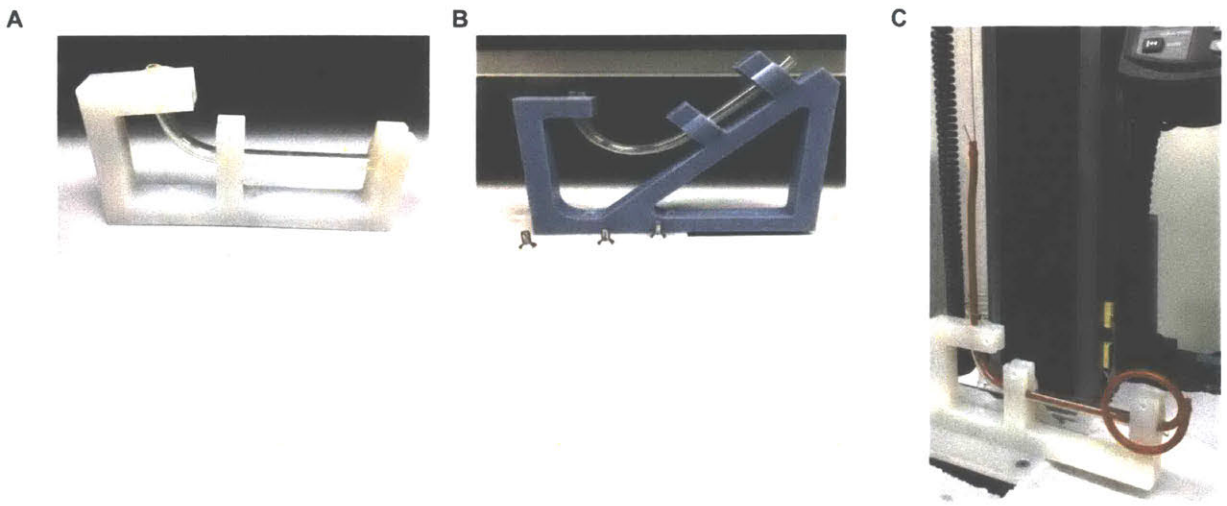


Figure 2.2: Fixtures to measure force of administration.
(A) 3D printed 90° fixture to simulate the bending angle of the neck. **(B)** 3D printed 45° fixture to simulate the bending angle of the neck. **(C)** Coiled drug-loaded GRS pulled through a 3D printed 90° fixture with measurement of forces by Instron.

2.2.3 *In Vivo* Evaluation of Gastric Retention

All animal experiments were performed in accordance with protocols approved by the Committee on Animal Care at the Massachusetts Institute of Technology and as previously described (*47–50*). The GRSs were administered to a large animal model (30-75 kg Yorkshire pigs). This model was chosen because of its similar gastric anatomy to humans and wide use in evaluating devices in the GI tract (*138*, *139*). Animals were fed daily in the morning and in the evening with a diet consisting of pellets (Laboratory mini-pig grower diet, 5081), in addition to a midday snack consisting of various fruits and vegetables. The pellets consisted of ground oats, alfalfa meal, wheat middlings, soybean meal, dried beet pulp, salts, and other micronutrients. Prior to administering the GRS, the pigs were sedated with Telazol® (5 mg/kg intramuscular), xylazine (2 mg/kg intramuscular), and atropine (0.04 mg/kg intramuscular), intubated, and maintained with isoflurane (1 to 3% inhaled). The GRSs were deployed in the stomach via an endoscopic guided overtube (Inner Diameter X Outer Diameter: 16.7 x 19.5 mm) from US Endoscopy. The overtube was removed once the devices were administered. For evaluation of the safety and residence time of the GRSs, the animals were clinically assessed twice a day for

evidence of GI obstruction including inappetence, abdominal distension, lack of stool, and vomiting. Additionally, the animals were evaluated radiographically every day 3-4 days for evidence of GI obstruction and/or perforation. Tissue samples were collected before and after the device was placed in the stomach, fixed in formalin, and then stained using hematoxylin and eosin for histopathological analysis (*140*, *141*). Macroscopic images were taken once the device was retrieved to study any possible mucosal damage.

2.2.4 Manufacturing of Retrieval Systems

The retrieval device was constructed using three 4.76 mm diameter x 4.76 mm length cylindrical neodymium magnets with pull force of 10.14 Newtons (K&J Magnetics, Inc.) and an Allegro A1324 linear Hall effect sensor (Modern Device), all housed in a 1-meter long Tygon® tube (Inner Diameter X Outer Diameter: 4.76 x 6.35 mm). The sensor and magnets were placed on one end of the Tygon® tube, with the sensing face of the sensor bent at a 45-degree angle relative to the magnets. Each pin of the sensor was soldered to a 26-gauge, solid electrical wire (Adafruit Industries LLC) and covered in heat shrink tubing to avoid shorting the sensor. A thin layer of Med3-4213 silicone adhesive was applied at the tip of the outermost magnet to give the magnets a slight downward offset from the top surface of the tubing and keep the magnets of the retrieval device slightly separated from the magnet of the drug delivery device upon connection. An Arduino Pro Mini 328 (SparkFun Electronics) received the output of the Hall effect sensor and sent a text output to a serial-enabled liquid crystal display (SparkFun Electronics). When the magnets of the retrieval device connected with the magnet of the GRS, defined by a Hall effect sensor output that exceeded a given voltage threshold for at least one minute, the liquid crystal display showed the message "The magnets are connected." A 3.7 V lithium ion battery (SparkFun Electronics) powered the microcontroller circuit. The stability of the Allegro A1324 Hall effect sensor was tested in air first and then after immersion in simulated gastric fluid, USP without pepsin (pH ~1.2; henceforth referred to as SGF). The sensing area of the insulated sensors was covered with two-part epoxy (Devcon). The insulated sensor was placed in 4 mL of SGF for 90

minutes and then removed. After this period, the sensors and a 4.76 mm x 4.76 mm cylindrical neodymium magnet were fixed in place, with 10 mm separating the sensing face of the sensor and the south pole of the magnet. The sensor voltage output was read and recorded via the Arduino integrated development environment serial monitor to compare with the voltage read prior to immersion in SGF.

2.2.5 *In Vitro* Stomach Model

A 3D model mimicking the human stomach was designed in SolidWorks and created to analyze feasibility of the delivery and retrieval of the GRS **(Figure 2.3)**. The 3D part was split into two halves and then printed on a Stratasys Objet30 3D printer. Polyethylene terephthalate (PETG) sheets from McMaster-Carr with 3.175 mm thickness were formed around the stomach halves using a heat gun. A band saw (Home Depot) was used to trim the excess material away, leaving the PETG half stomach with a 25.4 mm border. The outline of the stomach shape designed on SolidWorks was used to generate a custom gasket for sealing the two halves of the *in vitro* model together. Two of these gaskets were laser cut out of 1.59 mm thick silicone rubber sheets (McMaster-Carr) using a Universal Laser Systems VLS6.60 and then glued onto each of the stomach halves with cyanoacrylate (Krazy Glue). About every 5 cm, clearance holes for M6 bolts (McMaster-Carr) were drilled around the perimeter of both halves. The nasal passage, pharynx, and esophagus were modelled out of a 0.6-meter long PETG tubing (Inner Diameter X Outer Diameter: 9.525 x 12.7 mm) from McMaster-Carr. The tubing was bent with a heat gun to form a 90-degree turn. To interface the tubing into one stomach half, a custom adapter was printed using a Formlabs Form 2 3D printer. The bottom end of the tubing was heated with a heat gun and press fit into the adapter. The upper section of the stomach half was also heated using a heat gun and fitted with the other side of the adapter. The two halves of the stomach were aligned, and 13 M6 bolts were used to secure the halves together and make the stomach model water tight.

Figure 2.3: 3D printed *in vitro* stomach model.

2.2.6 *In Vivo* Evaluation of Retrieval Systems

For *in vivo* evaluation of the retrieval device interaction with the GRS, the animals were sedated, intubated, and maintained with isoflurane as described above. The GRS was first deployed in the stomach via an endoscopic guided overtube, and radiographs confirmed placement of the device in the gastric cavity. The retrieval device was then inserted into the overtube without endoscopic guidance to demonstrate the ability of the Hall effect sensor on the retrieval device to detect the magnet on the GRS. Radiographs were captured of the retrieval device as it entered the gastric cavity, contacted the GRS as indicated on the liquid crystal display board, and successfully retrieved the GRS.

2.3 Results and Discussion

2.3.1 Geometries Compatible with Gastric Retention

A large dose GRS for long-term treatment should (i) have a size and shape that can fit through the esophagus of a patient to non-surgically access the stomach, (ii) have the ability to adopt an alternative conformation in the stomach that prevents passage through the pylorus, (iii) achieve high concentrations of drug loading, (iv) be composed of biocompatible materials that are stable for an extended duration in the acidic gastric environment, (v) have no potential for gastrointestinal obstruction or perforation, and (vi) either be able to degrade into forms that can safely pass or be retrieved after the drug has been released from the device (*48*). Inspired by the rapid deployment of a gastric balloon through similar means, the GRS was designed such that it could be administered through an NG tube, which is inserted via the nose to access the stomach **(Figure 2.4)** (*142*). After reaching the stomach, the GRS forms a coil shape and continually releases grams of drug over the course of weeks, whereupon the device is retrieved back through an NG tube. The assembled GRS consists of a superelastic nitinol wire as the retention frame upon which drug pills are strung with a retainer and tubing at the ends of the device (*133*).

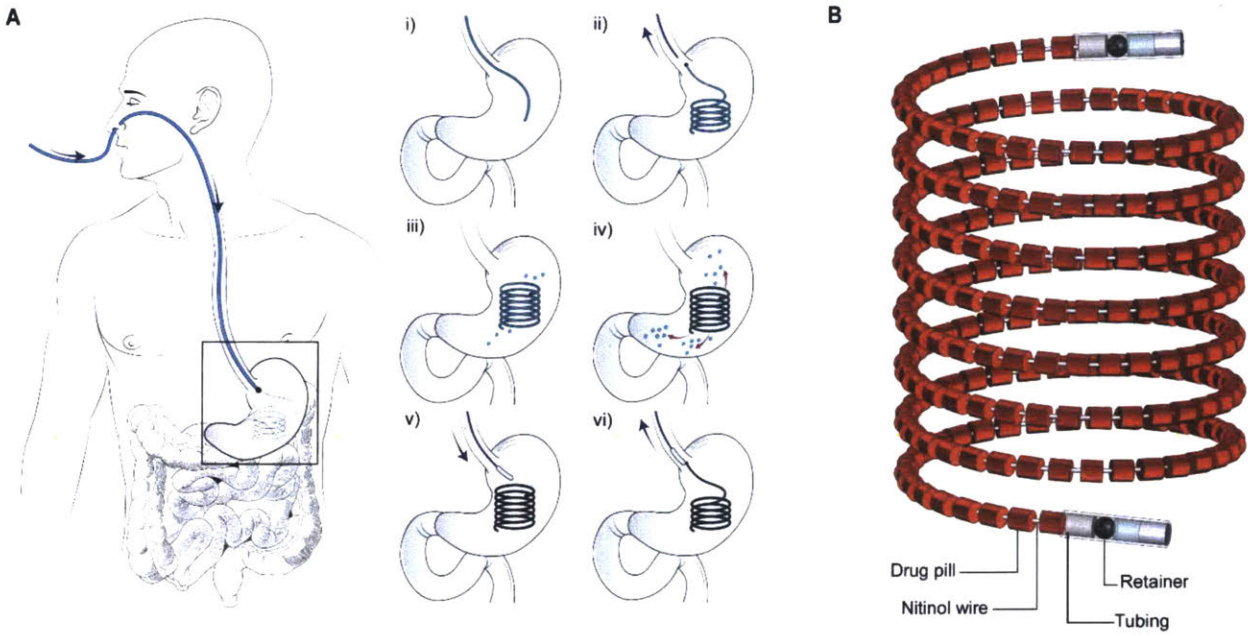


Figure 2.4: Design of gastric resident system (GRS) administered and retrieved through a nasogastric (NG) tube.
(A) (i-ii) An NG tube is first placed as a conduit for the large dose GRS to be non-surgically administered, and then the NG tube is removed from the patient. (iii-iv) The GRS resides in the gastric cavity while releasing drugs. (v-vi) An NG tube is again placed in the patient for deployment of a retrieval device to attach and remove the GRS from the gastric cavity. Black arrows indicate direction of movement of the NG tube and retrieval device, and red arrows indicate drug release. **(B)** The GRS consists of a series of drug pills on a coiled superelastic nitinol wire; the ends are protected with a retainer and tubing.

Several shapes compatible with gastric retention were considered and designed in SolidWorks **(Figure 2.1 and Figure 2.5)**. These include: pretzel, toroid, cone, star, and cylindrical **(Figure 2.1 and Figure 2.5)** For the same length of material, a pretzel would take up the most volume, while the toroid, cone, and star are difficult to manufacture and may entangle in the stomach. The cylindrical-shaped (coil) system was chosen since it has the highest surface area to volume ratio and is the easiest to manufacture out of these designs. Additionally, to tailor the drug loading and duration of therapy, the length of the GRS and formulation of drug pills can be modified **(Figure 2.6)**. The diameter of the tubing through the NG tube is restricted by the largest NG tube available, which is 20 French or 6.67 mm (*143*). Details of the drug pills will be discussed in Chapter 3.

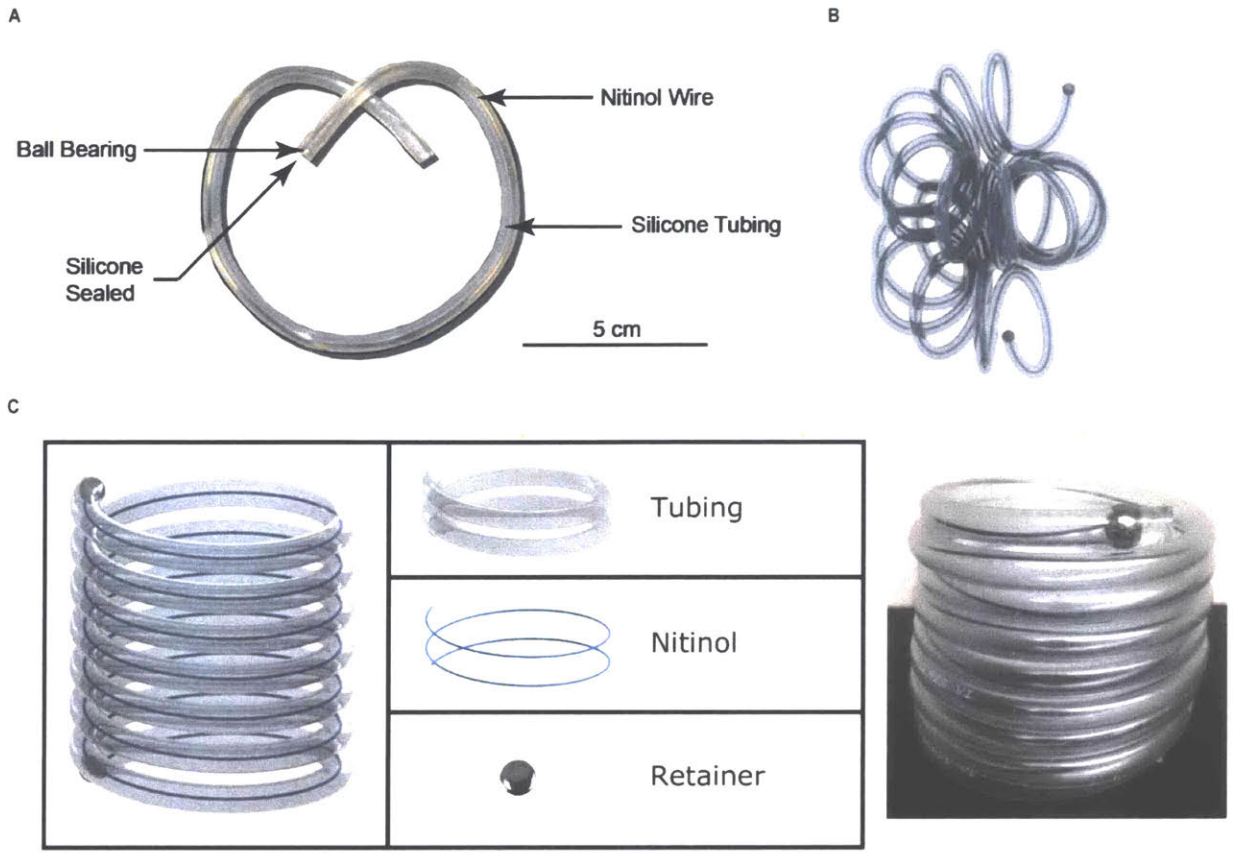


Figure 2.5: Selected shapes for gastric retention.
(A) Pretzel shape. **(B)** Toroid shape. **(C)** Cylindrical or coiled shape with a representative photograph of a device without drug. The GRS contains tubing, nitinol and a retainer.

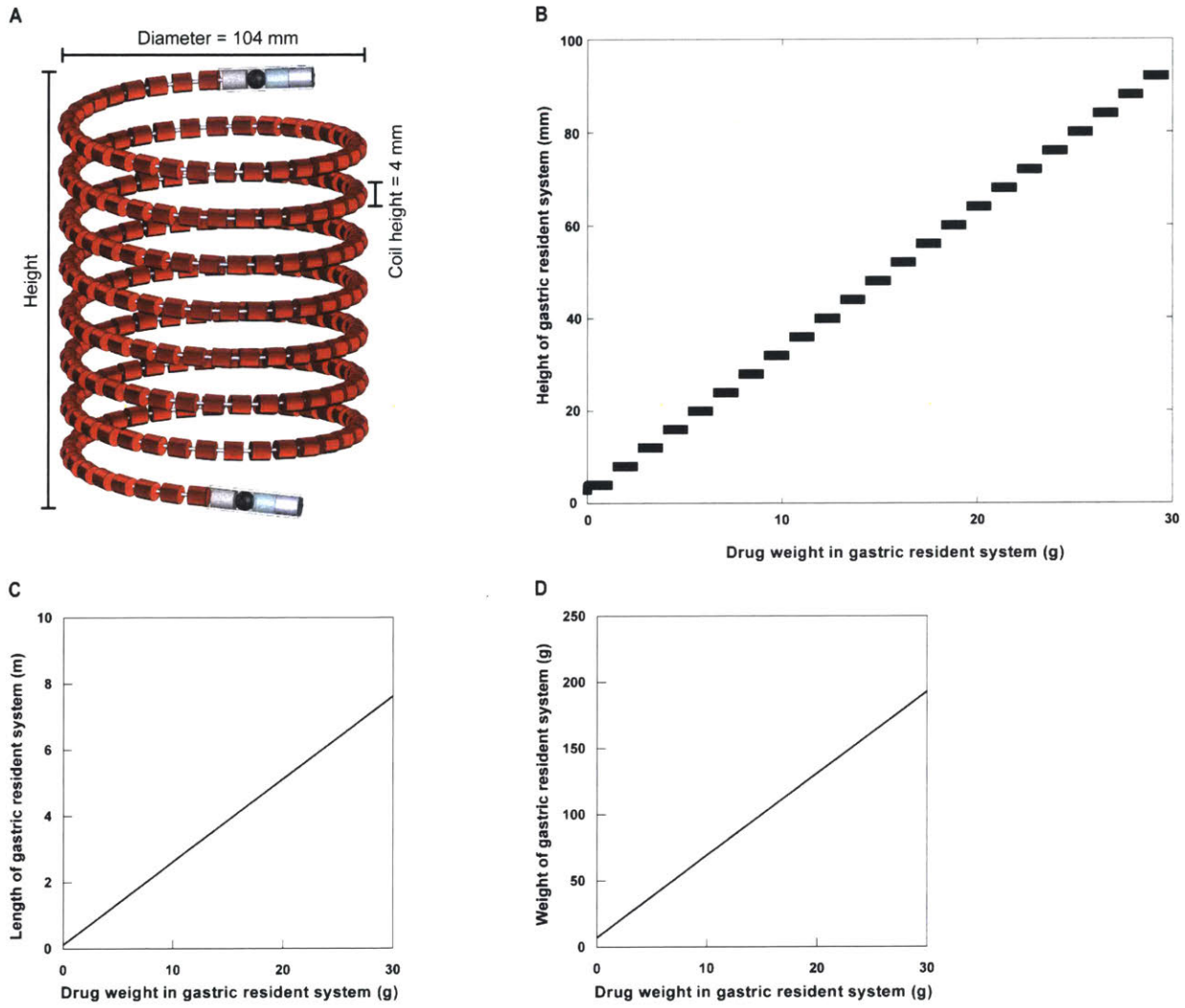


Figure 2.6: Physical parameters of the coiled GRS as drug weight increases.
(A) Diagram of the GRS and plot of height of device versus drug weight. The coil height is fixed at 4 mm due to the size of the measured drug pill height, and the diameter of the overall GRS is kept constant at 104 mm based on the size of the nitinol fixture (n=3). **(B)** The calculated height of the GRS as a function of the drug weight, calculated by the number of pills that can fit on a single coil based on measurements of the pill height and diameter of the GRS. The number of coils is discrete; between a certain range of drug weight, the height of the device will remain the same. **(C)** The calculated overall end-to-end length of the uncoiled GRS according to the drug weight. **(D)** The calculated total GRS weight according to the drug weight, incorporating the weight of the polymer matrix, nitinol wire, and ends of the device.

2.3.2 Assembly of the Gastric Resident System Using Biocompatible Materials

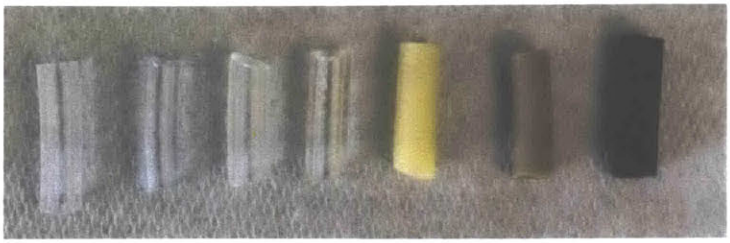
The designs proposed for gastric retention cannot be delivered in their final geometries via the esophagus to the stomach since the esophagus has a maximum diameter of 2 cm. Therefore, shape-memory materials, which are able to "memorize" a permanent shape but can

be manipulated to take on a certain temporary shape, must be employed (*144*, *145*). One such material is nitinol, a nickel-titanium alloy with the ability to show high elastic deformation (*145*, *146*). Nitinol wire can be wrapped around a fixture and set in its final shape. Many studies have exploited the use of nitinol in medical applications. For example, it is widely used for manufacturing surgical devices and implants because of its biocompatibility (*145*, *146*). However, nitinol wire is sharp and can lead to gastrointestinal perforation (*147*). Therefore, it must be protected and housed in the drug loading reservoir – an acid-resistant, elastic, and biocompatible tube.

Various tubings with outer diameter of 6.35 mm (to be compatible with the inner diameter of NG tubes) were selected and purchased from McMaster-Carr. These include different Tygon® formulations, Latex, gum rubber, santoprene, polyethylene, and silicone rubber **(Figure 2.7)**. Based on acid-resistance, ease of placing the nitinol wire, and ability to comply with the coiled nitinol shape, low temperature Tygon® PVC tubing for chemicals (ND 100-65) tubing was chosen (*148*). Importantly, it is made from biocompatible non-di(2-ethylhexyl) phthalate polymer materials. The nitinol can then be strung through the tubing and then sealed with retainers and medical silicone adhesive as inspired by a bladder retentive device (*133*).

Another approach without nitinol is to use heat to create tubing curvature. THV, a flexible material, was identified through a conversation with experts at Zeus Industrial Products, Inc. (*149*). The advantage of not using nitinol is to simplify the process of manufacturing with respect to both time and materials, thereby reducing cost and complexity. THV was successfully able to form a coil curvature **(Figure 2.8A)**. Multi-lumen designs were also made and extruded with THV to achieve separate chambers for loading of different drugs with a lumen for nitinol as well **(Figure 2.8B)** (*150*).

A



B

Figure 2.7: Selection of tubing for the GRS.
(A) Representative photographs of tubing: Tygon® PVC, Tygon®, Latex, Gum rubber, Santoprene, Polyethylene, Silicone rubber. **(B)** Photograph of experiment to measure acid-resistance of tubing in different pH conditions.

A B

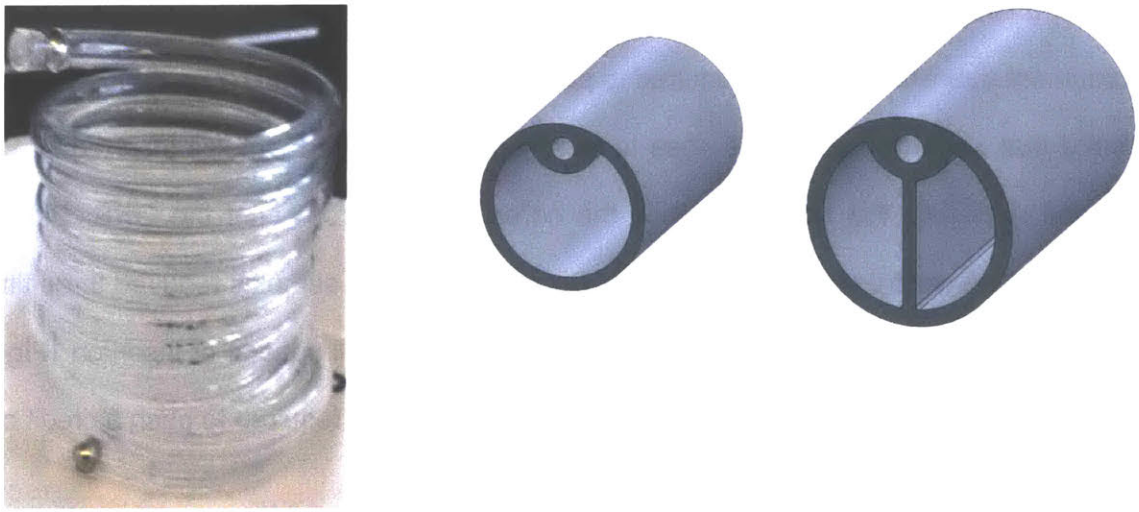


Figure 2.8: THV coil and multilumen tubing.
A) Representative photograph of coiled THV tubing GRS without nitinol. **(B)** Multilumen designs for nitinol and drug compartments.

2.3.3 *In Vitro* Administration of the Gastric Resident System

The GRS will be administered through a NG tube that passes through the nose, down the esophagus, and into the stomach (*135*). The shape-memory and superelasticity properties of nitinol will allow the coiled device to take on a linear shape as it is inserted into the NG tube and then to recoil into its programmed shape following deployment from the esophagus. Misplacement of the NGT during this "blind" procedure as well as applications of excessive force on the NGT can cause serious health complications such as "lung perforations," massive bleeding "due to puncturing of the esophagus," neurological damage, mediastinal complications, and death (*151*). Studies have shown that skilled practitioners "with more than 25 years' experience" had average insertion forces of 4.9N +/- 1.8 N, while those with lower experience had average insertion forces of 8.4 +/- 2.5 N (*152*). These forces were measured by a force gauge that was mounted onto a catheter, simulating an NG tube. Practitioners were told to push the catheter until practitioners "felt a level of resistance that would make them stop" in order to ensure the safety of the patient.

To characterize the force of administering the GRS compared to the force of administering an NG tube, an *in vitro* assay was designed using 3D printed parts and the Instron **(Figure 2.2)**. The experiment quantifies the force required to push a straight tube versus a coiled tube through a 90° bend that would represent the nose to esophagus. The linear samples inserted into the angled bend represent the NG tube, while the coiled samples represent the GRS. Different speeds of insertion were used with a 90° bend. On average, coiled samples required three times as much force to administer compared to the linear samples at all speeds of insertion **(Figure 2.9)**. The force to administer the coiled sample is roughly the force required to push a credit card through an automated teller machine (*153*).

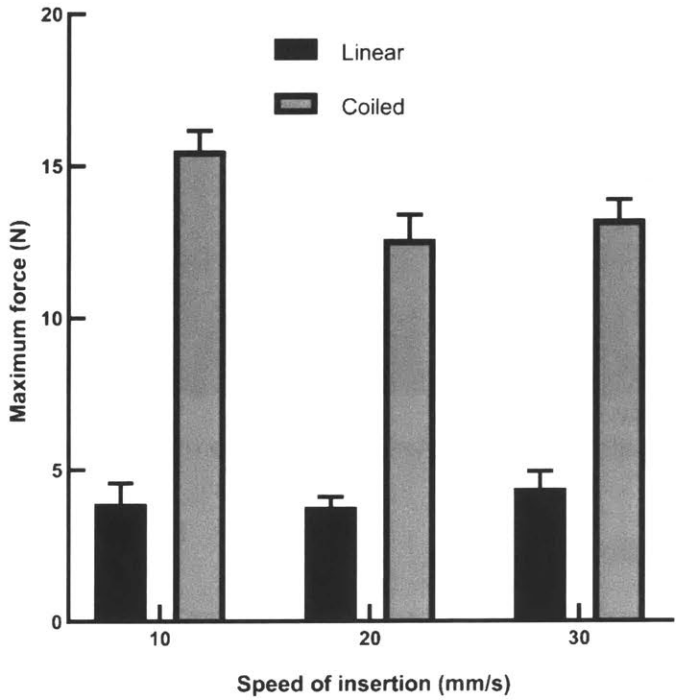


Figure 2.9: Force of administration of linear and coiled samples.
The maximum force during insertion of the linear and coiled samples was measured at three different speeds of insertion. Error bars represent SD for n=3 samples in each group.

2.3.4 *In Vivo* Administration of the Gastric Resident System

A coiled nitinol wire inside tubing was deployed to the gastric cavity of 30- to 75-kg Yorkshire pigs to demonstrate transesophageal administration *in vivo*. Yorkshire pigs have similar gastric anatomy to humans and have been previously used to evaluate long-acting drug delivery platforms (*138*, *139*). Representative serial abdominal radiographs during device deployment and revealed the feasibility of the GRS to pass through the esophagus and form a coil in the stomach within 50 s **(Figure 2.10)**. The GRS was able to curl back into its original coil shape in the gastric cavity after passing through the esophagus because of the superelasticity of nitinol (*154*).

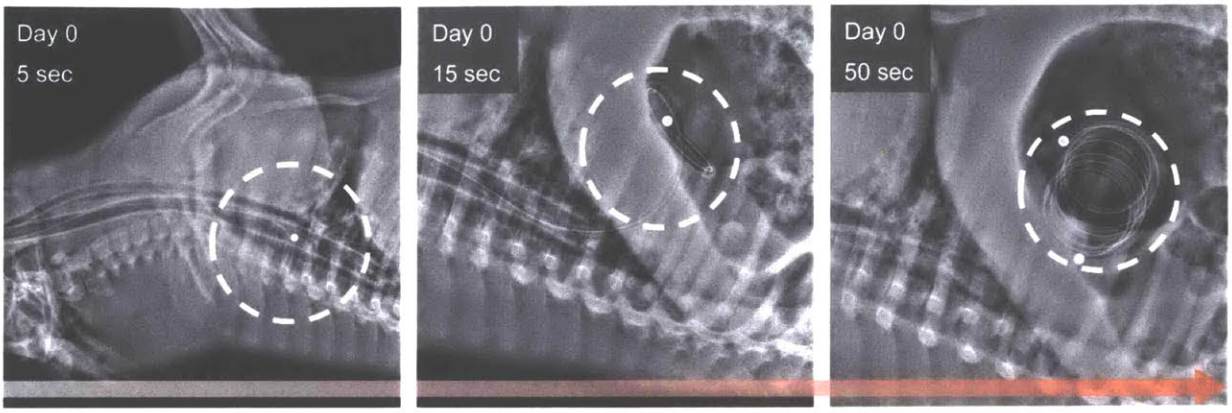


Figure 2.10: Administration of the GRS *in vivo*.
Representative radiographs of the GRS immediately after deployment in a swine model. Dashed circles indicate GRS location.

2.3.5 *In Vivo* Evaluation of Gastric Retention

Safe long-term gastric residence was evaluated by serial radiographs obtained over the course of 1 month and through endoscopic evaluation **(Figure 2.11)**. Even after prolonged gastric residence of these large devices, mucosal surfaces of the animals' stomachs did not show injury, erosions, or ulcerations; in addition, the animals did not show any weight loss, evidence of GI obstruction, or limitation in the passage of food or liquid **(Figure 2.12)**.

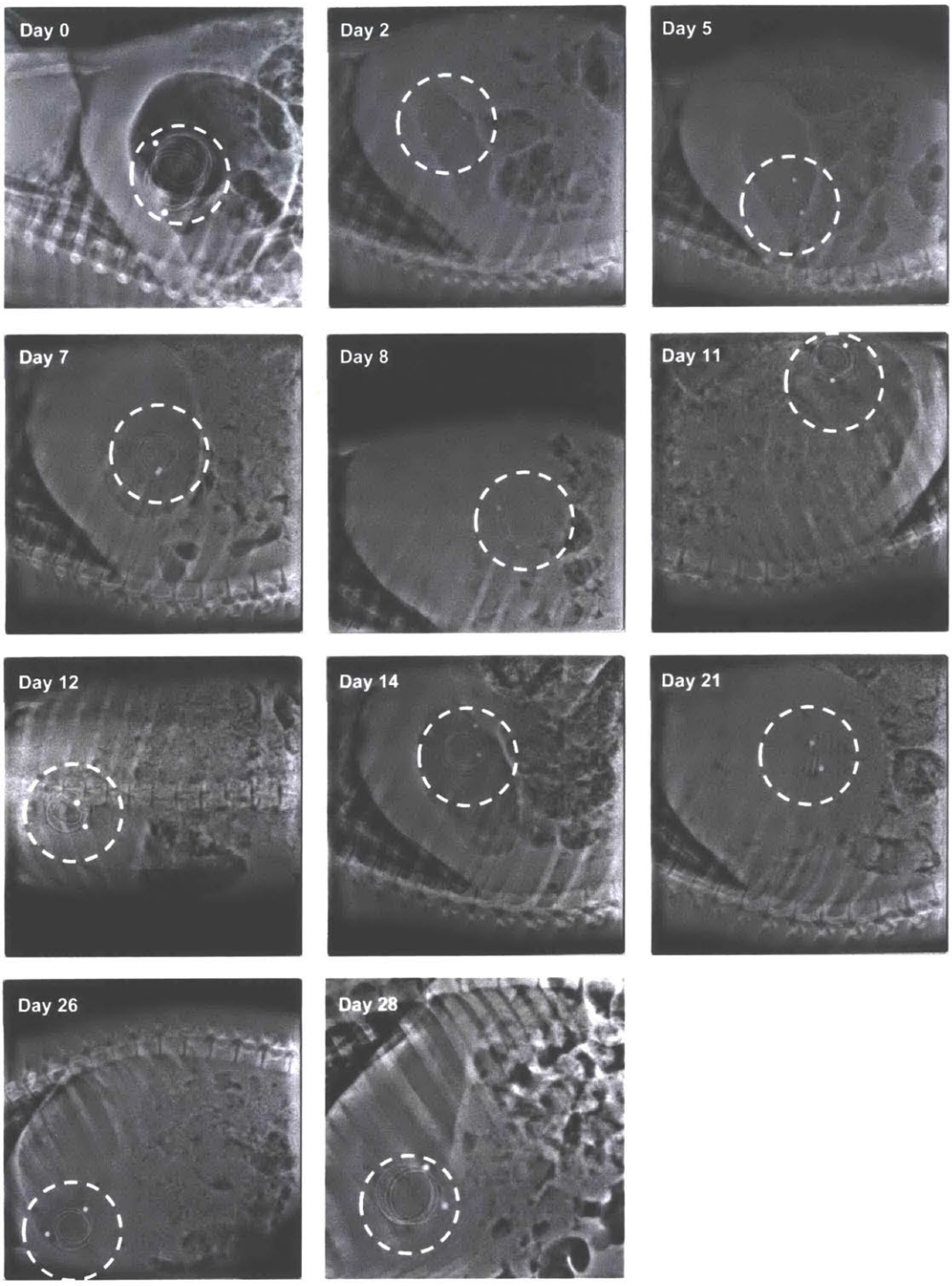


Figure 2.11: Serial radiographs of the GRS over 1 month in a swine model.
Representative radiographs of the gastric cavity were taken every few days over the course of 1 month to monitor for safe long-term gastric residence of the GRS (n=3). The dotted lines encircle the GRS in the gastric cavity of the swine.

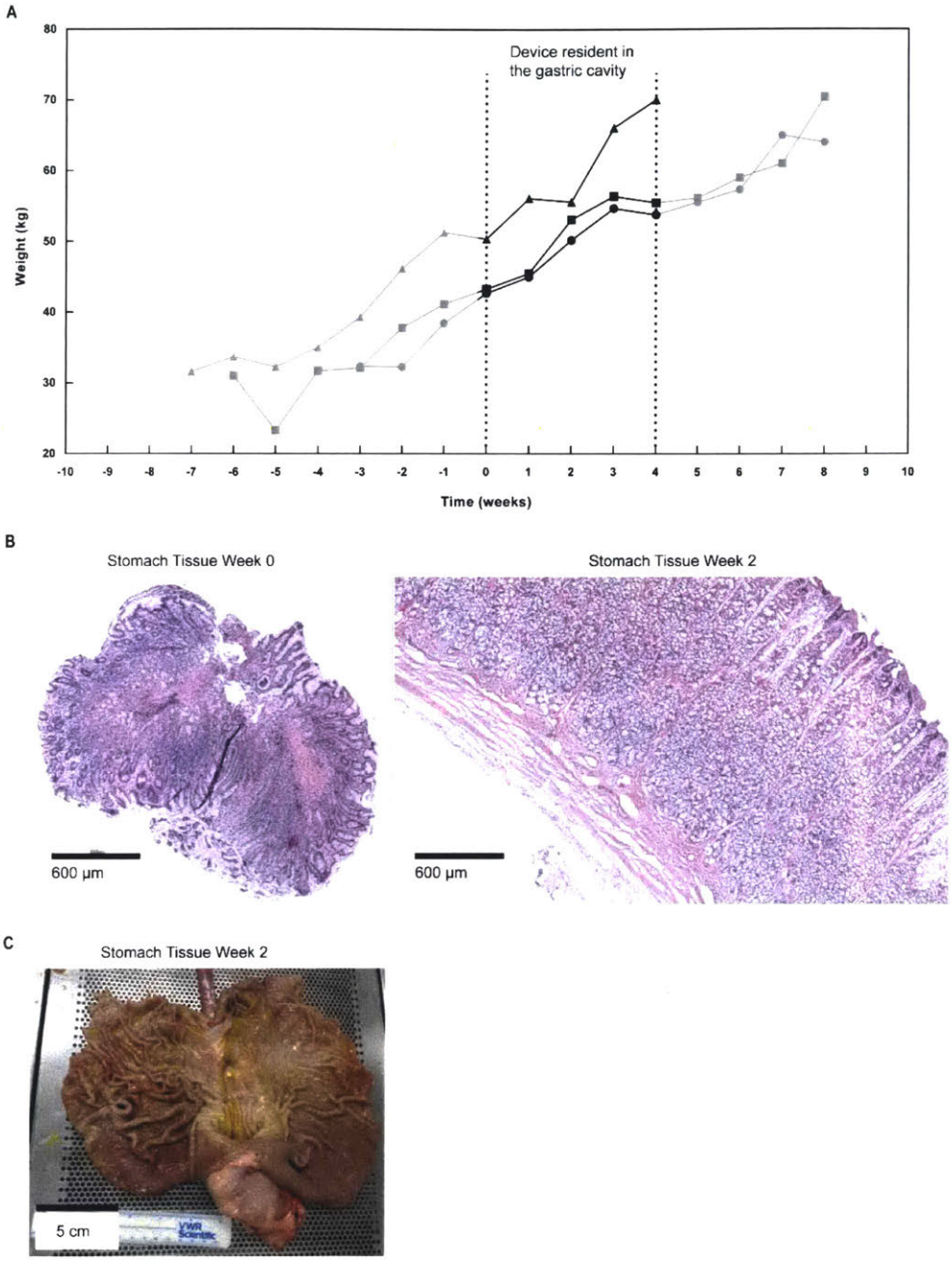


Figure 2.12: Effect of the GRS on the weight and stomach tissue of swine.
(A) The animals' weight was measured every week from when it was brought into the animal facility until when it was euthanized. Week 0 denotes the week that the GRS was administered to the gastric cavity of the animal. At the end of week 4, the GRS was retrieved from the gastric cavity, and the animal is either euthanized immediately or is used for other studies with the weight being measured every week. **(B)** After 2 weeks of gastric residence for the GRS, the stomach mucosa was assessed for any damage. A representative hematoxylin and eosin stain of stomach tissue at week 0 (prior to deployment of the GRS) and at week 2 (when the GRS is retrieved, and the animal is euthanized) is shown (n=3). **(C)** Representative macroscopic image of the stomach tissue at the end of week 2 when a GRS was retrieved from the gastric cavity and the animal is euthanized to assess any damage to the mucosa (n=3).

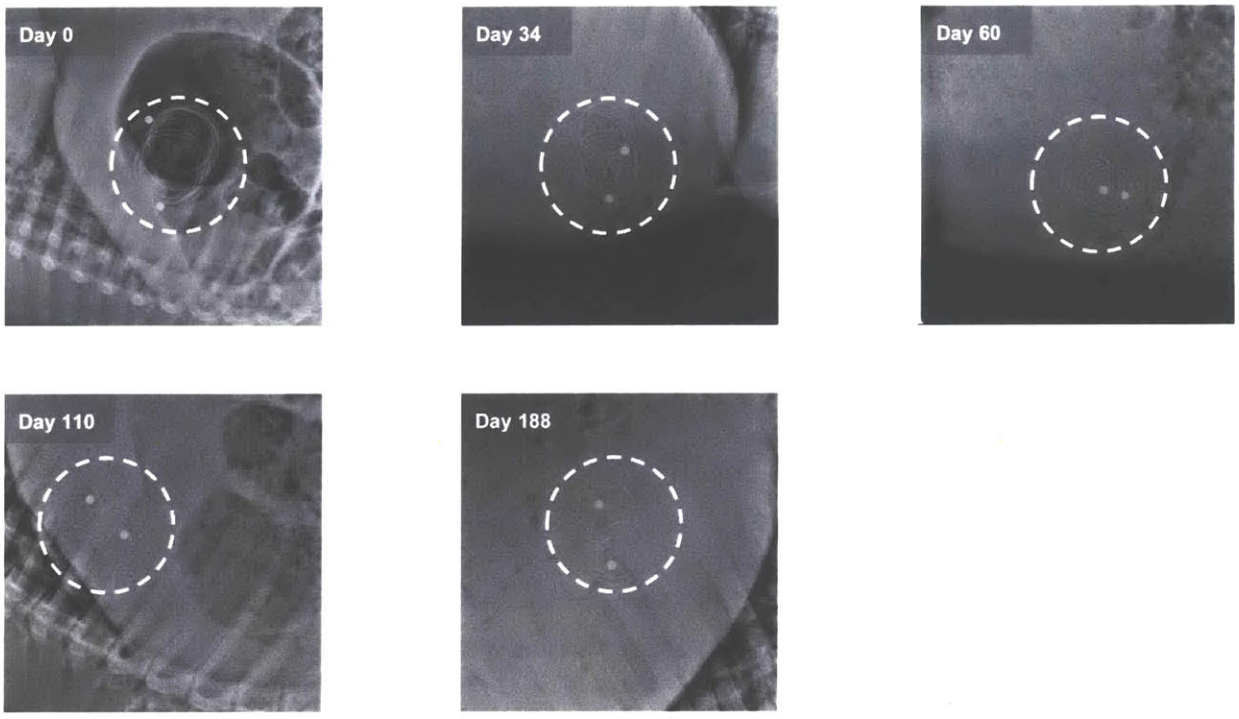


Figure 2.13: Retention of GRS for 6 months in swine.
Radiographs of the gastric cavity were taken every month over the course of 6 months to monitor for safe long-term gastric residence of the GRS (n=1). The dotted lines encircle the GRS in the gastric cavity of the swine.

2.3.6 *In Vitro* Retrieval of the Gastric Resident System

The GRS was designed to be retrieved through an NG tube after the release of the drug payload in the gastric cavity. The retrieval device consists of a Hall effect sensor to determine the distance between a magnet on the end of the GRS and a magnet at the end of retrieval device **(Figure 2.14)** (*155*). To ensure the stability of the Hall effect sensor in a low pH environment, it was placed it in SGF for 90 min; the measured voltage was comparable to the voltage measured in air before immersion in SGF **(Figure 2.15A)**. A 3D printed *in vitro* human stomach model was constructed to test the feasibility of the retrieval procedure **(Figure 2.15B)**. A magnet was placed on each end of the GRS to maximize likelihood of retrieval. Inspired by fish hooks and tools for endoscopy, other designs for retrieval included barbs or snares in addition to the magnet to latch onto the GRS and provide additional mechanical attachment **(Figure 2.16)** (*156–159*).

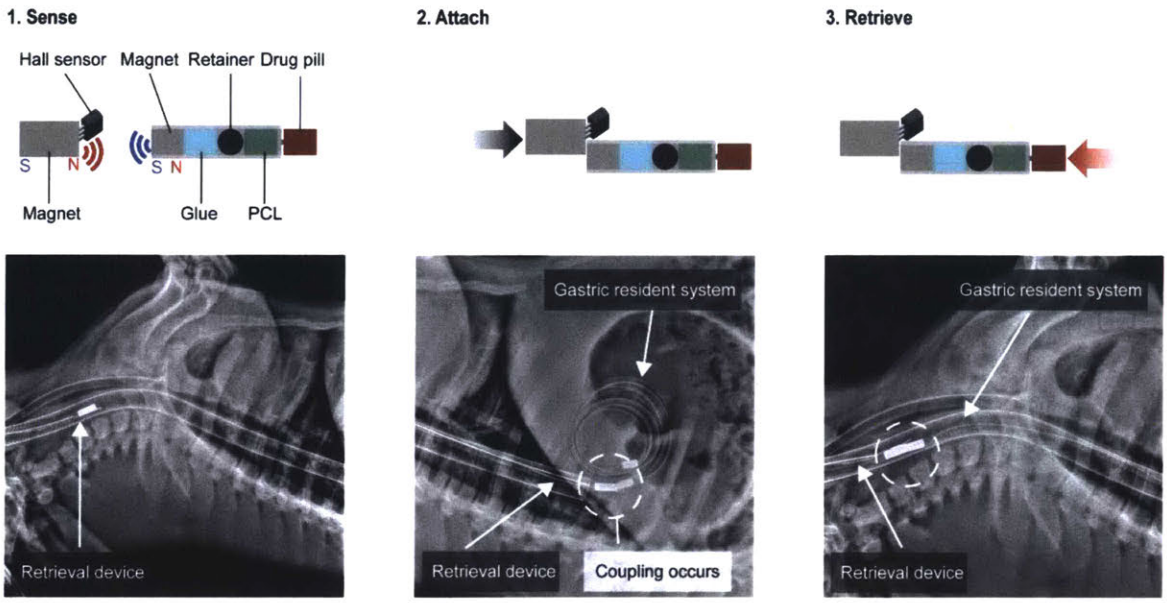


Figure 2.14: *In vitro* and *in vivo* retrieval of the GRS in swine.
The retrieval device consists of a Hall effect sensor and a magnet that can detect and attach to the magnets on either end of the GRS. Representative stepwise radiographs of the retrieval process executed in a swine model are shown below. Dashed circles indicate coupling of retrieval device with GRS. The components of both ends of the GRS [glue, a retainer, and a poly(Ɛ-caprolactone) (PCL) plug] are also shown.

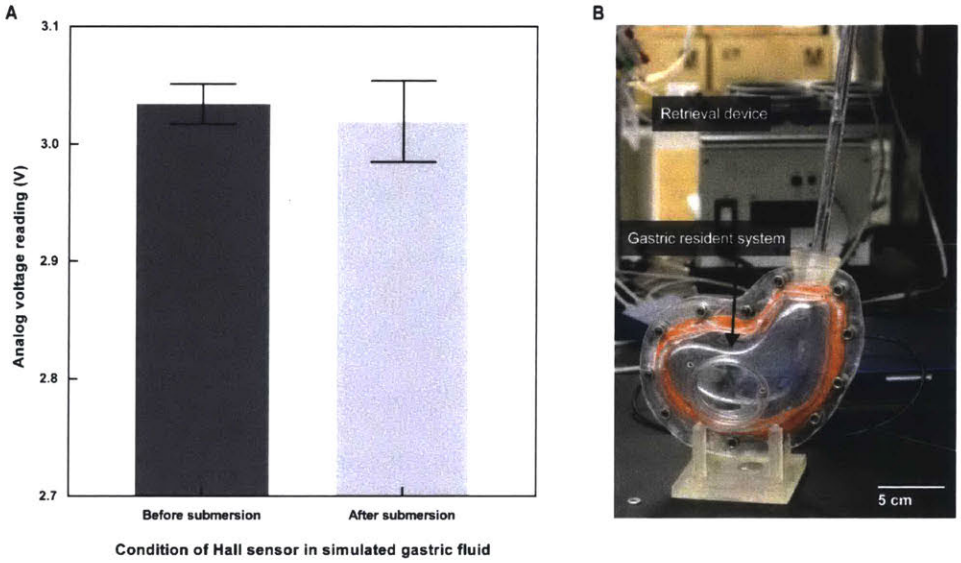


Figure 2.15: Hall effect sensor acid stability and retrieval using an *in vitro* stomach model
(A) Voltage reading of the Hall effect sensor before and after submersion in SGF. Error bars represent the standard deviation for n=3 samples in each group. **(B)** Photograph of a three-dimensional printed stomach model used to test sensing and magnetic attachment of the retrieval device to the GRS.

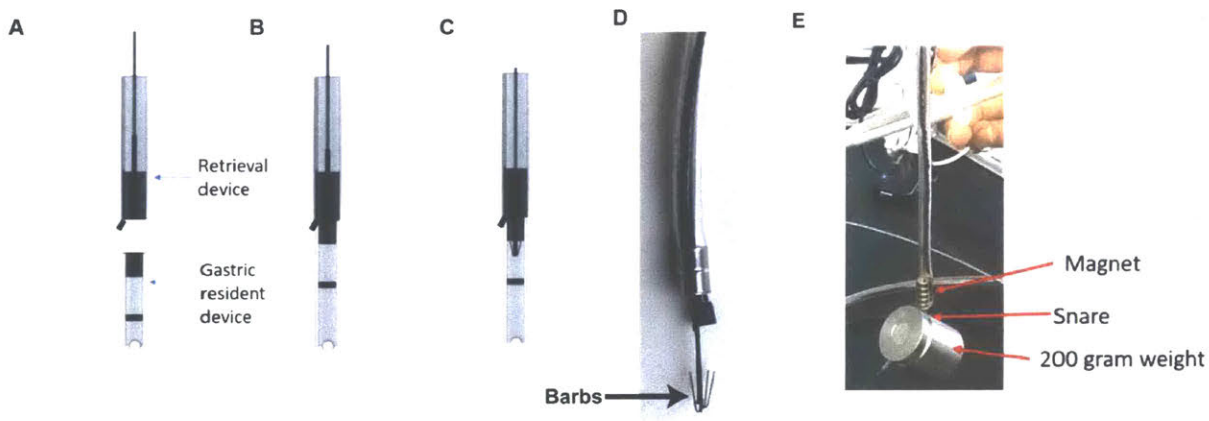


Figure 2.16: Retrieval designs using barbs and a snare.
(A) The retrieval device senses the GRS using a Hall effect sensor. **(B)** The retrieval device and GRS contact using magnets. **(C)** Barbs from the retrieval device can then be actuated to provide firm attachment and grip to the GRS. **(D)** Representative photograph of retrieval device prototype with barbs. **(E)** Representative photograph of retrieval device prototype with snare capable of lifting 200 g weight.

2.3.7 *In Vivo* Retrieval of the Gastric Resident System

In vivo demonstration of GRS retrieval with the magnet system was successful, as demonstrated by representative serial radiographs **(Figure 2.14)**. The retrieval process took roughly 2 minutes to deploy, sense, attach, and retrieve. Further *in vivo* work will need to be conducted with the barb and snare design to ensure that those aspects do not detach from the retrieval systems. Additionally, long-range sensors and testing retrieval on a full stomach will help locate and further test the success of the system in the field.

2.3.8 Ideas for Gastric Residence Without Retrieval Systems

The design described above requires a retrieval system because nitinol is not biodegradable. While the GRS must be retrievable in case of an emergency, it would be ideal if a patient does not have to come back to the clinic just for the retrieval procedure. Several of the GRS systems that have been published can be triggered to degrade or dissolve (*48*, *50*). Although the nitinol could potentially be replaced by a biodegradable shape-memory polymer, this has not been explored yet for a multigram GRS due to potential costs of synthesis and reduction in mechanical performance (*144–146*, *160–165*). Two GRSs were brainstormed to potentially avoid the need for retrieval. One involves magnetic assembly of many swallowable capsules to form a

GRS, which can then be triggered to disassemble using timed absorption of a swellable polymer or gel **(Figure 2.17)** (*166*). The advantage of this approach is it does not need a NG tube. The other involves modular block assembly of a GRS followed by soluble linkers that break up into smaller pieces, as inspired by the star-shaped dosage form **(Figure 2.18)** (*48*).

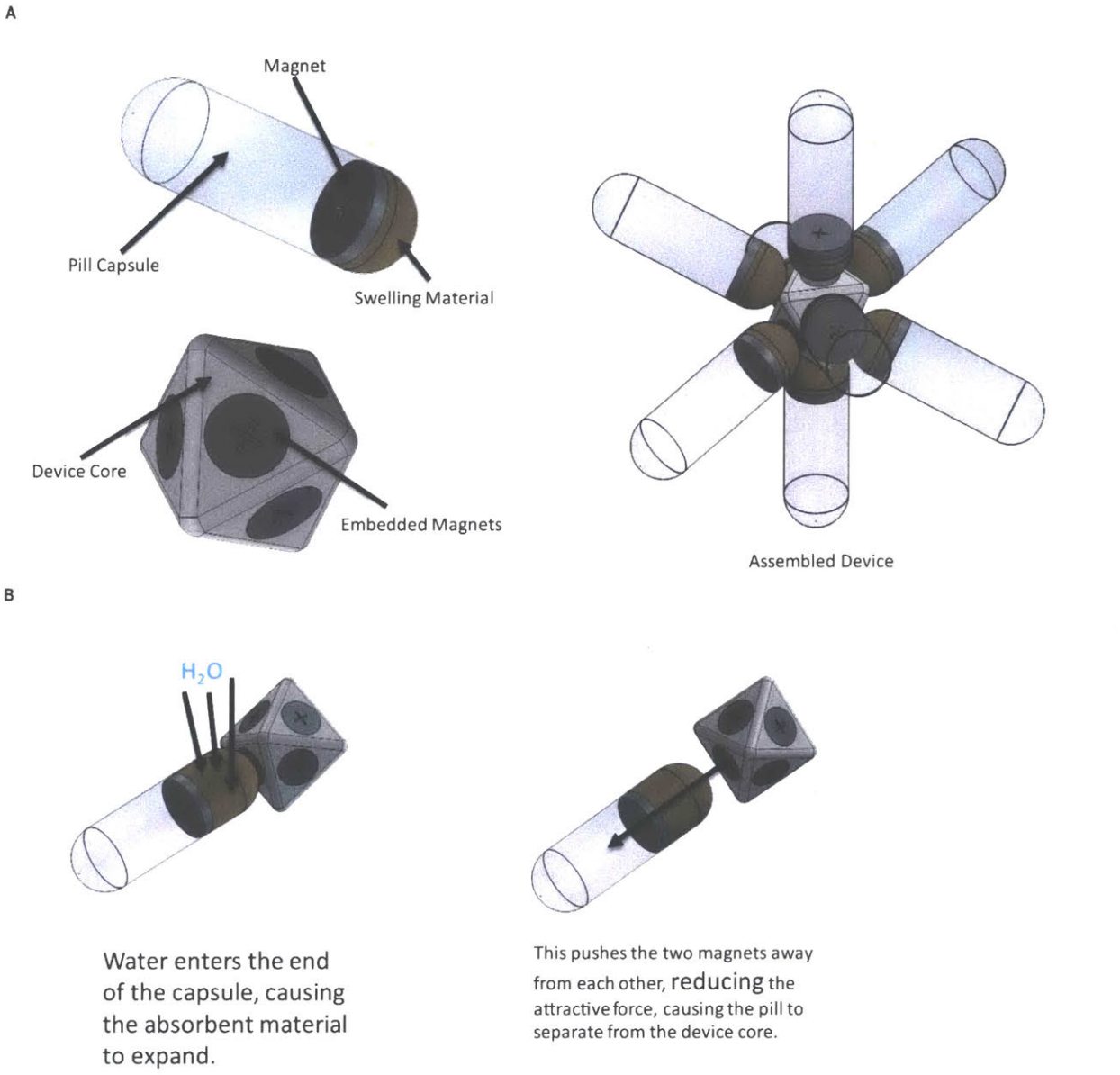


Figure 2.17: Magnetic capsule GRS assembly and disassembly.
(A) A patient would swallow many magnetic capsules that contain a nondegradable capsule shell, a swellable polymer, and a magnet that facilitates attachment to a central magnetic piece to form a macrostructure that can reside in the gastric cavity. **(B)** Timed disassembly of a magnetic GRS can occur through entry of fluid to the capsule, which swells a polymer and causes the magnetic force to decrease as the magnets move apart.

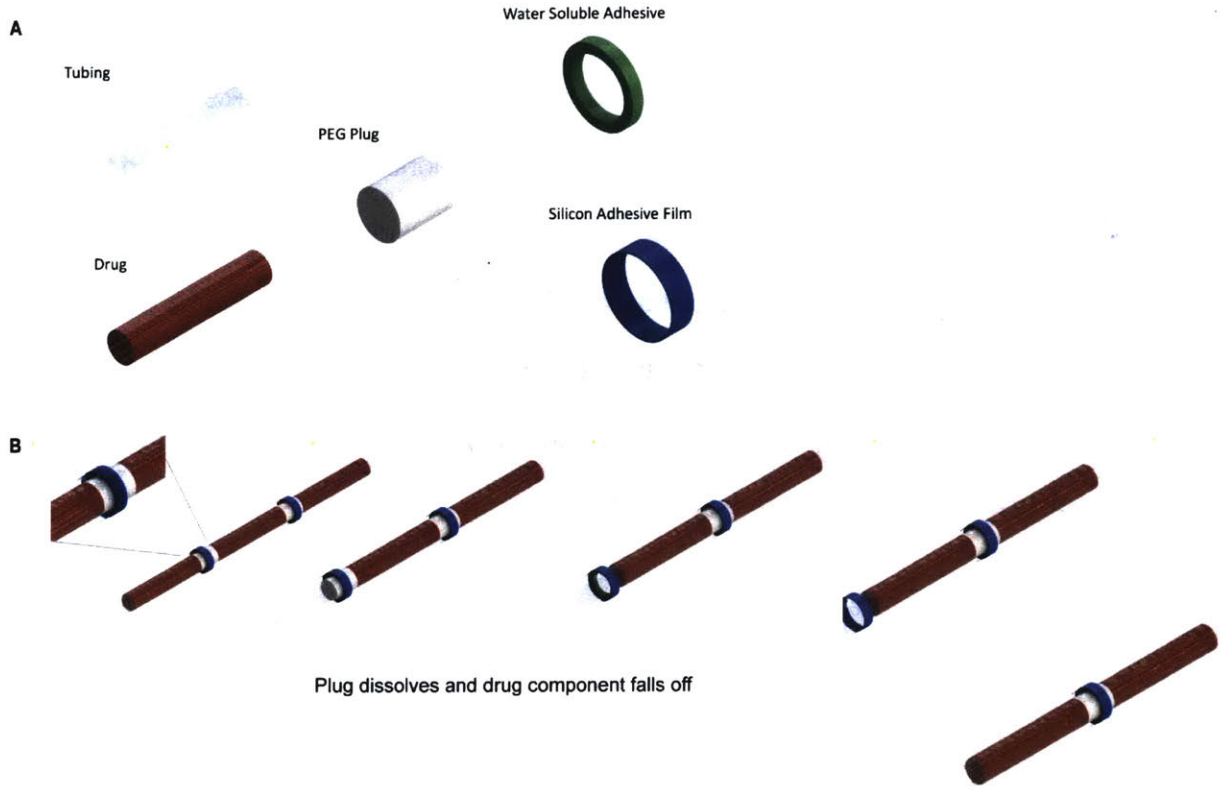


Figure 2.18: Disassembly of unit blocks of the GRS.
(A) Components of the GRS to enable disassembly. **(B)** Biodegradable plug would dissolve over time, causing a unit block to fall off, and then another drug layer can release prior to another unit disassembling.

2.4 Conclusion

The results shown here demonstrate the potential of a coiled GRS to be safely administered, to reside safely in the gastric cavity for at least 1 month, and to be retrieved through the esophagus. Further work can explore other GRS designs including different shapes, use of only biodegradable materials, and triggered disassembly. On the retrieval side, barbs and snares with more long-range sensors can be added and tested *in vivo.* This approach describes here requires a NG tube for administration; however, in the future, potentially multigram GRSs can use self-assembly of swallowable objects to avoid an NG tube.

Chapter 3: Controlled Release Profiles from the Gastric Resident System

3.1 Introduction

The challenge with designing drug depot systems for diseases such as TB is to ensure the drug is being absorbed in the therapeutic range, and there is no potential for dose dumping (*21*, *167*). Here, we describe the capacity of the GRS to provide sustained release of the drug *in vitro* and *in vivo* using a panel of TB antibiotics. Using drug embedded in silicone pills, the release can be tuned using excipients and coatings. Ideas for enabling pulsatile release of drug are also discussed. These include both polymer and electromechanical actuation systems.

3.2 Materials and Methods

3.2.1 Manufacturing of Coated Drug-Silicone Pills for Gastric Resident System

Doxycycline hyclate was purchased from MedChem Express LLC. Isoniazid was purchased from Sigma-Aldrich Corporation, and moxifloxacin was purchased from ArkPharm, Inc. Rifampicin, ethambutol, and pyrazinamide were purchased from Hangzhou Hysen Pharma Co. Ltd. Drug pills were made using the following protocol: The drug was sieved through a 75 μm sieve (McMaster-Carr) in order to fabricate pills using a consistent drug particle size (*168–170*) **(Figure 3.1)**. Then, the drug was added to the vinylpolysiloxane (VPS) base (Zhermack Elite Double 22) and mixed at 3200 rpm for 30 seconds using a SpeedMixer DAC 150.1 FVX-K (FlackTek Inc.) **(Figure 3.2)**. To prevent drug loss, ensure that all the drug is mixed into the matrix before proceeding. After 2 minutes of cooling, poly(ethylene glycol) (PEG) molecular weight 3500 (Sigma-Aldrich Corporation) or molecular weight 400 (Sigma-Aldrich Corporation) was added and mixed into the drug-VPS base matrix using the SpeedMixer at 2700 rpm for 30 seconds. After 2 minutes of cooling, the VPS catalyst (Zhermack Elite Double 22) was added and mixed using the SpeedMixer at 1750 rpm for 30 seconds. Drug loading percentages were determined relative to the final cured silicone mixture weight: doxycycline hyclate (32%), isoniazid (32%), ethambutol (25%), pyrazinamide (30%), moxifloxacin (20%), and rifampicin (54%). The viscous uniform blend was poured into a disposable polystyrene Petri dish (VWR), and individual pills were extracted using a 4 mm Miltex disposable biopsy punch (Integra) **(Figure 3.3)**. A 0.5 mm biopsy punch (Electron Microscopy Sciences) was used to core out a hole in the center of the drug-VPS pill to allow the nitinol wire to pass through. When preparing *in vivo* devices, a custom-built 3D printed hole punch was used to core out central holes in a high-throughput manner **(Figure 3.4)**. The pills were spray-coated in a DKE stainless steel pan (ERWEKA GmbH) with a 9.5 L capacity attached to an AR 403 drive unit (ERWEKA GmbH) **(Figure 3.5)**.

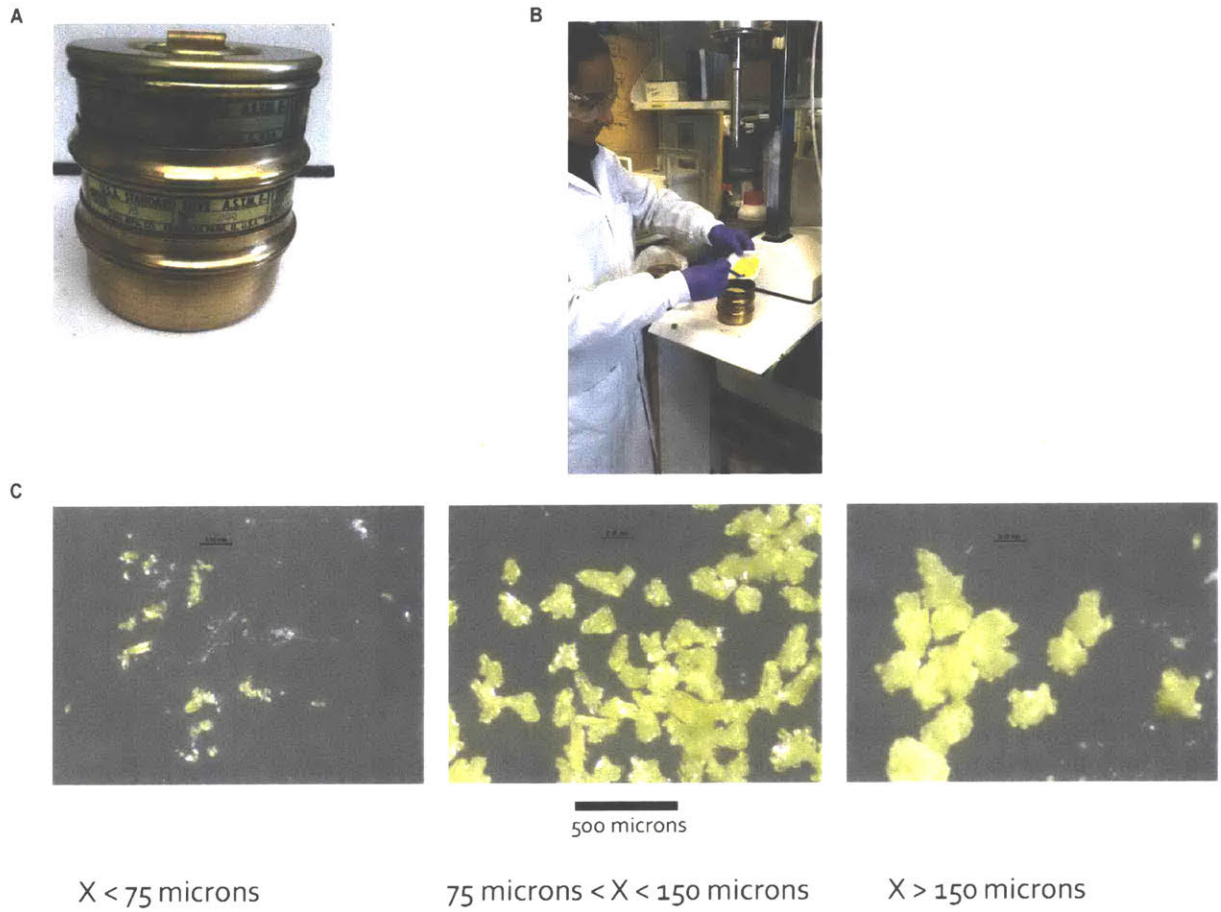


Figure 3.1: Sieving drug to use consistent particle size.
(A) Photograph of sieve. **(B)** Drug added to sieves to segment different particle sizes. **(C)** Images of doxycycline hyclate particles after sieving.

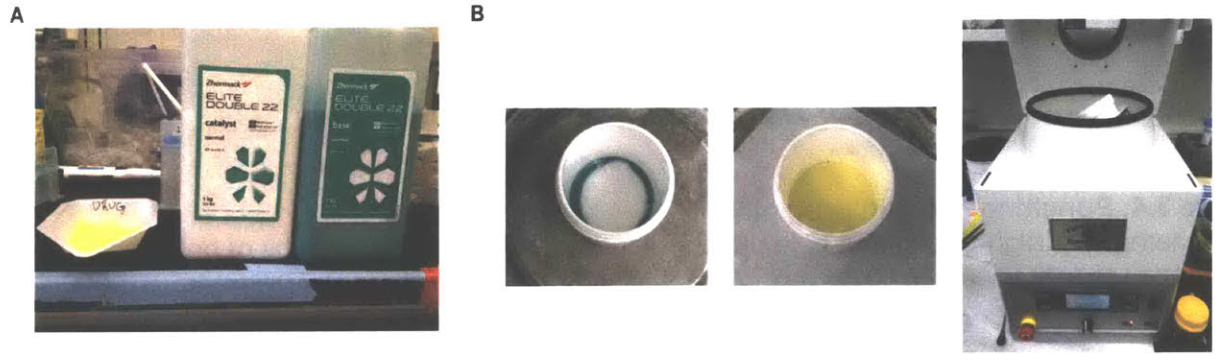


Figure 3.2: Mixing drug with silicones using SpeedMixer.
(A) Mixing drug powder with base and catalyst. **(B)** Add silicone base and catalyst then drug powder and mix in a SpeedMixer.

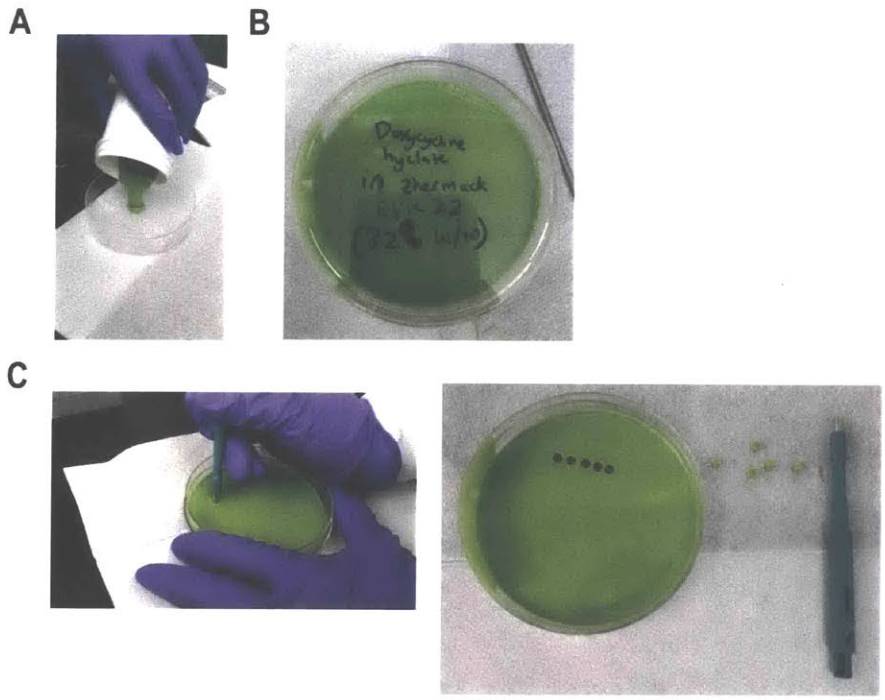


Figure 3.3: Curing and punching drug pills.
(A) Pour mixture of drug with silicones into Petri dish. **(B)** Cured drug-silicone matrix in Petri dish. **(C)** Punching pills out with biopsy punch.

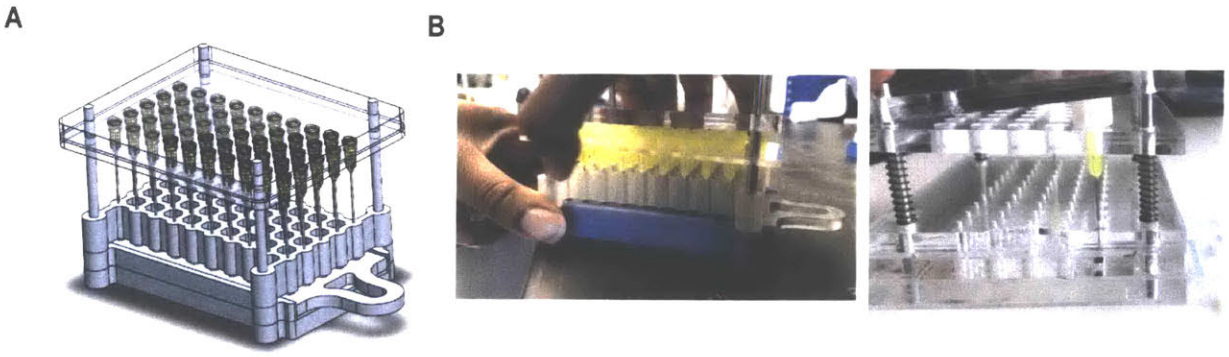


Figure 3.4: Punching holes in drug pills.
(A) Schematic of high-throughput hole puncher for drug pills. **(B)** Photographs of hole punch with biopsy punch.

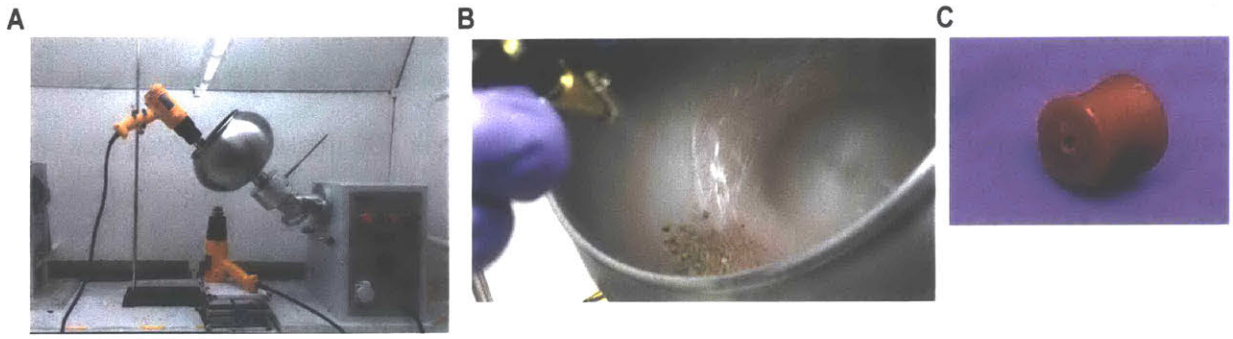


Figure 3.5: Coating of drug pills.
(A) Setup of coating apparatus. **(B)** Nozzle used to spray polymer on drug-VPS pills. **(C)** Representative photograph of coated drug-VPS pills with hole in the center.

The Eudragit RS 100 (Evonik Corporation) solution was prepared as recommended by Evonik (*171*). Briefly, the Eudragit RS 100 pellets were dissolved in 50% of a diluent mixture, composed of 342.90 grams of acetone (Sigma-Aldrich Corporation), 514.20 grams of isopropanol (Sigma-Aldrich Corporation), and 42.90 grams of water. In a separate beaker, an excipient mixture of talc (<10 µm particle size from Sigma-Aldrich Corporation), triethyl citrate (Sigma-Aldrich Corporation), and red dextrose food dye (CK Products) was homogenized into the remaining 50% of the diluent mixture for 15 minutes. The excipient mixture was then poured into the beaker containing the Eudragit solution and stirred. Lastly, the spray suspension was passed through a 500 µm sieve (McMaster-Carr).

To prepare a PCL spray solution, PCL molecular weight 45,000 (Sigma-Aldrich Corporation) was added to acetone at 5% weight per volume. The solution was then placed on a hot plate with a stir bar at 50 °C and 200 rpm. The PCL pellets started to fully dissolve and form a homogenous solution after one hour. The spray gun used was a 0.8 mm nozzle, handheld Master E91 airbrush (TCP Global) attached to beakers in the kit with a spray volume of 18 mL and held at a 90° angle to the rotating pan with a 7 cm distance from its outer diameter. The coating pan was tilted at a 45-degree angle for all the formulations and rotated at 70 rpm for the Eudragit RS 100 solution and at 300 rpm for the PCL solution. A heat gun (Uline) was placed directly underneath the coating pan and set to 50 °C to induce film formation on the pills sprayed

with Eudragit RS 100. The Eudragit RS 100 sprayed pills were dried for 2 hours after spraying in a circulating air oven set at 40 °C. The typical batch size for spraying was 100 pills. It took 120 minutes to spray pills with 300 mL of Eudragit RS 100, and it took 100 minutes to spray pills with PCL.

The nitinol wire was inserted into the 0.5 mm hole of the coated drug-VPS pills, and after the desired loading was achieved with pills, each end of the nitinol wire was crimped using a pair of pliers **(Figure 3.6)**. PCL molecular weight 37,000 (Sigma-Aldrich Corporation) pellets were then pressed into two 3-inch (76.2 mm) long pieces of Tygon tubing (Inner Diameter X Outer Diameter: 4.76 x 6.35 mm), which was obtained from McMaster-Carr. The end of each tube was then filled with Med3- 4213 silicone adhesive (NuSil), followed by a 6.35 mm stainless steel ball bearing. Once completely packed with the pellets, the tubes were heated at 100 °C to melt the PCL using a heat gun. Each crimped end of the nitinol was then slowly inserted into the molten PCL and set into place as the PCL cooled at room temperature to solidify around the nitinol wire. More silicone adhesive was used to seal the free ends of the tubes at both ends of the device.

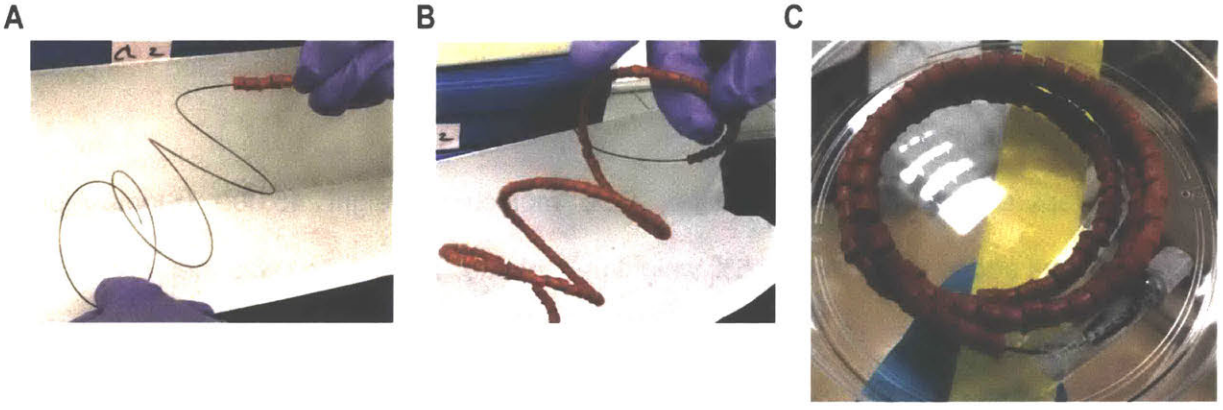


Figure 3.6: Assembly of drug pills on nitinol wire.
(A) Setup of coiled nitinol wire with pills added. **(B)** Drug loading completed on nitinol wire. **(C)** Representative photograph of device ready for deployment with sealed ends.

3.2.2 *In Vitro* Drug Release

Individual pills made of drug-VPS for doxycycline hyclate, isoniazid, ethambutol, pyrazinamide, moxifloxacin were used to evaluate long-term release kinetics in SGF. Pill formulations were

incubated in a New Brunswick Innova 44 shaking incubator (Eppendorf) at 37 °C and 200 rpm in 50 mL of SGF for up to 28 days, with solution exchanges at specified time intervals. Drug concentrations were then analyzed using a High-Performance Liquid Chromatography (HPLC). Because of the lack of a validated HPLC method for evaluating isoniazid in SGF, water was used to study differences between isoniazid formulations. Three intact rifampicin devices were fabricated by loading 2 grams of drug into VPS pills. The devices were incubated in 500 mL of nanopure water for up to 26 days in a shaking incubator at 37 °C and 200 rpm, with media exchange at specified time intervals. Water was used as a solvent for the drug release study because rifampicin rapidly degrades in acid (*172*). The drug concentrations samples were then measured on an Infinite M200Pro (Tecan) reader (absorbance, 475 nm) (*173*).

3.2.3 High-Performance Liquid Chromatography

An Agilent 1260 Infinity II HPLC system (Agilent Technologies, Inc.) equipped with a Model 1260 quaternary pump, Model 1260 High Performance autosampler, Model 1260 thermostat, Model 1260 Infinity Thermostatted Column Compartment control module, and Model 1260 diode array detector was utilized as described previously (30, 31, 62). Data processing and analysis was performed using OpenLab CDS ChemStation (Agilent Technologies, Inc.). All solvents used were purchased from Sigma-Aldrich Corporation. For doxycycline hyclate, chromatographic isocratic separation was carried out on an Agilent 4.6x50 mm AdvanceBio RPmAb SB-C8 analytical column with 3.5 µm particles, maintained at 55 °C. The optimized mobile phase consisted of 20 mM dipotassium phosphate buffer and acetonitrile (pH 6 adjusted with triethylamine) [60:40 (v/v)] at a flow rate of 0.85 mL/min over a 4 min run time. The injection volume was 5 µl, and the selected ultraviolet (UV) detection wavelength was 293 nm. For isoniazid and pyrazinamide, chromatographic isocratic separations were carried out on an Agilent 4.6x150 mm ZORBAX Eclipse Plus C-18 analytical column with 5 µm particles, maintained at 30 °C. The optimized mobile phase consisted of 10 mM sodium dibasic phosphate buffer and acetonitrile (pH 6.75 adjusted with phosphoric acid) [95:5 (v/v)] at a flow rate of 1.00 mL/min over a 6 min run

time. The injection volume for both drugs was 20 µl, and both drugs were analyzed using a UV detection wavelength of 238 nm.

For moxifloxacin, chromatographic separation was carried out on an Agilent 4.6x50 mm Poroshell 120 EC-C18 analytical column with 2.7 µm particles, maintained at 50 °C. The optimized gradient consisted of nano-pure water and acetonitrile starting at [95:5 (v/v)] at 0 minutes then ramping to [50:50 (v/v)] at 2.5 minutes and descending to [95:5 (v/v)] by 5 minutes. A constant flow rate was maintained at 1.00 mL/min, and a post-run of 1 minute was utilized. The injection volume was 5 µl, and the UV detection wavelength of 293 nm was selected.

For ethambutol, chromatographic separation was achieved using a method described previously (*174*). A Waters 3.9x300 mm µBondapak C18 analytical column with 10 µm particles, maintained at 35 °C, was utilized in an isocratic elution method. The optimized mobile phase consisted of buffered nano-pure water (1.0 mM Cu(II)SO4, 4 g sodium 1-heptanesulfonate, titrated to pH 4.50 with 10 mM HCl) and tetrahydrofuran [75:25 (v/v)]. A constant flow rate was maintained at 1.50 mL/min for 15 minutes, and a post-run of 1 minute was utilized. The injection volume was 20 µl, and the ultraviolet (UV) detection wavelength of 260 nm was selected.

3.2.4 Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry

Drug concentrations in serum from *in vivo* experiments were analyzed using Ultra-Performance Liquid Chromatography–Tandem Mass Spectrometry (UPLC-MS/MS). Analysis was performed with a Waters ACQUITY UPLC-I-Class System aligned with a Waters Xevo–TQ-S mass spectrometer (Waters Corporation). Liquid chromatographic separation was performed on an Acquity UPLC Charged Surface Hybrid C18 (50mm × 2.1mm, 1.7 µm particle size) column at 50 °C. The mobile phase consisted of aqueous 0.1% formic acid, 10mM ammonium formate solution (Mobile Phase A) and acetonitrile: 10mM ammonium formate, 0.1% formic acid solution (95:5 v/v) (Mobile Phase B). The mobile phase had a continuous flow rate of 0.6 mL/min using a time and solvent gradient composition. For the analysis of doxycycline hyclate, the initial composition (100% Mobile Phase A) was held for 1 minute, following which the composition was

changed linearly to 50% Mobile Phase A over the next 0.25 minutes. At 1.5 minutes, the composition was 20% Mobile Phase A. At 2.5 minutes, the composition was 0% Mobile Phase A and 100% Mobile Phase B, which was held constant until 3 minutes. The composition returned to 100% Mobile Phase A at 3.25 minutes and was held at this composition until completion of the run, ending at 4 minutes, where it remained for column equilibration. The total run time was 4 minutes. For the analysis of rifampicin, the initial composition (95% Mobile Phase A) was held for 0.5 minutes, following which the composition was changed linearly to 15% Mobile Phase A over the next 1.25 minutes. At 1.76 minutes, the composition was 0% Mobile Phase A and 100% Mobile Phase B, which was held constant until 3.25 minutes. The composition returned to 95% Mobile Phase A at 3.50 minutes and was held at this composition until completion of the run, ending at 4.50 minutes, where it remained for column equilibration. The total run time was 4.5 minutes.

For both the analysis of doxycycline hyclate and rifampicin, the sample injection volume was 2.5 µL. The mass spectrometer was operated in the multiple reaction monitoring mode. The mass to charge transitions (m/z) used to quantitate doxycycline hyclate, demeclocycline hydrochloride, rifampicin, and rifapentine were 445.19>154.1, 465.13>154.09, 823.5>151.17, and 877.55>151.18, respectively. Sample introduction and ionization was by electrospray ionization (ESI) in the positive ionization mode. Waters MassLynx 4.1 software was used for data acquisition and analysis.

Stock solutions of doxycycline hyclate, rifampicin, internal standards (IS) demeclocycline hydrochloride and rifapentine were prepared in methanol at a concentration of 500 µg/mL. A twelve-point calibration curve was prepared in analyte-free, blank serum ranging from 1–5000 ng/mL. 100 µL of each serum sample was spiked with 200 µL of 250 ng/mL IS in acetonitrile to elicit protein precipitation. Samples were vortexed and sonicated for 10 minutes and centrifuged for 10 minutes at 13000 rpm. 200 µL of supernatant was pipetted into a 96-well plate containing

200 µL of nanopure water. Finally, 2.5 µL was injected onto the UPLC–ESI–MS system for analysis.

3.2.5 *In Vivo* Evaluation of Gastric Resident Systems

All animal experiments were performed in accordance with protocols approved by the Committee on Animal Care at the Massachusetts Institute of Technology and as previously described (*47–50*). To assess the oral pharmacokinetics of immediate release formulations and gastric retentive drug delivery devices, we administered them to a large animal model (30-75 kg Yorkshire pigs). Animals were fed daily in the morning and in the evening with a diet consisting of pellets (Laboratory mini-pig grower diet, 5081), in addition to a midday snack consisting of various fruits and vegetables. The pellets consisted of ground oats, alfalfa meal, wheat middlings, soybean meal, dried beet pulp, salts, and other micronutrients.

The immediate release formulation was prepared by weighing and filling 100 mg of doxycycline hyclate in a "00" gelatin capsule (Purecaps USA) 15 minutes prior to dosing. Prior to dosing, the pigs were sedated with Telazol® (5 mg/kg intramuscular), xylazine (2 mg/kg intramuscular), and atropine (0.04 mg/kg intramuscular), intubated, and maintained with isoflurane (1 to 3% inhaled). Immediate release and GRS formulations were deployed in the stomach via an endoscopic guided overtube (Inner Diameter X Outer Diameter: 16.7 x 19.5 mm) from US Endoscopy. The overtube was removed once the devices were administered. For evaluation of the safety and residence time of the gastric retentive drug delivery devices, the animals were clinically assessed twice a day for evidence of GI obstruction including inappetence, abdominal distension, lack of stool, and vomiting. Additionally, the animals were evaluated radiographically every 3-4 days for evidence of GI obstruction and/or perforation. Tissue samples were collected before and after the device was placed in the stomach for histopathological analysis, and macroscopic images were taken once the device was retrieved to study any possible mucosal damage. Blood samples were obtained from an external mammary vein on the

ventral surface of the pig at indicated time points. Serum samples were separated from blood by centrifugation (3220 rpm, 10 min at 4 °C) and were stored at -80 °C for further analysis.

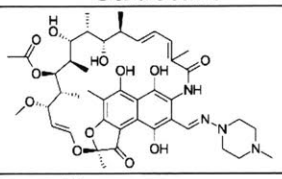
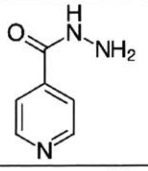
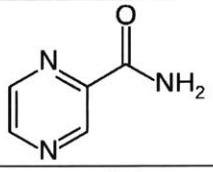
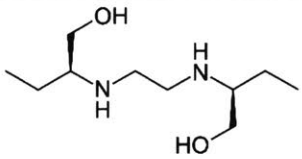
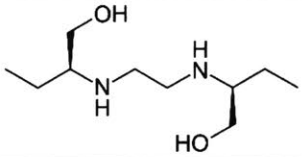
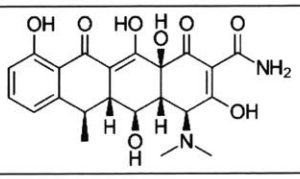
3.3 Results and Discussion

3.3.1 *In Vitro* Release of Antibiotics from Coated Drug-Silicone Pills

Pills of a single drug mixed inside a silicone matrix were fabricated and encapsulated in a polymer coating to enable tailored dosing of each drug **(Figure 3.7A)**. VPS was selected as a drug release matrix because of its flexibility, rapid curing time, and low-temperature mixing process with drug. Because of their mechanical and chemical properties, polysiloxanes have been extensively used for controlled drug delivery applications (*32*, *168*, *175*, *176*). A 300-μm-thick Eudragit RS 100 polymer coating was added to prevent the burst release of drug from the surface of the matrix (*177–180*). Each pill had a height and diameter of 4 mm with a 0.5-mm hole in the center through which to pass the nitinol wire and contribute to the assembled GRS **(Figure 3.7A)**.

Drug-VPS pills for multiple antibiotics used for TB treatment including doxycycline hyclate, isoniazid, ethambutol, pyrazinamide, moxifloxacin, and rifampicin were assembled **(Table 3.1)** (*84*, *181*, *182*). As demonstrated with doxycycline hyclate, the drug release rate from the VPS matrix in SGF can be tuned by varying the amount of a hydrophilic polymer, poly(ethylene glycol) (PEG), mixed within the VPS **(Figure 3.7B)**. The PEG domains act as channels inside the hydrophobic VPS matrix that can dissolve and form pores for the doxycycline hyclate to release. Furthermore, formulations that were coated with Eudragit RS 100 showed a linear kinetic profile with limited burst release of doxycycline hyclate **(Figure 3.7B)**. The drug-VPS pills were also able to release isoniazid, ethambutol, pyrazinamide, moxifloxacin, and rifampicin *in vitro*, indicating that the VPS matrix is compatible with a wide variety of TB drugs **(Figure 3.7, C to G)**.

Table 3.1: Common antibiotics used for treatment of TB.

Drug	Structure	Mechanism of Action
Rifampicin		Inhibits bacterial DNA-dependent RNA polymerase (*183*)
Isoniazid		Inhibits synthesis of mycolic acids (*184*)
Pyrazinamide		Unknown (*185*)
Ethambutol		Disrupts arabinogalactan synthesis and increases cell wall permeability (*186*)
Moxifloxacin		Inhibits DNA gyrase (*187*)
Doxycycline hyclate		Inhibits the synthesis of bacterial proteins by binding to the 30S ribosomal subunit (*188*)

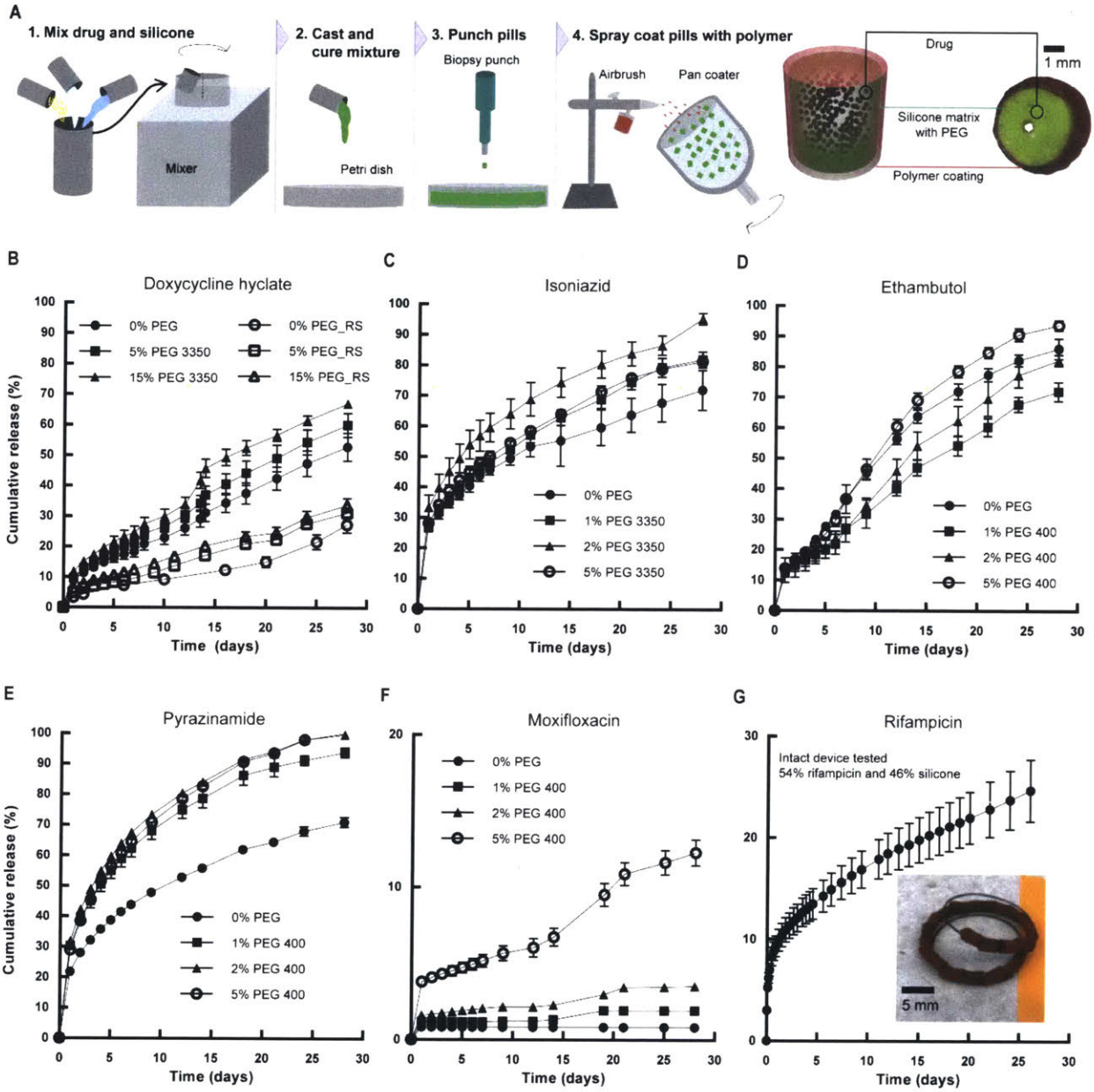
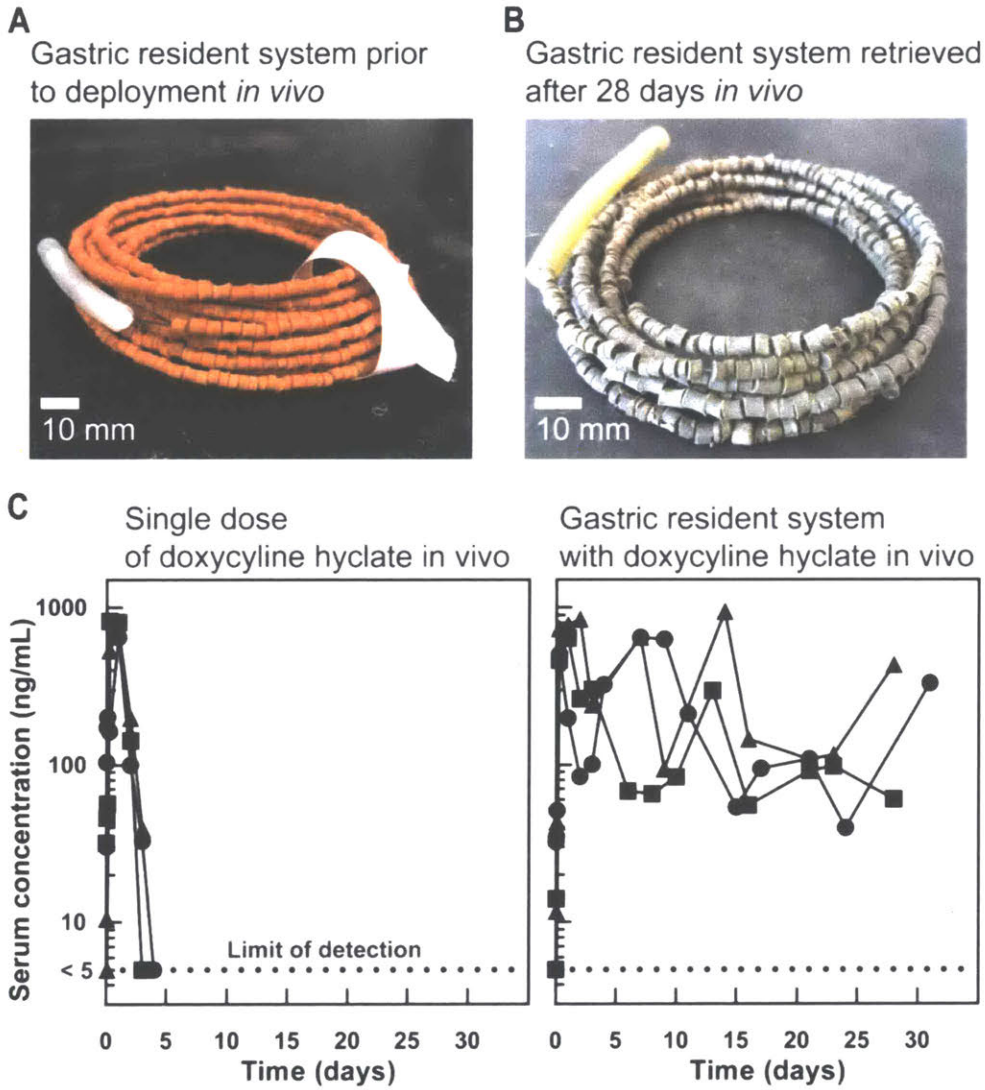


Figure 3.7: Fabrication and *in vitro* release of TB antibiotics from individual drug pills. **(A)** Coated drug pills are made by mixing drug with silicones and extracting individual pills from the homogeneous matrix using a biopsy punch before spray-coating pills in a pan coater. A schematic visualization and a cross-sectional image of the Eudragit RS 100 – coated doxycycline hyclate pill are shown. **(B)** *In vitro* release of doxycycline hyclate from a drug pill in SGF with formulations including different concentrations of PEG and Eudragit RS 100 coatings. **(C)** *In vitro* release of isoniazid from a drug pill in water. **(D)** *In vitro* release of ethambutol from a drug pill in SGF. **(E)** *In vitro* release of pyrazinamide from a drug pill in SGF. **(F)** *In vitro* release of moxifloxacin from a drug pill in SGF. **(G)** *In vitro* release of rifampicin in water from devices with 2 g of drug and 0% PEG. Inset: Image of the rifampicin-loaded device. Error bars represent SD for n=3 samples in each group.

3.3.2 *In Vivo* Release of Antibiotics from Gastric Resident System with Coated Drug-Silicone Pills

Having demonstrated controlled release with coated drug-matrix pills *in vitro* for 1 month, we prepared the GRSs loaded with 10 g of doxycycline hyclate as a model drug **(Figure 3.8A)** and administered them in swine. The GRS was assembled to contain 600 pills using four different formulations – two each with Eudragit RS 100 or PCL coatings – which released drug simultaneously **(Figure 3.9)** (*189–191*). After 28 days of gastric residence *in vivo*, the GRS was safely retrieved **(Figure 3.8B)**. The serum concentration profile of a 100-mg single dose is shown in Figure 3.8C. The drug was absorbed rapidly, and detectable concentrations were observed within 15 min. No drug was detectable after 3 days with the single-dose formulation. In contrast, drug was detectable for at least 28 days when doxycycline hyclate was dosed in the GRS. We also incorporated rifampicin into the GRS and achieved detectable serum concentrations for a week *in vivo* **(Figure 3.10)**.



D

Formulation	Total drug incorporated (g)	AUC (ng/mL x day)	Duration of release (days)
Single dose	0.1	1019±203	3
GRS	10	7118±3170	>28

Figure 3.8: *In vivo* release of doxycycline hyclate from the GRS in a swine model.
(A) Representative photograph of a GRS after assembly of drug pills along a nitinol wire before deployment *in vivo*. **(B)** Representative photo of a retrieved GRS after 28 days *in vivo* in a swine model. **(C)** Left: Concentration-time profiles of doxycycline hyclate in serum after administering a single dose of 100 mg (n=3). Right: Concentration-time profiles of doxycycline hyclate in serum after administering the GRS, which had 10 g of drug across four formulations (n=3; Figure 3.9). **(D)** Area under the curve (AUC) and the duration of drug release for a single dose compared to the formulations of the GRS administered *in vivo*, with the mean value and SD reported for n=3 samples in each group.

A

Formulation: Amount	Doxycyline hyclate	Silicone	PEG	Coating: Thickness
1: 1 gram	32%	66%	2%	Eudragit RS 100: 210 μm
2: 2 grams	32%	68%	0%	Eudragit RS 100: 300 μm
3: 3 grams	32%	68%	0%	PCL: 350 μm
4: 4 grams	32%	68%	0%	PCL: 650 μm

B

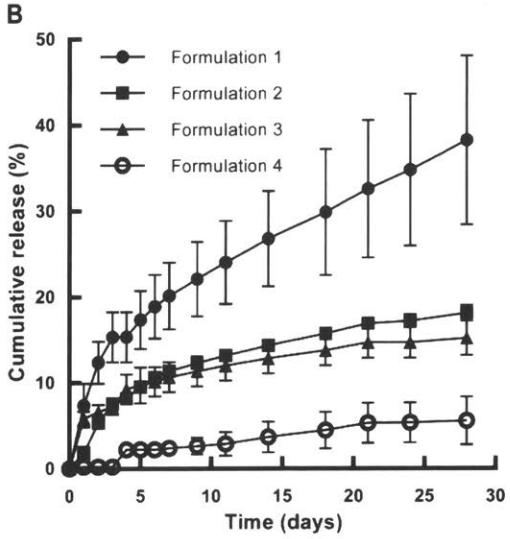


Figure 3.9: *In vivo* formulations and their corresponding 4-week *in vitro* drug release profiles of doxycycline hyclate–silicone pills of the 10 g GRS.
(A) Table of in vivo formulations for the doxycycline hyclate-silicone pills of the 10 g GRS assembled 1 gram of formulation 1, 2 grams of formulation 2, 3 grams of formulation 3, and 4 grams of formulation 4. Formulation 1 contained PEG, whereas the others did not. All drug pills were coated with either Eudragit RS 100 (formulations 1 and 2) or with poly(Ɛ-caprolactone) (PCL) (formulations 3 and 4). (B) *In vitro* release profiles of doxycycline hyclate from drug-silicone pills over 4 weeks in SGF. Error bars represent SD for n=3 samples in each group.

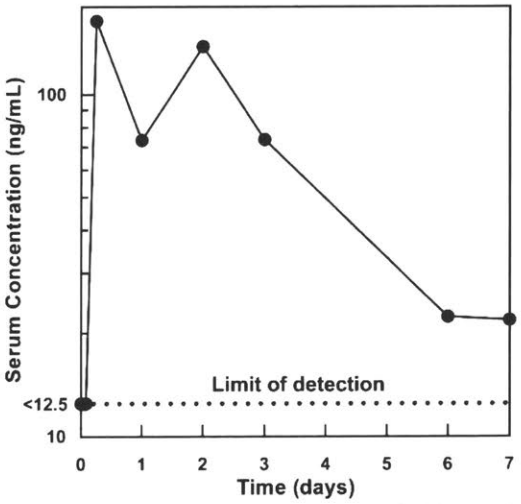


Figure 3.10: *In vivo* release of rifampicin from the GRS in a swine model.
A GRS with 2 grams of rifampicin formulated with 54% rifampicin and 46% silicone was administered to a swine model for 7 days, and the serum concentrations of rifampicin were recorded.

3.3.3 *In Vitro* Release of Rifampicin from Orifices in Tubing

Sustained release can be achieved using passive diffusion with micro-drilled holes in a biocompatible tube housing drug powder. This mechanism has been previously described in other drug delivery devices (*133*, *192*). Ingress of liquid dissolves the powder and forms an initially saturated solution inside the tube. The drug solution is pushed out through the drilled orifices due to an increase in the hydrostatic pressure inside the tube. In order to achieve a target release rate, the number of holes and the size of the holes can be tuned. Initially, the drug release rate will be zero-order. After complete dissolution of the drug, the drug release rate will begin decreasing and no longer be zero-order since the osmotic driving force diminishes.

The release rate of rifampicin was determined as a function of the number and size of holes in the tube **(Figure 3.11)**. The holes can be fabricated using a biopsy punch, drilling, or laser cutting. Biopsy punched-holes are the most precise method, as they do not result in as much of a taper or burning of the tube as the drilling or laser cutter approach. To measure the release rate, a dissolution testing apparatus with a paddle can be used to simulate physiological conditions (motion in the stomach at 37 °C) (*167*, *193–195*). The device was incubated in 1000 mL of SGF. At specified time intervals, 1 mL of the release medium was withdrawn automatically, and an equal volume of SGF was replaced. Then, the rifampicin solution was analyzed by an ultraviolet-visible spectrophotometer to determine the drug concentration at every time point. To corroborate experimental results, the time-changing concentration of rifampicin in the release medium was modelled in COMSOL Multiphysics using the convection-diffusion equation **(Equation 1)**. The diffusion coefficient *D* can be estimated using the Stokes-Einstein relation and assuming rifampicin is a spherical molecule **(Equation 2)** (*196*, *197*).

$$\frac{\partial c}{\partial t} = \nabla \cdot (D\nabla c) - \nabla \cdot (\vec{v}c) + R \qquad \textbf{Equation 1}$$

c: concentration of drug; D: diffusion coefficient; $\vec{v}$: velocity of release media
R: source or sink of drug

$$D = \frac{}{6\pi\eta\left[\frac{3(MW)}{4\pi N\rho}\right]^{1/3}} \qquad \textbf{Equation 2}$$

k: Boltzmann constant; T: temperature of the media; η: viscosity of the media
MW: molecular weight of drug; N: Avogadro's number; ρ: density of the drug

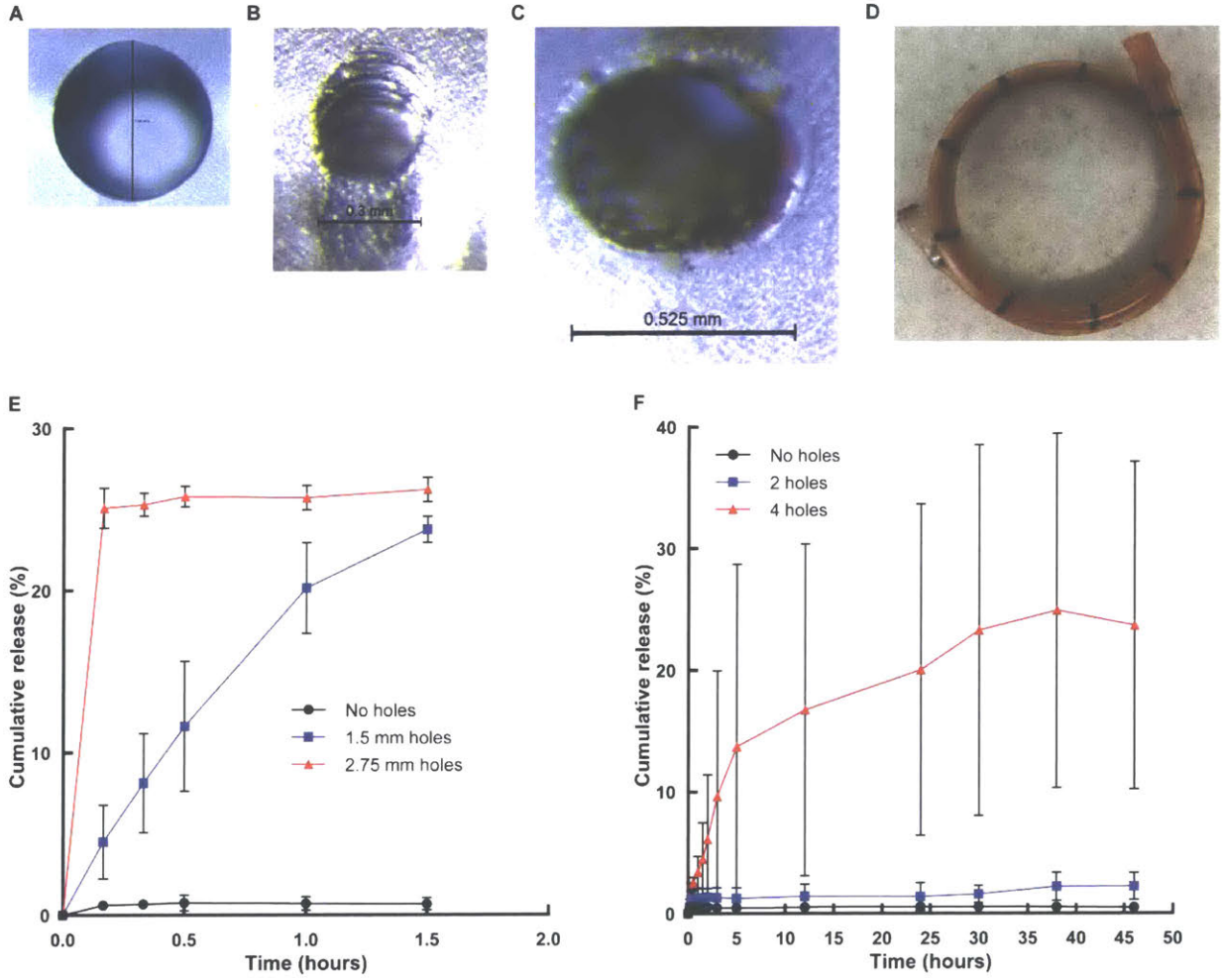


Figure 3.11: *In vitro* release of rifampicin from cylindrical-shaped tubing with orifices. **(A)** Orifice in tube from biopsy punch. **(B)** Orifice in tube from micro-drill bits. **(C)** Orifice in tube from laser cutter. **(D)** Representative photograph of device with rifampicin used in release studies. **(E)** Ten holes of two different sizes (1.5 mm or 2.75 mm) were drilled in a 30 cm long cylindrical device filled with rifampicin. **(F)** Either 2 or 4 holes of size 750 μm were drilled in a 30 cm long cylindrical device filled with rifampicin.

3.3.4 *In Vivo* Release of Rifampicin from Orifices in Tubing

Having demonstrated that the size and number of holes does determine the release rate of rifampicin from orifices in tubing, *in vivo* evaluation of coiled GRSs packed with rifampicin powder and orifices was conducted **(Figure. 3.12)**. The GRSs were all 122 cm long filled with 10 g of rifampicin with 5 micro-drilled holes, each 140 μm in diameter. This approach was unable to achieve 4 weeks of drug release of rifampicin. It could be possible that the micro-drilled holes were blocked by food particles or the orifices were not large or placed frequently enough. Past 10 days, the serum concentrations from all GRSs was 0 ng/mL. Therefore, the approach with micro-drilled holes was not successful, and most of the 10 g of rifampicin remained within the GRS after retrieval. Drug diffusion through orifices was not pursued further due to the erratic drug release profiles *in vivo*.

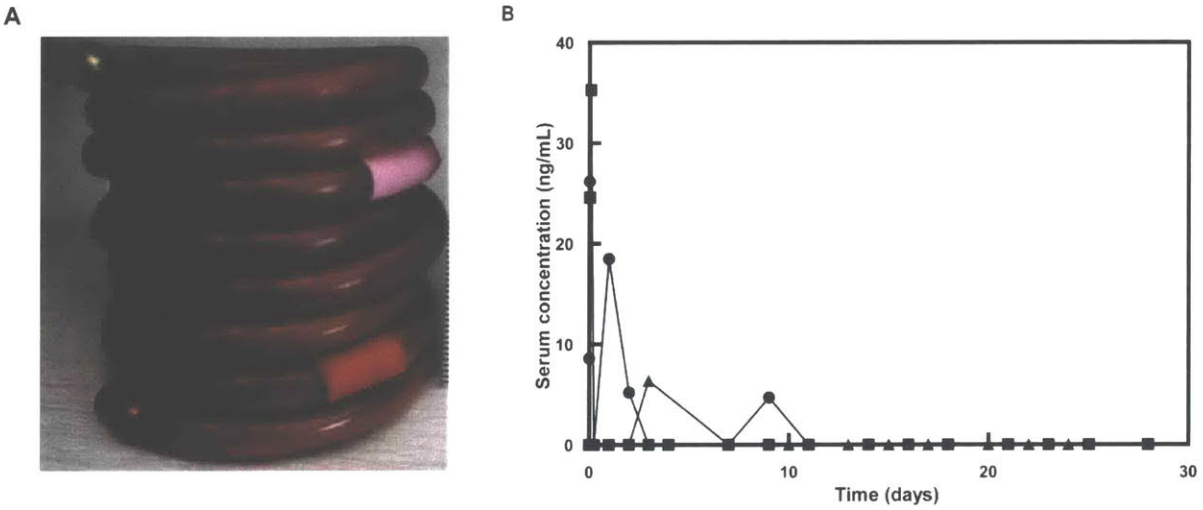


Figure 3.12: *In vivo* release of rifampicin from the GRS with orifices in a swine model. **(A)** Representative photographs of the GRS with rifampicin. The tape, covering the micro-drilled holes, is removed prior to deployment in a swine model. **(B)** Concentration-time profiles of rifampicin in serum after administering the GRS, which had 10 g of drug (n = 3).

3.3.5 Ideas for Pulsatile Release of Gastric Resident System

Bacteria resist antibiotics by modifying their cell wall proteins or target of the drug, inactivating the antibiotic, or overexpressing their efflux pump proteins to expel the antibiotic and reduce its efficacy (*198*). Engineering strategies to delay antibiotic resistance and eventually

overcome it are critical now. Currently, researchers are attempting to do this by studying drug interactions, with regards to synergy and antagonism to optimize killing of microbes. These combination treatments typically lead to increased dosage and toxicity (*199*). Alternating antibiotic therapy, whereby drugs are administered one at a time with periodic switching, has been shown to reduce the overall rate of resistance by slowing acquisition of resistance to one of the two component drugs, sometimes as effectively as mixed treatment (*199*). Alternating-drug therapy slows evolution by constraining mutational paths toward resistance. Negative cross-resistance occurs when a mutation conferring resistance to one drug and collateral sensitivity to a second drug are outcompeted by wild-type cells. Collateral sensitivity cycling, which builds on the finding that resistance to one drug can perturb drug susceptibility profiles in the bacterial cell and lead to collateral resistance and sensitivity towards other drugs, may guide the choice of treatment regimens with regards to drug combinations (**Figure 5**) (*200–203*). While mechanisms and drug networks to further understand and characterize collateral sensitivity are being developed, there are no drug delivery technologies to enable antibiotic cycling *in vivo* for month-long bacterial infections (*201*, *204–206*).

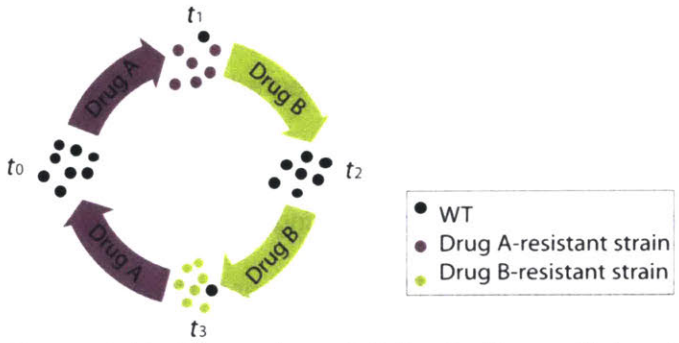


Figure 3.13: General model illustrating collateral sensitivity cycling.
Resistant strains are eradicated when drugs A and B, which have reciprocal collateral sensitivty profiles, are rotated. At time t_0, the wild-type (WT) disease-causing cell population is treated with drug A first. At t_1, resistance to drug A develops, and treatment is switched to drug B. The drug A-resistant cells have become collaterally sensititive to drug B, and by t_2, all drug A-resistant cells are killed. At t_3, resistance to drug B develops, and treatment is switched back to drug A, to which drug B-resistance cells have become collaterally sensitive. This results in elimination of drug-B resistant cells at t_0. Reproduced with permission from (*200*).

The coiled GRS can incorporate drug compartments within a long tube, with each drug compartment holding a different drug and covered with films or caps to enable pulsatile release for drug cycling **(Figure 3.14A)**. Two challenges to overcome including 1) making compartments of a fixed quantity of drug and 2) identifying materials to seal and erode over large holes drilled in the biocompatible tube. Compartments within the tube can be made with either medical adhesive glue or blocks of high molecular weight PCL, an extremely slow-degrading polymer (*207*). Then, drug can only escape out of its compartment through the drilled holes, which will be covered with films or caps of polyanhydrides that undergo surface erosion. A polymer can be assigned a dimensionless erosion number ε, which is the ratio between the diffusion time and the degradation time (*208*). If $\varepsilon \gg 1$, then surface erosion occurs; else, if $\varepsilon \ll 1$, then bulk erosion occurs.

For a 30-day drug-releasing device with an interval of 24 hours between each pulse, the degradation rate of the polyanhydrides used in the device needs to have a large range. Previously, it has been shown that by copolymerizing varying amounts of methacrylated sebacic acid and methacrylated 1,6-bis(carboxyphenoxy)hexane, the degradation network of the final network can be controlled from 2 days to 1 year (*209*). After synthesizing the monomers, they can be photopolymerized at different intensities to control the ratio of methacrylated sebacic acid to methacrylated 1,6-bis(carboxyphenoxy)hexane, and therefore affect the degradation rate of the final network. Disks of these anhydrides can be made by melting the polymer in a mold shaped in a plug for the tube. Alternatively, an extruder can be used for both making drug filaments and the polyanhydride plugs (*210*, *211*). Besides polyanhydride plugs, PCL is another surface erodible polymer for which films and caps can be made by solvent casting or extruding **(Figure 3.14B)** (*207*, *212–214*). Other polymers to try for making films include poly lactic-co-glycolic acid, poly(b-amino ester)s, shape-memory polymers from PCL, and metal or gold films for electrochemical dissolution inspired by the "microchip" **(Figure 3.14C)** (*22*, *163*, *215–224*).

Electromechanical mechanisms can also be incorporated into the GRS such that "gates", which are made of nitinol or other shape memory alloys, can change conformation and open via

Joule heating from an electric current **(Figure 3.15A-B)** (*134*, *225–227*). An example is using a nitinol spring threaded into a drug compartment **(Figure 3.15C)**. An alternative approach, which maximizes drug loading, is to push pills using a pill ejector system (PES), inspired by the actual PEZ dispenser (*228*, *229*). Two ideas for the PES, a spinning disk and four-bar linkage are shown in **Figure 3.16** (*230*).

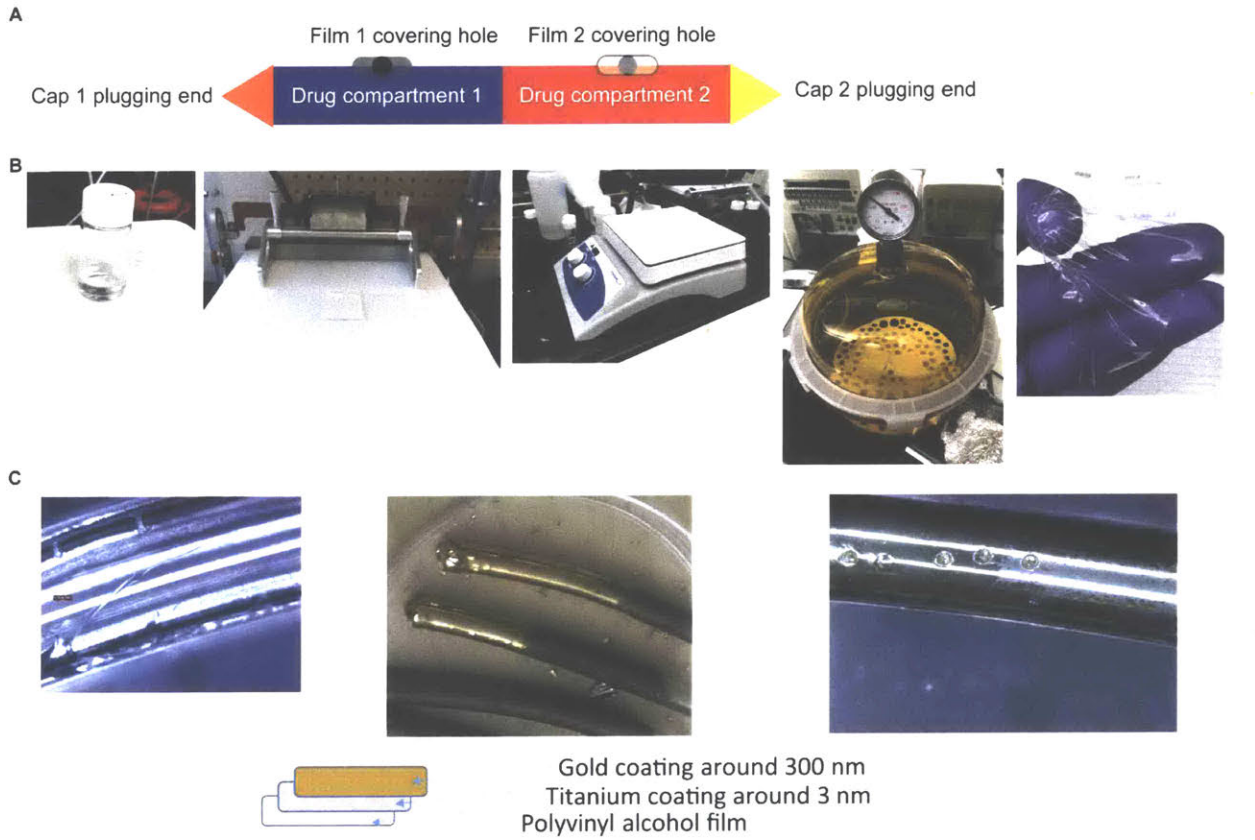


Figure 3.14: Approaches for enabling pulsatile release using films and caps.
(A) Diagram of separate drug compartments covered by different films or different caps. These films and caps can degrade over time or be activated to degrade such that drug can come out of the drug compartment at a given time. **(B)** The process of solvent casting includes dissolving the polymer in a solvent, casting it onto a surface, using a blade to precisely tune the height of the film, and then drying it on a hot plate and then keeping the films dry in a desiccator. An example of a poly lactic-co-glycolic acid film is shown. **(C)** Coating orifices on tubes with gold thin films with adhesion layers of titanium and polyvinyl alcohol.

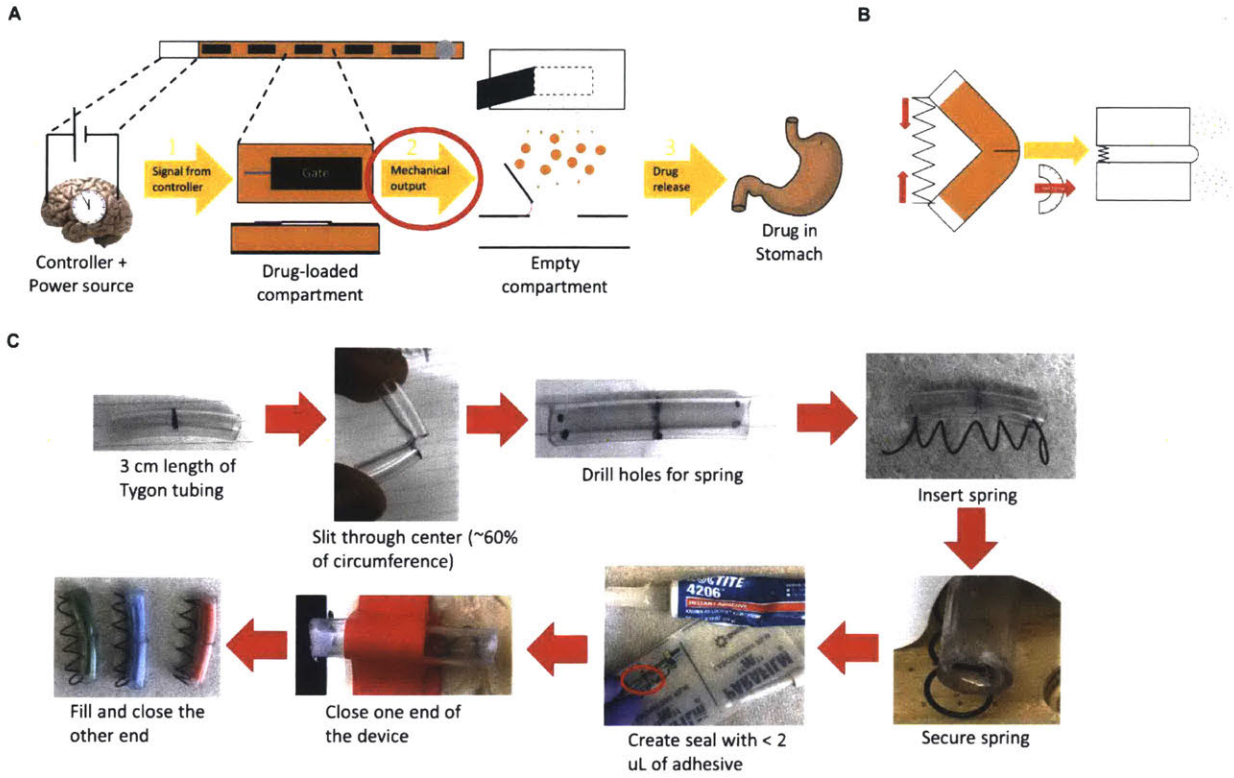


Figure 3.15: Actuation of "gates" on drug-loaded compartments by an electrical current. **(A)** Diagram of separate drug compartments covered by "gates" such as a nitinol spring that can be actuated to then open and allow drug release. **(B)** The compressive force from the spring actuation produces stress on the seal so the drug can be released in a burst. **(C)** Process of fabricating nitinol springs as actuators on drug-loaded compartments.

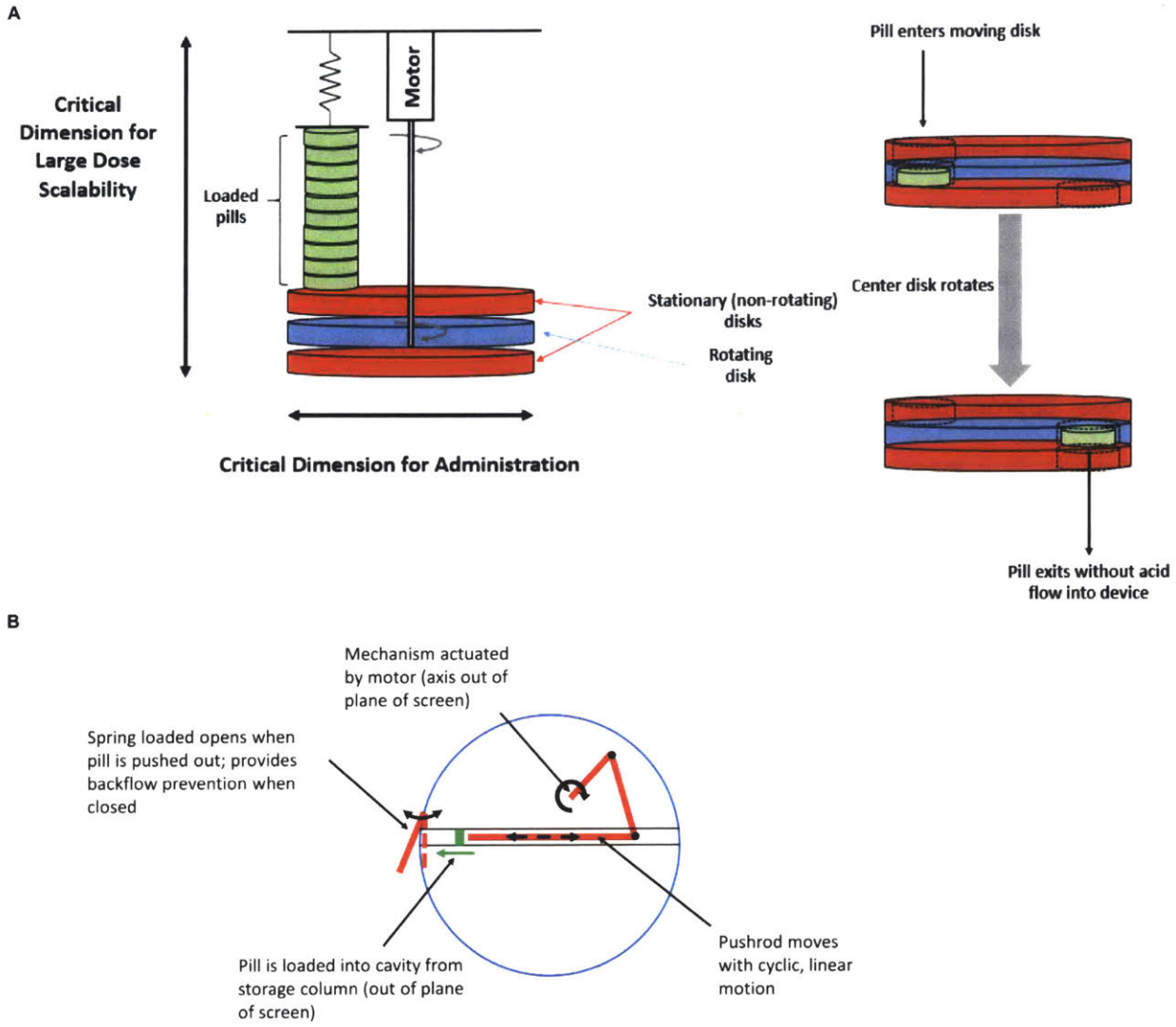


Figure 3.16: Diagrams of ideas for the pill ejector system (PES).
(A) Pills are loaded and drop down to a moving disk, controlled by a motor, and then exit the disk as it rotates. **(B)** Diagram of four-bar linkage system.

3.4 Conclusion

The results shown here demonstrate drug delivery from the GRS both *in vitro* and *in vivo* with a panel of antibiotics used for TB treatment. Further work includes formulation development for all drugs followed by testing *in vivo* with iteration to achieve target pharmacokinetic profiles. More coatings, polymer matrices, and excipients can be studied for all drugs to build a library of formulations with corresponding release kinetic profiles. Lastly, this chapter concludes with numerous approaches to enable pulsatile release using polymer and electromechanical mechanisms. Drug loading capacity, ease of manufacturing, and cost are parameters to consider when moving forward with translation of the GRS.

Chapter 4: Demonstrating Applications of the Gastric Resident System

4.1 Introduction

For this approach to be translated successfully, it must be acceptable and feasible to patients and health care providers. Here, we describe results from a field questionnaire in TB clinics in India as well as an economic analysis on the cost savings from a GRS system. Lastly, we demonstrate the potential for the GRS to be a platform to treating other diseases, such as hepatitis C.

4.2 Materials and Methods

4.2.1 Field Questionnaire in India

The study was approved by the following institutions and committees: 1) Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects, 2) the Institutional Ethics Committee of Maulana Azad Medical College and Associated Lok Nayak Hospital, Govind Ballabh Pant Hospital, and Guru Nanak Eye Centre, New Delhi, 3) the New Delhi TB Centre, 4) the Ethical Committee of Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, New Delhi, 5) the National Institute of Tuberculosis and Respiratory Diseases, New Delhi, and 6) the State Tuberculosis Officer of New Delhi for Delhi District Tuberculosis Centres at Gulabhi Bagh, Nehru Nagar, and Safdarjung Hospital. Copies of the questionnaires can be found in the **Appendix**. The four approaches for improving adherence were chosen by incorporating both behavioral and technological interventions as described the literature (*1*, *5*). Three routes of administration are compatible with multigram dosing and deployment through the esophagus: 1) placing an NG tube to deploy a GRS, 2) swallowing many capsules, and 3) drinking water-drug mixture (inspired by the recent developments in gastric resident hydrogels) (*50*, *231*). These options were presented to health care providers and patients with approximate volumes of the drug necessary. Emphasis on the need for these routes to be administered in a TB clinic was placed to maximize the efficacy of the DOTS strategy. The questionnaire for health care providers was written in English and given to the providers on paper to fill out in English. Participants provided written informed consent. The questionnaire for patients was administered orally in Hindi with interpreters from Operation Asha. The translation was prepared by Ms. Manju Bajiya at Operation ASHA. Patients provided oral informed consent prior to participating in the survey. The surveys for the health care providers and the patients were piloted in January 2017 in New Delhi and in Mumbai with the guidance and assistance of healthcare professionals at Operation ASHA and Safdarjung Hospital. Based on the pilot study, we revised the wording of some questions in

both questionnaires and developed an application on an Android tablet to record questionnaire answers from the patient. Props (a representative sterile NG tube, 30 "000" capsules, and a 2 L water bottle) were added to communicate the three routes of administration to the patients participating in the questionnaire. From August 2017 to November 2017, the full study was conducted with the support of the Ministry of Health and Family Welfare of the Government of India and Operation ASHA. All health care providers who filled out more than 90% of the questionnaire were included in the analysis. All 300 patients who provided consent for the study were included in further analysis.

4.2.2 Economic Model for Cost of Nonadherence of Tuberculosis Patients in India

The economic model was based on a conceptual framework developed by David Collins at Management Sciences of Health and applied in Kenya and the Philippines (*232*, *233*). It describes the current impact of a treatment interruption for drug-susceptible TB (DSTB) patients on morbidity and mortality as well as the estimated financial impact of that treatment interruption in New Delhi, India from 2013-2014 (*234*). The data, assumptions, and economic calculations were derived from a global literature review, a review of the National Tuberculosis Control Program (NTP) data, and from an expert panel of doctors, pharmacists, and NTP staff from Philippines. India and the Philippines have a similar GDP per capita and cost per TB patient, so the Philippines data set was used for diagnostic and treatment costs (*235*). The following key assumptions were used: 1) a: 3 months is the mean length of treatment before loss-to-follow-up (LTFU), 2) b: no patients are infectious with drug-sensitive TB at the start of the period because they have all completed the intensive phase of treatment, 3) c: 3 months is the average length of interruptions, 4) d: 10% of patients are treated in the private sector during the LTFU, 5) e: 10% of patients develop multi-drug resistant TB (MDR-TB) when treated in the private sector, 6) f: 10% of patients develop MDR-TB while untreated, 7) g: 70% of the MDR-TB patients return to the public sector for treatment after LTFU, 8) h: 70% of the DSTB patients return to the public sector

for treatment after LTFU, and 9) i: the number of patients per month infected by active LTFU patients is 0.1. Sensitivity analysis was conducted for these 9 parameters.

4.2.3 Stability of Hepatitis C Drugs

To determine drug stability at low pH, the drugs were dissolved in SGF and then placed in a shaker incubator at 37 °C and 100 rpm. At various times, aliquots were withdrawn and stored at −20 °C until analysis. Drug concentrations in the solution were analyzed using HPLC and reported as a percentage of the initial concentrations.

4.2.4 Manufacturing of Coated Drug-Polycaprolactone Pills

Drug pills were made using the following protocol: Drug was added in to the PCL of desired molecular weight and mixed in a SpeedMixer at 3500 rpm for 30 seconds. This led to formation of a melt-mixed PCL and drug aggregate, which was scooped into a 3D printed model with aid of a spatula. The 3D printed mold was used to form drug pills of a specified dimension. The pills were then spraycoated with PCL as described in Chapter 3. Then, holes in the pill were drilled using a drill press.

4.3 Results and Discussion

4.3.1 Acceptability and Feasibility of Gastric Residents Systems in Tuberculosis Clinics in India

A field questionnaire was conducted in India, the highest burden TB country in the world, to understand the acceptability and feasibility of the GRS (*70*). The questionnaire included 111 TB health care providers and 300 patients with TB at DOTS clinics in India **(Table 4.1 and 4.2)**. Most participants believed that a long-term drug delivery device administered through an NG tube was acceptable and feasible in the field **(Figure 4.1 and 4.2)**. Health care providers were willing to invest the most amount of money in developing solutions to reduce the frequency of administering medication, and they felt the NG tube would be the quickest mode to delivery long-term treatment for TB as compared to swallowing 30 capsules or drinking 2 L of water. Results indicated that over 90% of providers have experience placing NG tubes. Most patients were willing to try the NG tube deployment as the mode of administering long-term TB treatment as compared to swallowing 30 capsules or drinking 2 L of water. These results are promising, although limitations of the field questionnaire will need to be assessed and addressed in further studies.

Table 4.1: Demographics of 111 TB health care providers who responded to the questionnaire study across TB clinics in New Delhi, India.

Characteristics	Health care providers (N=111) n(%)
Age (years)	
18-24	2 (1.8)
25-34	64 (57.7)
35-44	16 (14.4)
45-54	15 (13.5)
55-64	14 (12.6)
Sex	
Male	81 (73.0)
Female	30 (27.0)
Occupation	
Nurses	13 (11.7)
Residents	52 (46.8)
Doctors	46 (41.4)
TB Experience	
<1 year	12 (10.8)
1-5 years	50 (45.0)
6-10 years	16 (14.4)
11-15 years	6 (5.4)
>15 years	27 (24.3)

Table 4.2: Demographics of 300 TB patients who responded to the questionnaire study across TB clinics in New Delhi, India.

Characteristics	Patients (N=300) n(%)
Age (years)	
18-24	54 (18.0)
25-34	57 (19.0)
35-44	104 (34.7)
45-54	65 (21.7)
55-64	14 (4.7)
65+	1 (1.7)
Not sure	5 (1.7)
Sex	
Male	181 (60.3)
Female	114 (38.0)
Other	1 (0.3)
Not sure	4 (1.3)
Time at clinic	
<10 minutes	115 (38.3)
10-30 minutes	133 (44.3)
30-60 minutes	39 (13.0)
>60 minutes	11 (3.7)
Not sure	2 (0.7)

A

Option	Description of adherence solution
A	Reduce frequency of administering medication
B	Send reminders to patients via cell phone or SMS
C	Send healthcare worker or family member to remind patient
D	Reward patients who take medication

D

Option	Route of administration
A	Nasogastric tube
B	Swallowing 30 "000" capsules
C	Drinking 2 Liters of water-drug mixture

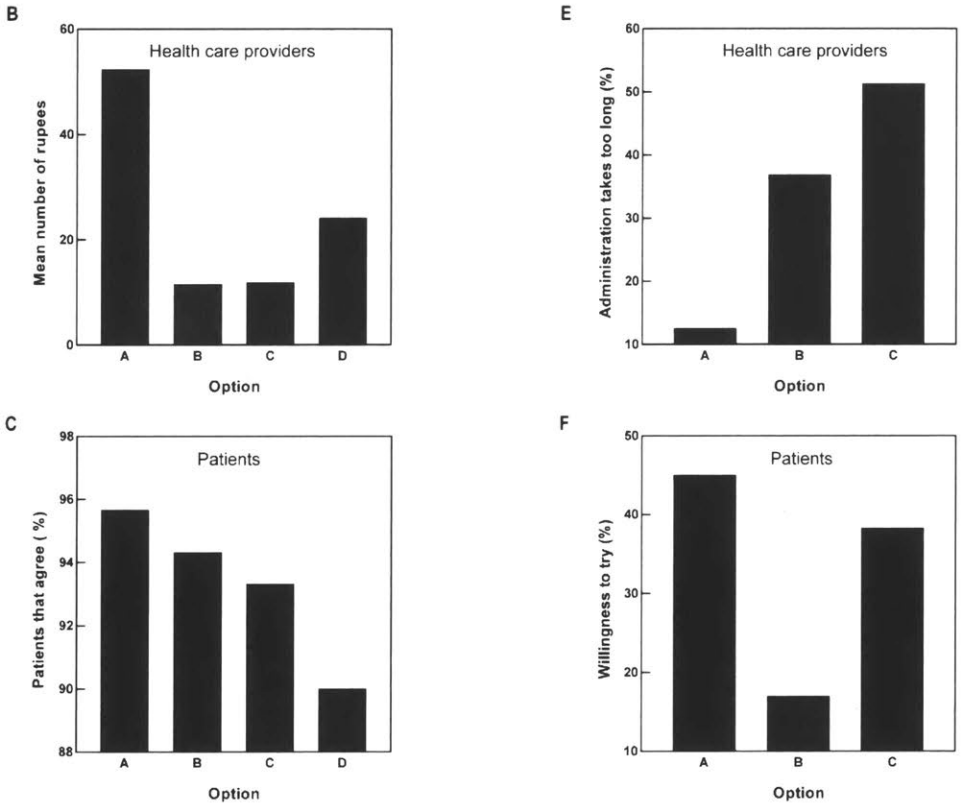


Figure 4.1: Field questionnaire results at TB clinics in New Delhi, India.
(A) Table of options presented to TB health care providers and patients with TB regarding four different methods of improving patient adherence to treatment. **(B)** Responses from health care providers on how they would allocate rupees towards four different options to improve patient adherence to treatment. **(C)** Responses from patients on whether each option would help them adhere to treatment. **(D)** Table of options presented to TB health care providers and patients with TB regarding three different routes of administering a long-term gastric resident device for TB treatment. **(E)** Responses from health care providers on the feasibility of three different routes of administration with respect to the time each option would take in a TB clinic. **(F)** Responses from patients on their willingness to try three different routes of administration for a long-lasting gastric resident device for TB treatment.

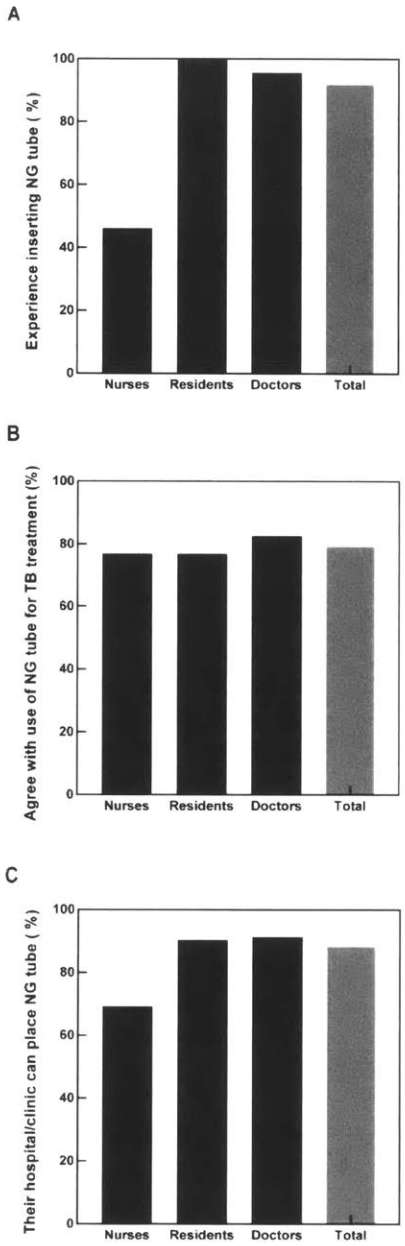


Figure 4.2: Field questionnaire results on NG tube deployment at TB clinics in New Delhi, India.
(A) Responses from all TB health care providers on their experience with inserting a NG tube previously. **(B)** Responses from all TB health care providers on whether they agree with using a NG tube for deploying TB treatment. **(C)** Responses from all TB health care providers on whether their hospital or clinic has the infrastructure to insert NG tubes in TB patients.

4.3.2 Economic Benefit of Gastric Resident System for Tuberculosis Treatment

A critical aspect for translational success also involved cost-effectiveness of a health care intervention (*236–239*). While the final cost of the GRS cannot be estimated, the cost associated

with nonadherence to TB treatment can motivate the use of the GRS intervention. An established model was used to evaluate the potential impact of a GRS on patients with TB, with savings estimated at more than $8000 per patient in New Delhi, India **(Table 4.3)** (*232*, *233*). Sensitivity analysis was also conducted and confirmed the main conclusion that an intervention like a GRS to ensure adherence to TB treatment could save money **(Table 4.4)**. Most of the money saved is for the household, as the patient with a GRS does not need to miss work or school to go to a DOTS clinic as frequently.

Table 4.3: Modelled impact of TB treatment interruptions on health and economic costs in New Delhi, India annually.

Number of patients whose treatment was interrupted	7068
Number of patients who develop MDR-TB as a result of the interruption	707
Number of patients who die as a result of the interruption	1560
Number of additional persons who develop MDR-TB as a result of the interruption	195
Total additional cost	
Provider cost	$4,631,892
Household cost	$52,905,330
Total	$57,537,222
Additional cost per patient	
Provider cost	$655
Household cost	$7,485
Total	$8,141

Table 4.4: Sensitivity analysis of economic model for TB treatment interruptions on health and economic costs in New Delhi, India annually.

	Number of patients whose treatment was interrupted	Number of patients who develop MDR-TB as a result of the interruption	Number of patients who die as a result of the interruption	Number of additional persons who develop MDR-TB as a result of interruption	Additional cost per patient to provider	Additional cost per patient to household	**Total additional cost per patient**
a = 3, b = 0%, c = 3, d = 10%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	707	1560	195	$ 655	$ 7,485	**$ 8,141**
a = 2, b = 0%, c = 3, d = 10%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	707	1560	195	$ 634	$ 7,144	**$ 7,778**
a = 4, b = 0%, c = 3, d= 10%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	707	1560	195	$ 677	$ 7,826	**$ 8,503**

a = 3, b = 10%, c = 3, d = 10%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	707	1560	195	$ 681	$ 7,573	**$ 8,253**
a = 3, b = 20%, c = 3, d= 10%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	707	1560	195	$ 706	$ 7,660	**$ 8,366**
a = 3, b = 0%, c = 2, d = 10%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	707	1560	181	$ 643	$ 7,481	**$ 8,123**
a = 3, b = 0%, c = 4, d= 10%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	707	1560	209	$ 668	$ 7,490	**$ 8,158**

a = 3, b = 0%, c = 3, d = 0%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	707	1560	195	$ 655	$ 7,488	**$ 8,143**
a = 3, b = 0%, c = 3, d = 20%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	707	1560	195	$ 655	$ 7,482	**$ 8,138**
a = 3, b = 0%, c = 3, d = 10%, e = 0%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	636	1548	195	$ 613	$ 7,401	**$ 8,014**
a = 3, b = 0%, c = 3, d = 20%, e = 20%, f = 10%, g = 70%, h = 70%, i = 0.1	7068	777	1572	195	$ 697	$ 7,570	**$ 8,267**

a = 3, b = 0%, c = 3, d = 10%, e = 10%, f = 0%, g = 70%, h = 70%, i = 0.1	7068	71	1454	195	$ 277	$ 6,675	**$ 6,952**
a = 3, b = 0%, c = 3, d = 10%, e = 10%, f = 20%, g = 70%, h = 70%, i = 0.1	7068	1343	1666	195	$ 1,034	$ 8,295	**$ 9,329**
a = 3, b = 0%, c = 3, d = 10%, e = 10%, f = 10%, g = 35%, h = 70%, i = 0.1	7068	707	1775	373	$ 598	$ 8,344	**$ 8,942**
a = 3, b = 0%, c = 3, d = 10%, e = 10%, f = 10%, g = 100%, h = 70%, i = 0.1	7068	707	1375	42	$ 705	$ 6,749	**$ 7,453**

a = 3, b = 0%, c = 3, d = 10%, e = 10%, f = 10%, g = 70%, h = 35%, i = 0.1	7068	707	3074	195	$ 626	$ 14,630	**$ 15,256**
a = 3, b = 0%, c = 3, d = 10%, e = 10%, f = 10%, g = 70%, h = 100%, i = 0.1	7068	707	262	195	$ 680	$ 1,361	**$ 2,041**
a = 3, b = 0%, c = 3, d = 10%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0	7068	707	1560	0	$ 485	$ 7,421	**$ 7,905**
a = 3, b = 0%, c = 3, d = 10%, e = 10%, f = 10%, g = 70%, h = 70%, i = 0.2	7068	707	1560	390	$ 826	$ 7,550	**$ 8,376**

4.3.3 Stability and *In Vitro* Release of Hepatitis C Drugs from Coated Drug-Polycaprolactone Pills

Worldwide, more than 70 million people are living with chronic hepatitis C virus (HCV), and ~1.7 million more are infected every year (*240*). HCV infection causes inflammation of the liver and has been the main indication for liver transplantation (*241*, *242*). The recent introduction of direct-acting antivirals (DAAs) has resulted in major advances towards curing HCV (*243*). However, lack of medication adherence to the DAAs is a major barrier to successful HCV treatment and can increase the risk of developing drug resistance and death (*244–247*). Adherence levels are driven by a variety of factors, including access to medication, stigma associated with being treated, and the quantity and duration of the treatment regimen (*1*). Technologies that can reduce the frequency of dosing stand to have a significant impact in treating HCV if they are also preferred by patients and health care providers. Thus, there is a critical need for a GRS that can help patients adhere to HCV treatment.

Two of the main hepatitis C drugs were tested for stability in acid. Preliminary data shows that sofosbuvir is unstable in acid after 7 days, and daclatasvir degrades by ~30% after 21 days of incubation **(Figure 4.3)**. After investigating a panel of other hepatitis C drugs, acid instability concerns were overcome by formulating the drug in a polymer matrix as previously described for ivermectin, an antimalarial drug (*48*). These polymers include combinations of poly(ethers), poly(anhydrides), and poly(esters) and poly(siloxanes) (*32*, *49*). Release kinetics of sofosbuvir mixed in a PCL matrix can be tuned by varying the molecular weight of the PCL **(Figure 4.4)**.

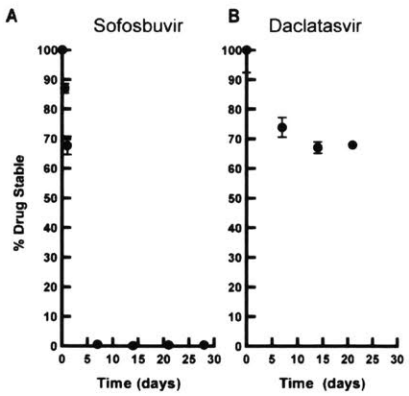


Figure 4.3: Stability of sofosbuvir and daclatasvir in acid.
HPLC Assessment of drug stability of sofosbuvir (A) and daclatasvir (B) in SGF (pH = 2). Error bars represent standard deviation for n=5 samples in each group.

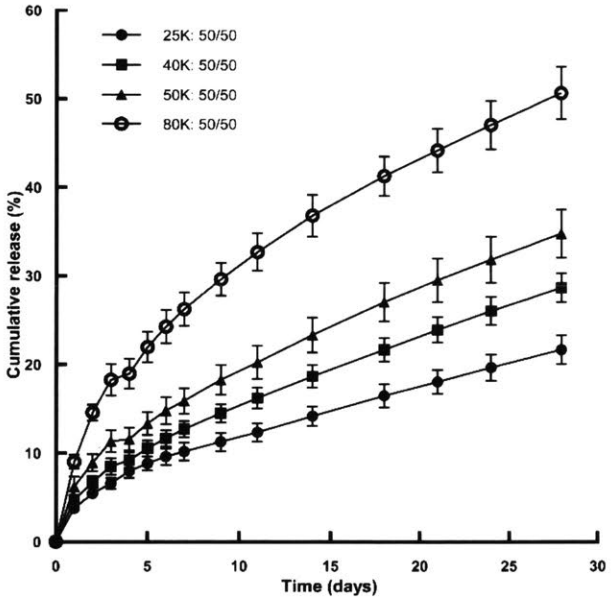


Figure 4.4: *In vitro* release profile of sofosbuvir from drug-PCL pill.
In vitro release of sofosbuvir from a drug pill in water with formulations including different molecular weights of PCL with drug to PCL ratio of 50:50 by weight.

4.4 Conclusion

The results shown here demonstrate the potential for translating the GRS for TB treatment as well as the ability of it to be used for other diseases, such as HCV. The field questionnaire highlights the importance of amplifying training of health care workers to deploy NG tubes safely so that the GRS can be implemented alongside DOTS interventions in the field where trained personnel are generally present (*248*, *249*). Because patients will be conscious during the NG tube procedure, they will be able to speak to a health care worker to ensure correct placement of the tube (*135*). One limitation of the field study is the incorporation of an NG tube description versus physical NG tube insertion into the questionnaire subjects. Although this questionnaire was administered to patients and health care providers with a comprehensive understanding of TB, ultimately, the physical discomfort of NG tube placement along with GRS retrieval requires further evaluation. The cost of this additional intervention as part of DOTS will need to be assessed in further fieldwork.

Chapter 5: Conclusions and Future Outlook

This work from this thesis has resulted in the first demonstration of a GRS capable of dosing grams of drugs. In Chapter 2, the design of a coiled nitinol wire in tubing was shown to safely reside in the gastric cavity of a swine model for at least 1 month with safe retrieval through the NG tube. Results from Chapter 3 demonstrated drug delivery of the GRS *in vitro* and *in vivo* for 1 month. Lastly, work in Chapter 4 highlighted potential for translation of the system from animals to use in humans.

Macrodevices consisting of multigram drug depots could have an impact across a range of diseases in addition to TB and could be coupled to other procedures such as endoscopy. Translation of this GRS will require further work on design, drug delivery, and social acceptability. Convergence of a variety of engineers with expertise in formulation development, manufacturing, and electronics will be critical to achieving the next steps. Specifically, designing a method for disintegration of the GRS without the need for retrieval stands to further improve adherence. Using an external magnet for this may be a promising approach. Formulations of drugs in polymer matrices will need to be optimized to maximize drug loading while achieving predictable pharmacokinetic profiles in the therapeutic range across many drugs. Other designs for pulsatile release can also enable new regimens of treating diseases. Lastly, electronics such as Bluetooth sensors and alcohol sensors can be attached to the GRS for communication with the patient or health care provider. The GRS has potential as a platform technology for improving medication adherence and thereby also improve outcomes for patients suffering from a myriad of diseases.

Appendix: Field Questionnaires in India

The following documents are included in this appendix:

1) Healthcare provider questionnaire (English)

2) Patient questionnaire (English)

3) Patient questionnaire (Hindi)

CONSENT TO PARTICIPATE IN INTERVIEW

Please read this form fully and consent where requested. You have been asked to participate in a study conducted by researchers at the Massachusetts Institute of Technology (M.I.T.) and Operation Asha in New Delhi. Insights gathered from you and other participants will be used in writing and publishing a paper and theses about patients with tuberculosis and healthcare providers who treat tuberculosis. Though direct quotes from you may be used in the paper with your permission, we will never ask you for your name or other identifying information. You were selected as a possible participant in this study because you are a healthcare provider who works with tuberculosis patients in India. You should read this information and ask questions about anything you do not understand before deciding whether or not to participate.

• This questionnaire is voluntary. You have the right not to answer any question, and to stop the questionnaire at any time or for any reason. In the event you choose to end the questionnaire, all information you provide will be deleted and omitted from the final paper. We expect that the questionnaire will take about 10-15 minutes.

• You will not be compensated for this questionnaire. You will receive no direct benefits from participating in this research study. However, your responses may help us learn more about developing drug delivery technologies for tuberculosis.

• If you have questions at any time about the study or the procedures, you may contact our research supervisor, Dr. Robert Langer via email at rlanger@mit.edu.

• This project will be completed by August 2018. All questionnaire responses will be stored securely.

I understand the procedures described above. My questions have been answered to my satisfaction, and I agree to participate in this study.

(Please check all that apply)

- ☐ **I have read the above information, and I voluntarily agree to participate.**
- ☐ **I am 18 years of age or older.**
- ☐ **I give permission for any direct quotes from in this questionnaire to be included in publications resulting from this study.**

If you feel you have been treated unfairly, or you have questions regarding your rights as a research subject, you may contact the Chairman of the Committee on the Use of Humans as Experimental Subjects, M.I.T., Room E25-143b, 77 Massachusetts Ave, Cambridge, MA, USA 02139, phone 1-617-253-6787.

For any questions about the questionnaire, please contact the study coordinators, Daniel Fulop (+91 98118 73418) or Malvika Verma (+91 70427 70938).

1. What is the name of the facility that you currently work in?

_____

2. What type of facility do you currently work in? Mark all that apply.

_____Sub Centre
_____Primary Health Centre
_____Community Health Centre
_____Sub-divisional Hospital
_____District Hospital
_____Tuberculosis Clinic
_____Tuberculosis Hospital
_____Medical College
_____Private Clinic
_____Mobile Clinic
_____Operation ASHA DOTS Clinic
_____Other: _____

3. How many patients do you see per working day? *Please provide a number estimate.*

_____ Less than 10
_____ 10-20
_____ 20-50
_____ 50-100
_____ More than 100

4. How many patients suffering from tuberculosis do you see per working day? *Please provide a number estimate.*

_____ Less than 10
_____ 10-20
_____ 20-50
_____ 50-100
_____ More than 100

5. How much time on average do you spend with a patient suffering from tuberculosis during a (non-diagnostic) visit? *Please provide a number estimate.*

_____ Less than 5 minutes
_____ 5-10 minutes
_____ 10-30 minutes
_____ 30-60 minutes
_____ More than 60 minutes

6. On average, how often do you see patients with tuberculosis?
_____ Every day
_____ 2-3 times a week
_____ Once a week
_____ Several times a month
_____ Once a month
_____ Once every 6 months or less often
_____ Never

7. Out of 100 patients, how many patients do you think miss a dose of their regimen?
_____ out of 100

8. Why do you think patients miss a dose of their regimen? *Mark all that apply.*
____ The patient suffers from side effects from the medication.
____ The patient feels that the medication does not work or the patient sees no effect from taking the medication.
____ The patient feels better and does not think he or she needs the medication.
____ The patient forgot to take the medication.
____ The patient moved or went to visit a different city and was unable to come to the clinic.
____ The patient feels a social stigma associated with taking the medication.
____ The patient is unable or does not want to come to the clinic.

If you selected "The patient is unable or does not want to come to the clinic," please continue to question 8A. Otherwise continue to question 8B.

8A. Why is the patient unable or why does the patient not want to come to the clinic?

_____

8B. Do you have any other reasons why patients might skip taking their medication?

_____

9. What can happen to patients who skip doses of tuberculosis medication? Mark all that apply.
____ They can get better.
____ They can stay sick and never get better.
____ They can infect others with tuberculosis.
____ It can be harder to treat tuberculosis in the future.
____ They can die.
____ Other: _____

10. If you had 100 rupees to help your patients adhere to treatment, how would you allocate it amongst the following programs? The total cost should add up to 100 rupees. Use integer numbers only.

_____ rupees to develop a medicine that can reduce number of times medication is taken: for example, only needing to take medication once a week or once a month, to replace the current 3-7 times a week.

_____ rupees to send reminders to patients to take their medication via cell phone call or SMS 3-7 times a week.

_____ rupees to send a healthcare worker or family member to the patient's home to remind them to take medication.

_____ rupees to provide a reward to patients if they take their medication.

We are developing solutions to provide anti-tuberculosis medication less frequently at the hospital. This would take the place of the patient coming to the tuberculosis clinic every day. We are working on different strategies to do this.

One strategy involves a Ryle's (nasogastric) tube placement for deployment of a drug delivery device with tuberculosis medication. Following deployment of the device, the Ryle's (nasogastric) tube can be removed in the same visit as deployment After all the medication has been released, the patient will return to the hospital for a new drug delivery device to be deployed via the Ryle's (nasogastric) tube.

11. Have you inserted a Ryle's (nasogastric) tube in a patient previously?

_____ Yes

_____ No

12. How many times have you placed a Ryle's (nasogastric) tube in a patient during the last year?

_____ 0

_____ 1-10 times

_____ 10-50 times

_____ 50-100 times

_____ 100-200 times

_____ More than 200 times

13. Do you agree or disagree with the following statements?
Agree____ or Disagree____ Ryle's (nasogastric) tubes can be used with patients infected with tuberculosis.
Agree____ or Disagree____ Our hospital (or clinic if *not* part of a hospital) places Ryle's (nasogastric) tubes.

If you selected Agree for "Our clinic/hospital places Ryle's (nasogastric) tubes," please continue to question 13A. Otherwise continue to question 14.

13A. Who is responsible for placing Ryle's (nasogastric) tubes in patients at your clinic/hospital?

_____ Medical student
_____ Medical intern/resident (MBBS/MD)
_____ Fellow (MBBS/MD)
_____ Attending/Consultant Generalist provider
_____ Attending/Consultant Specialist provider
_____ Attending/Consultant Infectious disease specialist provider
_____ Pharmacy Student
_____ Pharmacist (B-PHARMA)
_____ Nurse (GNM)
_____ Nurse (BSc.N)
_____ Nurse practitioner
_____ Medical Assistant
_____ Other: _____

14. Would you (or your staff) be able to place Ryle's (nasogastric) tubes to deliver a drug delivery device with tuberculosis medication?

_____ Yes
_____ No

15. Do you anticipate any challenges in providing these in your practice?

_____ No
_____ Yes

If you selected "Yes," what are the challenges? *Mark all that apply.*

_____ Ryle's (nasogastric) tube procedures will require training of myself and my clinical support staff.
_____ A Ryle's (nasogastric) tube procedure will take too long.
_____ Patients will not agree to the Ryle's (nasogastric) tube procedure.
_____ Other: _____

Additionally, we are exploring alternative methods that involve taking up to 30 large capsules in one visit to the hospital to deliver tuberculosis medication.

16. Would you (or your staff) be able to support the directly observed administration of these capsules?

_____ Yes
_____ No

17. Do you anticipate any challenges in providing these in your practice?

_____ No
_____ Yes

If you selected "Yes," what are the challenges? *Mark all that apply.*

_____ Direct observation of administering 30 large capsules will require training of myself and my clinical support staff.
_____ Direct observation of administering 30 large capsules will take too long.
_____ Patients will not agree to swallowing 30 large capsules in one visit.
_____ Other: _____

Another strategy we are exploring involves drinking 2 liters of water, which contains tuberculosis medication. The water and medication mixture would need to be administered during one visit to the hospital.

18. Would you (or your staff) be able to support the directly observed administration of 2 liters of water-medication mixture?

_____ Yes
_____ No

19. Do you anticipate any challenges in providing these in your practice?

_____ No
_____ Yes

If you selected "Yes," what are the challenges? *Mark all that apply.*

_____ Direct observation of administering 2 liters of the water-drug mixture will require training of myself and my clinical support staff.
_____ Direct observation of administering 2 liters of the water-drug mixture will take too long.
_____ Patients will not agree to drinking 2 liters of the water-drug mixture in one visit.
_____ Other: _____

20. Depending on the availability of these different methods, do you think patients suffering from tuberculosis would be willing to take their medication using any of these options? All the options would need to be directly observed at your clinic/hospital. **Check all that apply.**

_____ Swallowing 30 capsules
_____ Ryle's (nasogastric) tube
_____ Drinking 2 liters of water-drug mixture

If you selected "Swallowing 30 capsules," then go to 20A. If you selected "Ryle's (nasogastric) tube", then go to 20B. If you selected "Drinking 2 liters of water-drug mixture", then go to 20C.

20A. How many times do you believe patients would be willing to come to the tuberculosis clinic to swallow 30 capsules in 1 one visit?

_____ Once per week
_____ Twice per month
_____ Once per month
_____ Once every 2 months
_____ Once every 4 months

20B. How many times do you believe patients would be willing to come to the tuberculosis clinic to have a device inserted through the Ryle's tube?

_____ Once per week
_____ Twice per month
_____ Once per month
_____ Once every 2 months
_____ Once every 4 months

20C. How many times do you believe patients would be willing to come to the tuberculosis clinic to drink 2 liters of a water-drug mixture?

_____ Once per week
_____ Twice per month
_____ Once per month
_____ Once every 2 months
_____ Once every 4 months

Demographics:

21. Are you between the age of

_____18-24?
_____25-34?
_____35-44?
_____45-54?
_____55-64?
_____65-74?
_____75+?

22. What is your gender?

_____Male
_____Female
_____Other

23. What is your highest level of education?

_____Nursing degree (GNM, BSc.N, NP)
_____Professional degree (MBBS/MD)_____
_____Doctoral degree (PhD)_____

24. Which of the following best describes you:

_____ Medical student
_____ Medical intern/resident (MBBS/MD)
_____ Fellow (MBBS/MD)
_____ Attending/Consultant Generalist provider
_____ Attending/Consultant Specialist provider
_____ Attending/Consultant Infectious disease specialist provider
_____ Pharmacist (B-PHARMA)
_____ Nurse (GNM)
_____ Nurse (BSc.N)
_____ Nurse practitioner
_____ Medical Assistant
_____ Other: _____

25. How long have you worked on the treatment of tuberculosis?

_____Less than 1 year
_____1-5 years
_____6-10 years
_____11-15 years
_____More than 15 years

[Fill this out before each interview. The information below refers to the location of the hospital or clinic.]

Hospital/Clinic Name:
Interpreter's Name:
Date:

Before Consent:

Have you already been surveyed?
_____ Yes
_____ No

[If subject answers No, then continue with consent form.]

Before Interview:

[Ensure subject agrees to participate in the interview by reading the lines below:]

CONSENT TO PARTICIPATE IN INTERVIEW

You have been asked to participate in a research study conducted by researchers at the Massachusetts Institute of Technology (M.I.T.) and Operation Asha in New Delhi. We have come here to understand your experience at the clinic today. Insights gathered from you and other participants will be used in writing and publishing a paper and theses about patients with tuberculosis and doctors who treat tuberculosis. Though direct quotes from you may be used in the paper with your permission, we will never ask you for your name or other identifying information. You were selected as a possible participant in this study because you are a patient at a tuberculosis clinic in India. You should listen to this information and ask questions about anything you do not understand before deciding whether or not to participate.

• This interview is voluntary. You have the right not to answer any question, and to stop the interview at any time or for any reason. In the event you choose to end the interview, all information you provide will be deleted and omitted from the final paper. We expect that the interview will take about 10-15 minutes.

• You will not be compensated for this interview, and what you say or do will not affect your treatment in any way.

• This project will be completed by August 2018. All questionnaire responses will be stored securely.

Please respond True or False to each option below:

[ ] You understand the procedures described above. Your questions have been answered to your satisfaction, and you agree to participate in this study.

[ ] You are 18 years of age or older.

[ ] You give permission for any direct quotes from this interview to be included in publications resulting from this study.

[Ensure subject responds True to all three statements and then take their fingerprint as evidence of consent:]

If you feel you have been treated unfairly, or you have questions regarding your rights as a research subject, you may contact the Chairman of the Committee on the Use of Humans as Experimental Subjects, M.I.T., Room E25-143b, 77 Massachusetts Ave, Cambridge, MA, USA 02139, phone 1-617-253-6787

We will now begin the interview. Any answers you provide will not affect your treatment. Please be honest with your answers, as this will support us in our research on tuberculosis to help patients.

Interview:

1. Are you at the clinic today to receive treatment for tuberculosis?

_____ Yes

_____ No

[If subject answers Yes, then continue to question 2. Otherwise say: "Thank you very much" and stop the survey.]

2. Why are you at the tuberculosis clinic today?

_____Directly observed treatment

_____Routine monitoring

_____Had side effects from treatment

_____Other_____

3. How much time did you spend commuting to the tuberculosis clinic today?

_____Less than 10 minutes

_____10-30 minutes

_____30-60 minutes

_____60-90 minutes

_____More than 90 minutes→ About how long?_____

4. How much did it cost to commute to the tuberculosis clinic today?

_____Zero rupees

_____1-10 rupees

_____10-50 rupees

_____50-100 rupees

_____100-300 rupees

_____300-500 rupees

_____More than 500 rupees→ About how much?_____

5. Did you have to miss work/school or arrange for paid child care to come to the tuberculosis clinic today?

_____Yes: Work_____ School____ Childcare____

_____No:

_____Not Applicable

6. Respond True____ or False____ or Not sure____for the following statements:

True____ or False____ or Not Sure___Tuberculosis is caused by bacteria.

True____ or False____ or Not Sure___ Tuberculosis is directly caused by smoking.

True____ or False____ or Not Sure____Tuberculosis directly causes lung cancer.

True____ or False____ or Not Sure___ Tuberculosis can be cured.

7. Out of 100 patients with tuberculosis, how many do you think miss a dose of their regimen?
_____ out of 100

8. Thinking about a time or times you missed a dose of your tuberculosis medication, please respond True or False:
[Change first person to 3rd person]

True____ or False____ I missed a dose because I suffered from side effects from the medication.
True____ or False____ I missed a dose because I feel that the medication does not work or I see no effect from taking the medication.
True____ or False____ I missed a dose because I felt better and did not think I needed the medication.
True____ or False____ I missed a dose because I forgot to take my medication.
True____ or False____ I moved or went to visit a different city and was unable to come to the clinic.
True____ or False____ I missed a dose because I came to the clinic, but there was nobody here to give me my treatment.
True____ or False____ I was unable or did not want to come to the clinic.

[If subject answers True to "I was unable or did not want to come to the clinic", then go to 8A. Otherwise, go to 8B.]

8A. Why were you unable or why did you not want to come to the clinic?

_____

8B. Do you have any other reasons why you might be unable to take your medication?

_____

9. What can happen to people with tuberculosis who skip doses of tuberculosis medication? Respond True or False or Not Sure:

True____ or False____or Not sure____They can get better.
True____ or False____ or Not sure____They can stay sick and never get better.
True____ or False____ or Not sure____They can infect others with tuberculosis.
True____ or False____ or Not sure____It can be harder to treat tuberculosis in the future.
True____ or False____ They can die.

10. Respond True or False if you think the following solutions would help you follow a treatment regimen.

True____ or False____ Reduce number of times medication is taken: for example, only needing to take medication once a week or once a month, to replace the current 3-7 times/week treatment. The medicine would still be just as effective, you would simply need to take it less frequently. The total treatment period remains the same.
True____ or False____ Send reminders to take medication via a cell phone call or SMS 3-7 times a week.
True____ or False____ Have a healthcare worker or family member come to your home to remind you take medication.
True____ or False____ Provide a reward to you if you take your medication.

We are developing solutions so that you can get medicine less frequently at the hospital. For example, you can go to the hospital once a week, once every 2 weeks, or once a month at a hospital. This would take the place of going to the tuberculosis clinic every day and save you time and money. We have different strategies to do this:

(A) One involves swallowing 30 large capsules in one visit to the hospital.
[Show jar with 30 "000" size capsules]

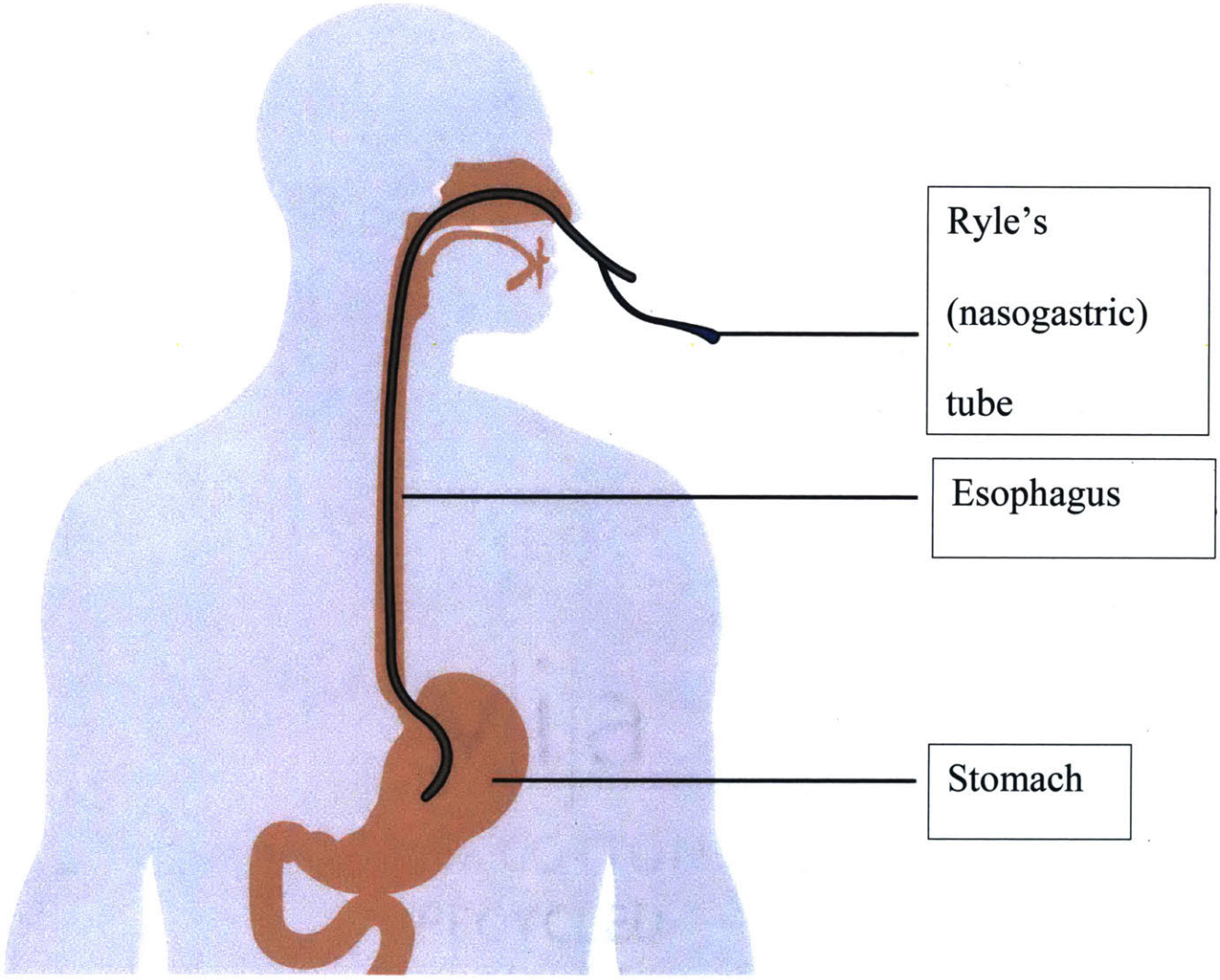
(B) Another involves the use of a Ryle's (nasogastric) tube to deploy a device containing your tuberculosis medication.
[Remove Ryle's (nasogastric) tube from package and show it to patient. Do not give it to them until later.]
This is how a Ryle's (nasogastric) tube works: First the doctor will put on a pair of clean gloves. Then the doctor will explain the Ryle's (nasogastric) tube procedure to you. The doctor will apply xylocaine jelly, a local anesthetic, to prevent pain and make sure the Ryle's (nasogastric) tube passes through your nose into your stomach. The xylocaine jelly will be applied to the tube and act as a lubricant.
[Show picture 1]
Then the tube is inserted through one nostril into the nose as shown here. The end of the tube travels all the way into the stomach as shown in this picture.
[Show picture 2]
Ryle's (nasogastric) tubes are commonly used for feeding and administering drugs when patients cannot swallow. The device containing your tuberculosis medicine will be inserted into the Ryle's (nasogastric) tube and deployed into the stomach. Following deployment of the device, the Ryle's (nasogastric) tube can be removed during the same visit to the hospital, so the whole procedure will last less than 10 minutes.

So, a doctor at a hospital will deploy a device through a Ryle's (nasogastric) tube into the stomach. This device will gradually release your medication. After all the medication has been

released, you will return to the hospital and have a Ryle's (nasogastric) tube placed again to remove the device and put in a new device for the next round of medication.

Here is a Ryle's (nasogastric) tube.
[Give subject the Ryle's (nasogastric) tube to hold.]

Picture 1



Picture 2
Attributed to Cancer Research UK
(https://commons.wikimedia.org/wiki/File:Diagram_showing_the_position_of_a_nasogastric_tube_CRUK_340.svg), https://creativecommons.org/licenses/by-sa/4.0/legalcode

(C) Another strategy involves drinking 2 liters of water, which contains the drug. The water-drug mixture would need to be swallowed in one visit to the hospital.
[Show one 2L bottle of Bisleri.]

11. Depending on the availability of these different methods, would you be willing to do any of these options? All of these options would be directly observed at the tuberculosis clinic. Respond Yes if you are willing and No if you are unwilling.
[Read out all options to subject and show pictures of the options. Mark which ones they are willing.]

Yes____ or No____

[If subject answers "Yes" then check boxes below.]

11A.

_____ Swallowing 30 capsules
_____ Ryle's (nasogastric) tube
_____ Drinking 2 liters of water-drug mixture

[If subject answers "Swallowing 30 capsules", then go to 11A. If subject answers "Ryle's (nasogastric) tube", then go to 11B. If subject answers "Drinking 2 liters of water-drug mixture", then go to 11C.]

11A_1. How many times would you be willing to come to the tuberculosis clinic to swallow 30 capsules in 1 one visit?

_____ Once per week
_____ Twice per month
_____ Once per month
_____ Once every 2 months
_____ Once every 4 months

11A_2. How many times would you be willing to come to the tuberculosis clinic to have a device inserted through the Ryle's tube?

_____ Once per week
_____ Twice per month
_____ Once per month
_____ Once every 2 months
_____ Once every 4 months

11A_3. How many times would you be willing to come to the tuberculosis clinic to drink 2 liters of a water-drug mixture?

_____ Once per week
_____ Twice per month
_____ Once per month

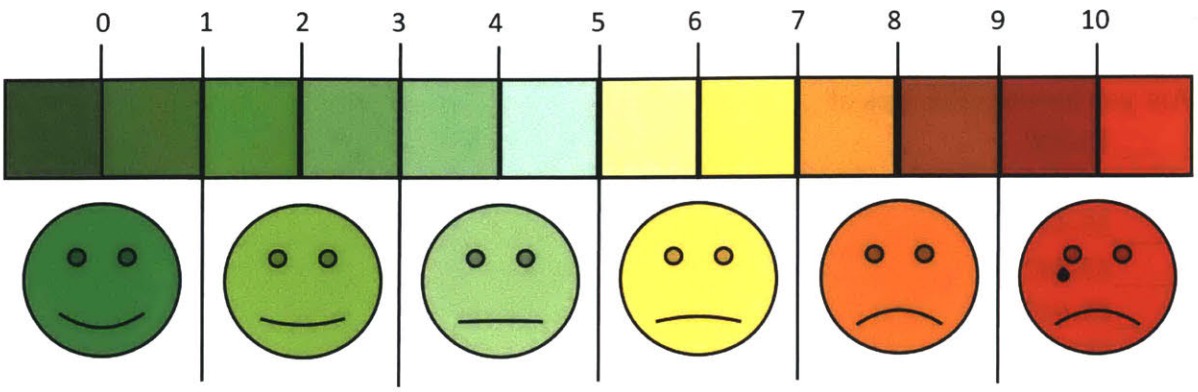
_____ Once every 2 months
_____ Once every 4 months

12. Have you ever had a Ryle's (nasogastric) tube placed in your stomach?
_____ Yes
_____ No
_____ Don't know/don't remember

13. On this scale, how would you perceive the discomfort of a Ryle's (nasogastric) tube placement? _____
[Show Picture 3 and have subject point to number on scale.]

14. On this scale, how would you perceive the discomfort of swallowing all 30 capsules in this jar in 1 visit to the hospital? _____
[Show Picture 3 and have subject point to number on scale.]

15. On this scale, how would you perceive the discomfort of drinking 2 liters of water in 1 visit to the hospital? _____
[Show Picture 3 and have subject point to number on scale.]



Picture 3: Visual Analog Scale

Demographics:

16. Are you between the ages of
_____18-24?
_____25-34?
_____35-44?
_____45-54?
_____55-64?
_____55-64?
_____65-74?
_____75+

17. What is your gender?
_____Male
_____Female
_____Other

18. What is your highest current level of education?
_____No formal education
_____1st-5th standard
_____6th-8th standard
_____ 9th-10th standard
_____11-12th standard
_____Bachelor
_____Master
_____Professional degree
_____Doctoral degree

19. What is your level of employment?
_____Employed for wages
_____Self-employed
_____Out of work and looking for work
_____Out or work but not currently looking for work
_____Homemaker
_____Student
_____Retired
_____Other

20. How many hours do you work (or go to classes) in a day?
_____ Hours per day

21. How many days do you work (or go to classes) in a week?
_____ Days per week

22. How often do you come to the clinic per week?
_____1X a week
_____2X a week
_____3X a week
_____4X a week
_____5X a week
_____6X a week
_____Every day
_____I come once every 2 weeks.
_____I come around once per month or less frequently.

23. In a typical visit, how much time passes from when you enter the clinic to when you leave the clinic?
_____Less than 10 minutes
_____10-30 minutes
_____30-60 minutes
_____More than 60 minutes→ About how long?_____

24. Is there anything else you would like to tell me about your experience at the clinic?

स्थानीय भाषा (हिंदी) के प्रत्यक्ष साक्षात्कार में प्रयोग किये जाने हेतु

प्रत्येक साक्षात्कार के पहले इसे जरूर भरें. नीचे दी गयी सूचना चिकित्सालय या क्लीनिक के स्थान के बारे में है .

ग्रामीण क्षेत्र या शहर

जिला

निकटतम शहर

राज्य

अस्पताल/ क्लीनिक का नाम

प्रशासक का नाम

दिनांक

अनुमति लेने के पहले

क्या आप इस सर्वेक्षण में पहले ही भाग ले चुके हैं?

हाँ_____

नहीं_____

(अगर प्रतिभागी नहीं में उत्तर देता है तब सहमति की प्रक्रिया आगे बढ़ाएं.)

साक्षात्कार के पहले

{सुनिश्चित करें कि अनुभागी साक्षात्कार से पहले निम्नलिखित बातों से सहमत हो }

आप से एक ऐसे शोध का हिस्सा बनने के लिए सहमति मांगी गयी है जो मेसाचुसेट्स इंस्टिट्यूट ऑफ़ टेक्नोलॉजी एवं ऑपरेशन आशा के खोजकर्ता द्वारा नयी दिल्ली में संचालित किया जा रहा है. हम आज यहाँ आपके क्लीनिक के अनुभवों को जानने के लिए आये हैं.आपके व अन्य अनुभागियों के अनुभवों का प्रयोग 'तपेदिक (टी.बी.) के रोगियों और इसका इलाज करने वाले डॉक्टर के बारे में खोजपत्र लिखने और प्रकाशित करने में किया जायेगा. यद्यपि आपकी कही हुई प्रत्यक्ष बातों का उल्लेख आपकी अनुमति से खोजपत्र में किया जा सकता है लेकिन आपका नाम और आपसे जुडी किसी पहचान के बारे में हम नहीं पूछेंगे. आपको इस कार्य के लिए चुना गया है क्योंकि आप टी.बी. के रोगी हैं और भारत के ट्यूबरक्लोसिस क्लीनिक में इलाज करा रहे हैं. आप को यह सूचना ध्यान से सुननी चाहिए और भाग लेने से पहले जो भी आपको न समझ में आ रहा हो उसके बारे में सवाल पूछ सकते हैं.

यह एक ऐच्छिक साक्षात्कार है.आपको किसी भी प्रश्न का उत्तर न देने का अधिकार है,और आप इस साक्षात्कार को किसी भी समय किसी भी कारण से छोड़ सकते हैं. अगर आप साक्षात्कार छोड़ने का निर्णय लेते हैं तो आपके द्वारा दी गयी सारी जानकारी को अंतिम खोजपत्र में से हटा दिया जायेगा. इस साक्षात्कार में 10 से 15 मिनट का समय लगने की संभावना है.

इस साक्षात्कार के लिए आपको कोई भुगतान नहीं किया जायेगा, और आप जो भी कहेंगे या करेंगे उसका आपके इलाज पर कोई प्रभाव नहीं पड़ेगा.

यह प्रोजेक्ट अगस्त 2018 तक पूरा हो जायेगा . सभी प्रश्नसूचि के उत्तरों को सुरक्षित करके रखा जायेगा.

कृपया नीचे दिए गए विकल्पों का हाँ या नहीं में उत्तर दें.

- आप ऊपर बताई गयी पूरी प्रक्रिया को समझ गए हैं.आपके प्रश्नों का संतुष्ट उत्तर आपको मिल गया है, और आप इस शोध में भाग लेने के लिए तैयार हैं.
- आप 18 साल या इससे ज्यादा उम्र के हैं.
- आप हमें इस साक्षात्कार में आपके द्वारा कही गयी किसी भी प्रत्यक्ष उक्ति को शोधपत्र में शामिल करने की अनुमति देते हैं.

(सुनिश्चित करें की अनुभागी सभी तीन बयानों के हाँ में जवाब दे और इसके बाद सहमति पत्र पर अनुभागी के अंगूठे का निशान लें.)

अगर आपको लगता है की आपके साथ सही व्यवहार नहीं किया गया या अगर आपके खोज विषय से जुड़े कुछ प्रश्न हैं तो आप "मानवों के प्रयोगात्मक विषय की तरह प्रयोग समिति" के चेयरमैन, एम् आई टी , कमरा संख्या E- 25 - 143B , 77 मेसाचुसेट्स एव, कैंब्रिज, USA 02139, फोन– 1-617-253-6787 से संपर्क कर सकते हैं.

अब हम इस कार्य की शुरुआत करेंगे. आपका दिया हुआ कोई भी उत्तर आपके इलाज को प्रभावित नहीं करेगा. कृपया ईमानदारी से उत्तर दें क्योंकि ये उत्तर टी.बी. रोगियों की मदद के लिए किये जा रहे हमारे खोज में मददगार होंगे.

साक्षात्कार

1- क्या आप आज टी.बी. के इलाज के लिए क्लीनिक आये हैं ?

हाँ-------

नहीं --------

(अगर अनुभागी का उत्तर हाँ में है तभी साक्षात्कार आगे बढ़ाएं वरना " धन्यवाद" कह कर सर्वेक्षण यही रोक दें.)

2- आप आज टी.बी. क्लीनिक में क्यों आये हैं ?

- प्रत्यक्ष इलाज के लिए: (DOTS) के लिये
- सामान्य निगरानी के लिए
- इलाज से हुए दुष्प्रभाव कि वजह से
- अन्य

3- आपको टी.बी. क्लीनिक तक आने में आज कितना समय लगा?

----------10 मिनट से कम

----------10 से 30 मिनट तक

----------30 से 60 मिनट तक

----------60 से 90 मिनट तक

----------90 मिनट से ज्यादा ----- लगभग कितना समय ?

4- टी.बी. क्लीनिक तक आने में आज आपका कितना खर्च हुआ?

---------- 0 रुपये

---------- 1 तो 10 रुपये

---------- 10 से 50 रुपये

---------- 50 से 100 रुपये

---------- 100 से 300 रुपये.

---------- 300 से 500 रुपये.

---------- 500 से अधिक ----- लगभग कितने रुपये?

5- क्या आपको टी.बी. क्लीनिक आने के लिए अपना काम/स्कूल छोड़ना पड़ता है या फिर बच्चे की देखभाल के लिए पैसे देने होते हैं ?

---------- हाँ: काम_____ स्कूल_____ बच्चे की देखभाल _____

---------- नहीं

---------- लागू नहीं होता.

6- नीचे दिए गए वाक्यों का सही___ या गलत____में उत्तर दें:

सही ____ या गलत _____ टी.बी. जीवाणु से होने वाली बीमारी है.

सही ____ या गलत _____ धूम्रपान करने से तपेदिक (टी.बी.) होता है.

सही ____ या गलत _____ टी.बी. से फेफड़ों का कैंसर होता है.

सही ____ या गलत _____ टी.बी. ठीक हो सकता है.

7- आपके अनुमान से प्रति सौ रोगियों में से कितने रोगियों की अपनी दवा की डोज़ छूट जाती होगी?

100 में से _____

8- आपने जब जब अपनी दवा की डोज़ छोड़ी है तब का ध्यान करते हुए इन सवालों के सही या गलत में उत्तर दीजिये :

सही_____ या गलत _____ दवा के दुष्प्रभाव के कारण आपने एक डोज़ छोड़ी थी.

सही_____ या गलत _____ आपने डोज़ छोड़ी क्योंकि मुझे लगा कि दवा काम नहीं कर रही है और मुझे इससे कोई फायदा नहीं हो रहा.

सही_____ या गलत _____ आपने दवा कि डोज़ छोड़ी क्योंकि मुझे लगा कि मैं बेहतर महसूस कर रहा हूँ और अब मुझे दवा कि जरुरत नहीं है.

सही_____ या गलत _____ आपने दवा कि डोज़ छोड़ी क्योकि मैं दवा लेना भूल गया/गयी था/थी.

सही_____ या गलत _____ मैं शहर से बाहर था/ थी और क्लीनिक पर नहीं आ पाया/पायी.

सही_____ या गलत _____ आपने डोज़ छोड़ी क्योकि मैं क्लीनिक पर आया लेकिन यहाँ कोई दवा देने वाला नहीं था.

सही_____ या गलत _____ मैं क्लीनिक नहीं आ पाया या नहीं आना चाहता था.

{अगर अनुभागी " मैं क्लीनिक नहीं आ पाया या नहीं आना चाहता था" का उत्तर हाँ में दे तो 8 A पर जाएँ. वरना 8 B पर जाएँ.}

8 A . आप क्लीनिक क्यों नहीं आ पाए या क्यों नहीं आना चाहते थे?

_____

8 B क्या कोई और कारण भी है जिसकी वजह से आप अपनी दवा नहीं ले पाए?

_____

9- जो रोगी टी.बी. की दवा की खुराक लेने में लापरवाही करते हैं उनके साथ क्या हो सकता है? सही या गलत में जवाब दें.

सही _____ गलत _____ वो ठीक हो सकते हैं.

सही _____ गलत _____ वो हमेशा बीमार रहेंगे और कभी ठीक नहीं होंगे.

सही _____ गलत _____ वे टी.बी.रोग से अन्य लोगों को संक्रमित कर सकते हैं.

सही _____ गलत _____ भविष्य में उनके टी. बी. का इलाज और कठिन हो सकता है.

सही _____ गलत _____ वे मर सकते हैं.

10- सही या गलत में जवाब दें अगर आपको लगता है की नीचे दिए गए विकल्प इलाज प्रक्रिया को सही तरीके से पूरा करने में मदद करेंगे.

सही_____ गलत _____ दवा लेने की समय या वक़्त घटाई जाये. उदाहरण के लिए, सप्ताह में 3 से 7 बार की जगह, सप्ताह में एक बार या महीने में एक बार ही दवा लेनी हो. दवा तब भी उतनी ही प्रभावी होगी, बस आपको इसे कम बार लेना होगा. पूरे इलाज का समय पहले जैसा रहेगा.

सही_____ गलत _____ हफ्ते में 3-4 बार मोबाइल फोन पर कॉल के द्वारा या मोबाइल संदेशों के द्वारा दवा लेना याद दिलाया जाये.

सही_____ गलत _____ सही तरीके और समय से दवा लेने पर इनाम दिया जाना चाहिए.

सही_____ गलत _____ हमारी तरफ से कोई आदमी आये या आपकी फॅमिली मैं से कोई आपके घर पर याद दिलाये की दवाई ले लीजिये

हम ऐसे समाधान विकसित कर रहे हैं जिससे आपको अस्पताल में दवा कम बार लेनी पड़े. उदाहरण के लिए आपको सप्ताह में एक बार, दो सप्ताह में एक बार या महीने में एक बार ही अस्पताल जाना पड़े. इससे आपको तपेदिक (टी.बी.) क्लीनिक रोज नहीं जाना पड़ेगा और समय की बचत होगी.

ऐसा करने के लिए हमारे पास कई योजनाएं हैं.

A - आपको 30 बड़े कैप्सूल पहली विजिट में निगलने होंगे.

(000 साइज के ३० कैप्सूल दिखाएँ)

B - दूसरे तरीके में राईल (नैसोगैसट्रिक) नलिका द्वारा टी बी की दवा की निर्धारित खुराक आपके शरीर में रखी जाये.

(पैकेज से राईल नलिका निकल कर रोगी को दिखाएँ. अभी उन्हें दे नहीं)

राईल नलिका इस प्रकार से काम करती है: पहले डॉक्टर हाथों में साफ़ दस्ताने पहनेगा. फिर डॉक्टर राईल नलिका प्रयोग करने की प्रक्रिया आपको बताएगा. डॉक्टर ज़ाईलोकेन जेली जो की एक दवा है, नलिका पर लगाएगा जिससे रोगी को किसी प्रकार के दर्द का अनुभव न हो. यह जेली जहाँ लगाते हैं वह हिस्सा कुछ देर के लिए सुन्न हो जाता है और नलिका आराम से आपके पेट तक पहुंच जाती है. यह जेली नलिका पर लगायी जाती है और चिकना करने का काम भी करती है.

{चित्र 1 दिखाएँ}

इसके बाद ये नाली आपके एक नासिका छिद्र से अंदर डाली जाएगी जैसा यहाँ दिखाया गया है. नली का एक सिरा आपके आमाशय पहुंचेगा.

{दूसरा चित्र दिखाएँ}

राईल नलिका तब प्रयोग की जाती है जब रोगी निगलने में असमर्थ होता है. तब इस नलिका के सहारे उसे खाना और दवाएं दी जाती हैं. वो यन्त्र जिसमे टी बी की दवा रखी जाती है उसे इस नलिका के प्रयोग से रोगी के पेट तक पहुँचाया जाता है. दवा यन्त्र पेट तक पहुँचाने और नलिका को हटाने का काम अस्पताल की एक ही विजिट में पूरा किया जा सकता है. इस तरह से इस पूरी प्रक्रिया में 10 मिनट से भी कम समय लगता है.

डॉक्टर दवा का यन्त्र राईल नलिका की मदद से रोगी के आमाशय में स्थापित कर देता है. यह यन्त्र आपकी दवा धीरे धीरे शरीर में छोड़ता है.जब सारी दवा आपके शरीर में पहुँच जाती है तब आपको

दोबारा अस्पताल आना होता है और राईल नलिका द्वारा दोबारा दवा यन्त्र स्थापित करने की प्रक्रिया करानी होती है.

यह राईल नैसोगैसट्रिक नलिका है

{ रोगी को राईल नैसोगैसट्रिक नलिका पकड़ने दें}

स- इससे अलग एक और तरीका है जिसमे २ लीटर पानी पीना होता है जिसमे दवा मिली होती है. ये दवा और पानी का पूरा मिश्रण एक ही अस्पताल विजिट में पीना होता है.

{ बिसलेरी की 2 लीटर की बोतल दिखाएँ)

11- उपलब्ध विकल्पों के अनुसार ,क्या आप इन विकल्पों में से कोई अपनाना चाहेंगे? ये सभी विकल्प ,टी.बी क्लीनिक की निगरानी में सम्पन्न किये जायेंगे.

अगर आप इन्हें अपनाना चाहते हैं तो " हाँ" में जवाब दें वरना "नहीं" में.

{ सारे विकल्पों को रोगियों के सामने स्पष्ट आवाज़ में दोहराएं और उन्हें तस्वीरें दिखाएँ. उन्हें जो विकल्प चाहिए उसे चिन्हित करें.}

_____ 30 कैप्सूल्स निगलना

_____ राईल (नैसोगैस्ट्रिक) नलिका का प्रयोग

_____ दवा और पानी का मिश्रण 2 लीटर पीना.

{अगर रोगी उत्तर देता है "30 कैप्सूल्स निगलना" तब 11 A पर जाएँ. अगर रोगी उत्तर देता है "राईल (नैसोगैस्ट्रिक) नलिका का प्रयोग " तब 11 B पर जाएँ. अगर रोगी उत्तर देता है "दवा और पानी का मिश्रण 2 लीटर पीना" तब 11 C पर जाएँ}

11 A- एक बार में 30 कैप्सूल्स निगलने के लिए आप टी.बी क्लीनिक पर कितनी बार आना चाहेंगे?

_____ एक सप्ताह में एक बार

_____ महीने में दो बार

_____ महीने में एक बार

_____ दो महीने में एक बार

_____ चार महीने में एक बार

11 B- राईल नलिका के प्रयोग से दवा का यन्त्र स्थापित करने के लिए आप टी.बी.क्लीनिक कितनी बार आना चाहेंगे?

_____ एक सप्ताह में एक बार

_____ महीने में दो बार

_____ महीने में एक बार

_____ दो महीने में एक बार

_____ चार महीने में एक बार

11 C- 2 लीटर दवा और पानी का मिश्रण पीने के लिए आप टी.बी.क्लीनिक कितनी बार आना चाहेंगे?

_____ एक सप्ताह में एक बार

_____ महीने में दो बार

_____ महीने में एक बार

_____ दो महीने में एक बार

_____ चार महीने में एक बार

12- क्या आप के पेट में कभी राईल (नैसोगैस्ट्रिक) नलिका डाली गयी है?

_____हाँ

_____ नहीं

_____ पता नहीं/ याद नहीं.

13- इस पैमाने पर, असुविधा के स्तर के अनुसार आप राईल नैसोगैस्ट्रिक नलिका को आप कौन सा स्थान देना चाहेंगे? _____

{चित्र ३ दिखाएँ और अनुभागी को पैमाने पर संख्या चिन्हित करने दें.}

14- इस पैमाने पर, असुविधा के स्तर के अनुसार आप एक बार में ३० कैप्सूल्स निगलने की असुविधा को कौन सा स्थान देना चाहेंगे?_____

{चित्र 3 दिखाएँ और अनुभागी को पैमाने पर संख्या चिन्हित करने दें.}

15- इस पैमाने पर, असुविधा के स्तर के अनुसार आप एकबार में 2 लीटर पानी पीने की असुविधा को आप कौन सा स्थान देना चाहेंगे? _____

जनसांख्यिकीय

_____

16- आपकी उम्र क्या है?

_____ 18 से 24 ?

_____ 25 से 34?

_____ 35 से 44?

_____ 45 से 54 ?

_____ 55 से 64?

_____ 65 से 74?

_____ 75+

17- आप कौन से लिंग से सम्बंधित हैं ?

_____ पुरूष

_____ महिला

_____ अन्य

18- आपकी पढाई का उच्चतम स्तर क्या है?

_____ कोई औपचारिक शिक्षा नहीं

_____ 1 से 5 कक्षा

_____ 6 से 8 कक्षा

_____ 9 से 10 कक्षा

_____ 11 से 12 कक्षा

_____ स्नातक_____

_____ परास्नातक _____

_____ प्रोफेशनल उपाधि_____

_____ डॉक्टरेट उपाधि _____

19- आपके रोजगार का स्तर क्या है?

मासिक वेतन पर रोजगार _____

स्वरोजगार _____

बेरोजगार और काम की तलाश जारी _____

बेरोजगार लेकिन काम की तलाश नहीं _____

घर की देख भाल_____

छात्र_____

सेवानिवृत्त _____

अन्य _____

20- आप एक दिन में कितने घंटे काम/ पढाई करते हैं?

_____ घंटे प्रतिदिन

21- आप एक सप्ताह में कितने दिन काम/ पढाई के लिए खर्च करते हैं?

_____ दिन प्रति सप्ताह

22-आप क्लीनिक पर एक सप्ताह में कितनी बार आते हैं?

_____ एक सप्ताह में एक बार

_____ एक सप्ताह में दो बार

_____ एक सप्ताह में तीन बार

_____ एक सप्ताह में चार बार

_____ एक सप्ताह में पांच बार

_____ एक सप्ताह में छह बार

_____ प्रतिदिन

_____ दो सप्ताह में एक बार

_____ महीने में एक बार या उससे भी कम

23- एक सामान्य विजिट में क्लीनिक में आने से लेकर क्लीनिक से जाने के बीच में आपका कितना समय लगता है?

_____ 10 मिनट से कम

_____ 10 से 30 मिनट

_____30 से 60 मिनट

_____60 मिनट से ज्यादा--- लगभग कितना समय?_____

24- क्या आप अपने क्लीनिक के अनुभव के बारे में हमे कुछ बताना चाहते हैं?

_____

References

1. E. Sabaté, "Adherence to Long-Term Therapy: Evidence for action" (Geneva, Switzerland, 2003), (available at http://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf).
2. E. Sabaté, "Adherence to Long-term Therapies: Policy for Action" (Geneva, Switzerland, 2001).
3. M. T. Brown, J. K. Bussell, Medication adherence: WHO cares? *Mayo Clin. Proc.* **86**, 304–314 (2011).
4. J. K. Aronson, Compliance, concordance, adherence. *Br. J. Clin. Pharmacol.* **63**, 383–384 (2007).
5. L. Osterberg, T. Blaschke, O. L., B. T., Adherence to medication. *N. Engl. J. Med.* **353**, 487–497 (2005).
6. A. O. Iuga, M. J. McGuire, Adherence and health care costs. *Risk Manag. Healthc. Policy*. **4**, 34–44 (2014).
7. D. M. Cutler, W. Everett, Thinking outside the pillbox - Medication adherence as a priority for health care reform. *N. Engl. J. Med.* **362**, 1553–1555 (2010).
8. C. E. Orfanos, From Hippocrates to modern medicine. *J. Eur. Acad. Dermatology Venereol.* **21**, 852–858 (2007).
9. M. J. Stirratt *et al.*, Self-report measures of medication adherence behavior: recommendations on optimal use Michael. *Transl. Behav. Med.* **5**, 470–482 (2015).
10. L. L. Zullig, H. Bosworth, Engaging patients to optimize medication adherence. *NEJM Catal.* (2017), (available at https://catalyst.nejm.org/optimize-patients-medication-adherence/).
11. R. Nieuwlaat *et al.*, Interventions for enhancing medication adherence (Review). *Cochrane Database Syst. Rev.* (2014),

doi:10.1002/14651858.CD000011.pub4.www.cochranelibrary.com.

12. G. Traverso, R. Langer, Perspective: Special delivery for the gut. *Nature*. **519**, S19 (2015).

13. H. Kishimoto, M. Maehara, Compliance and persistence with daily, weekly, and monthly bisphosphonates for osteoporosis in Japan: analysis of data from the CISA. *Arch. Osteoporos.* **10**, 1–6 (2015).

14. S. D. Saini, P. Schoenfeld, K. Kaulback, M. C. Dubinsky, Effect of medication dosing frequency on adherence in chronic diseases (Structured abstract). *Am. J. Manag. Care*. **15**, e22–e33 (2009).

15. A. J. Claxton, J. Cramer, C. Pierce, B. A, A systematic review of the associations between dose regimens and medication compliance. *Clin. Ther.* **23**, 1296–1310 (2001).

16. K. Park, The controlled drug delivery systems: Past Forward and Future Back. *J. Control. Release*. **190**, 3–8 (2014).

17. A. C. Anselmo, S. Mitragotri, An overview of clinical and commercial impact of drug delivery systems. *J. Control. Release*. **190**, 15–28 (2014).

18. A. C. Anselmo, Y. Gokarn, S. Mitragotri, Non-invasive delivery strategies for biologics. *Nat. Rev. Drug Discov.* (2018), doi:10.1038/nrd.2018.183.

19. S. Ummadi, B. Shravani, N. G. R. Rao, M. S. Reddy, B. Sanjeev, Overview on controlled release dosage form. *Int. J. Pharma Sci.* **3**, 258–269 (2013).

20. R. Langer, New methods of drug delivery. *Science (80-.).* **249**, 1527–1534 (1990).

21. J. M. Byers, What Is a therapeutic range? *Lab. Med.* **11**, 784–787 (1980).

22. J. T. Santini, A. C. Richards, R. Scheidt, M. J. Cima, R. Langer, Microchips as controlled drug-delivery devices. *Angew. Chemie - Int. Ed.* **39**, 2396–2407 (2000).

23. S. Arora, J. Ali, A. Ahuja, S. Baboota, J. Qureshi, Pulsatile drug delivery systems: An approach for controlled drug delivery. *Indian J. Pharm. Sci.*, 295–300 (2006).

24. T. Bussemer, I. Otton, R. Bodmeier, Pulsatile Drug-Delivery Systems. *Crit. Rev. Ther.*

Drug Carrier Syst. **18**, 433–458 (2001).

25. D. Jain, R. Raturi, V. Jain, P. Bansal, R. Singh, Recent technologies in pulsatile drug delivery systems. *Biomatter.* **1**, 57–65 (2011).

26. J. T. Santini, M. J. Cima, R. Langer, A controlled-release microchip. *Nature.* **397**, 335–338 (1999).

27. C. Alvarez-lorenzo, A. Concheiro, Smart drug delivery systems: from fundamentals to the clinic. *Chem. Commun.* **50**, 7743–7765 (2014).

28. D. Liu, F. Yang, F. Xiong, N. Gu, The smart drug delivery system and its clinical potential. *Theranostics.* **6**, 1306–1323 (2016).

29. O. S. Fenton, K. N. Olafson, P. S. Pillai, M. J. Mitchell, R. Langer, Advances in biomaterials for drug delivery. *Adv. Mater.* **1705328**, 1–29 (2018).

30. M. W. Tibbitt, J. E. Dahlman, R. Langer, Emerging frontiers in drug delivery. *J. Am. Chem. Soc.* **138**, 704–717 (2016).

31. G. Benagiano, H. Gabelnick, I. Brosens, Long-acting hormonal contraception. *Women's Heal.* **11**, 749–757 (2015).

32. A. Mashak, A. Rahimi, Silicone polymers in controlled drug delivery systems: A review. *Iran. Polym. J.* **18**, 279–295 (2009).

33. J. M. Anderson, M. S. Shive, Biodegradation and biocompatibility of PLA and PLGA microspheres. *Adv. Drug Deliv. Rev.* **28**, 5–24 (2012).

34. J. Kost, R. Langer, Responsive polymer systems for controlled delivery of therapeutics. *Trends Biotechnol.* **10**, 127–131 (1992).

35. R. Farra *et al.*, First-in-human testing of a wirelessly controlled drug delivery microchip. *Sci. Transl. Med.* **4**, 1–8 (2012).

36. C. G. Wilson, in *Controlled Release in Oral Drug Delivery*, C. G. Wilson, P. J. Crowley, Eds. (Springer US, Boston, MA, 2011; https://doi.org/10.1007/978-1-4614-1004-1_2), pp. 27–48.

37. B. G. Meerveld, A. C. Johnson, D. Grundy, in *Gastrointestinal Pharmacology. Handbook of Experimental Pharmacology* (2017), pp. 1–16.

38. M. Ruiz, Diagram of a human digestive system (2006), (available at https://en.wikipedia.org/wiki/File:Digestive_system_diagram_edit.svg).

39. M. R. Phillips, S. Zaheer, G. T. Drugas, Gastric trichobezoar: case report and literature review. *Mayo Clin. Proc.* **73**, 653–656 (1998).

40. S. Palmisano *et al.*, Intragastric balloon device: Weight loss and satisfaction degree. *Obes. Surg.* **26**, 2131–2137 (2016).

41. S. R. Kethu *et al.*, Endoluminal bariatric techniques. *Gastrointest. Endosc.* **76**, 1–7 (2012).

42. U. K. Mandal, B. Chatterjee, F. G. Senjoti, Gastro-retentive drug delivery systems and their in vivo success: A recent update. *Asian J. Pharm. Sci.* **11**, 575–584 (2016).

43. A. Streubel, J. Siepmann, R. Bodmeier, Gastroretentive drug delivery systems. *Expert Opin. Drug Deliv.* **3**, 217–233 (2006).

44. A. K. Nayak, R. Maji, B. Das, Gastroretentive drug delivery systems: A review. *Asian J. Pharm. Clin. Res.* **3**, 2–10 (2010).

45. R. Talukder, R. Fassihi, Gastroretentive delivery systems: a mini review. *Drug Dev. Ind. Pharm.* **30**, 1019–1028 (2004).

46. D. H. Altreuter *et al.*, Changing the pill: developments toward the promise of an ultra-long-acting gastroretentive dosage form. *Expert Opin. Drug Deliv.* **15**, 1189–1198 (2018).

47. S. Zhang *et al.*, A pH-responsive supramolecular polymer gel as an enteric elastomer for use in gastric devices. *Nat. Mater.* **14**, 1065–1071 (2015).

48. A. M. Bellinger *et al.*, Oral, ultra–long-lasting drug delivery: Application toward malaria elimination goals. *Sci. Transl. Med.* **8**, 1–12 (2016).

49. A. R. Kirtane *et al.*, Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy. *Nat. Commun.* **9**, 1–12 (2018).

50. J. Liu *et al.*, Triggerable tough hydrogels for gastric resident dosage forms. *Nat. Commun.* **8**, 124 (2017).

51. A. Hayward *et al.*, Scalable gastric resident systems for veterinary application. *Sci. Rep.* **8**, 1–10 (2018).

52. Y. L. Kong *et al.*, 3D-Printed gastric resident electronics. *Adv. Mater. Technol.* **4**, 1–11 (2019).

53. V. D. Prajapati, G. K. Jani, T. a. Khutliwala, B. S. Zala, Raft forming system - An upcoming approach of gastroretentive drug delivery system. *J. Control. Release.* **168**, 151–165 (2013).

54. M. J. Ferrua, R. P. Singh, Modeling the fluid dynamics in a human stomach to gain insight of food digestion. *J. Food Sci.* **75**, 151–162 (2010).

55. K. Schulze, Imaging and modelling of digestion in the stomach and the duodenum. *Neurogastroenterol. Motil.* **18**, 172–183 (2006).

56. B. Laulicht, A. Tripathi, V. Schlageter, P. Kucera, E. Mathiowitz, Understanding gastric forces calculated from high-resolution pill tracking. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 8201–8206 (2010).

57. Y.-A. L. Lee, S. Zhang, J. Lin, R. Langer, G. Traverso, A Janus Mucoadhesive and Omniphobic Device for Gastrointestinal Retention. *Adv. Healthc. Mater.* **5**, 1141–1146 (2016).

58. R. Cargill *et al.*, Controlled gastric emptying. 1. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs. *Pharm. Res.* **5**, 533–536 (1988).

59. N. Salessiotis, Measurement of the diameter of the pylorus in man. Part I. Experimental project for clinical application. *Am. J. Surg.* **124**, 331–333 (1972).

60. "Lyndra" (2018).

61. R. Kanasty *et al.*, A pharmaceutical answer to nonadherence: Once weekly oral

memantine for Alzheimer's disease. *J. Control. Release.* **303**, 34–41 (2019).

62. T. M. Daniel, The history of tuberculosis. *Respir. Med.* **100**, 1862–1870 (2006).

63. M. S. Vasava *et al.*, Drug development against tuberculosis: Past, present and future. *Indian J. Tuberc.* **64**, 252–275 (2017).

64. J. Frith, History of tuberculosis. Part 1 – Phthisis, consumption and the White Plague. *J. Mil. Veterans. Health.* **22**, 29–35 (2014).

65. M. Reid *et al.*, The Lancet Commission on tuberculosis: building a tuberculosis-free world. *Lancet.* **391**, 1132–1133 (2019).

66. T. M. Daniel, P. A. Iversen, Hippocrates and tuberculosis. *Int. J. Tuberc. Lung Dis.* **19**, 373–374 (2015).

67. Tuberculosis. *Nat. Rev. Dis. Prim.* **2** (2016), doi:10.1038/nrdp.2016.77.

68. R. Jain *et al.*, *Novel Nanotechnology Based Delivery Systems for Chemotherapy and Prophylaxis of Tuberculosis* (Elsevier Inc., 2018; https://linkinghub.elsevier.com/retrieve/pii/B9780128133514000341).

69. LabCE, Pathogenesis of Tuberculosis (TB) Infection, (available at https://www.labce.com/spg631661_pathogenesis_of_tuberculosis_tb_infection.aspx).

70. World Health Organization, "Global Tuberculosis Report 2018" (Geneva, Switzerland, 2018), (available at http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf).

71. World Health Organization, "Global Tuberculosis Report 2018" (Geneva, Switzerland, 2018), (available at http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf?ua=1).

72. J. Y. Kim, A. Shakow, A. Castro, C. Vande, P. Farmer, The burden of tuberculosis: Economic burden (2). *Tuberc. Control* (2003), (available at http://www.who.int/trade/distance_learning/gpgh/gpgh3/en/index7.html).

73. G. A. Roth *et al.*, Global, regional, and national age-sex-specific mortality for 282 causes

of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* **392**, 1736–1788 (2018).

74. J. O'Neill, "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations" (London, United Kingdom, 2016), (available at https://amr-review.org/sites/default/files/160518_Final paper_with cover.pdf).

75. "The Price of a Pandemic: Counting the cost of MDR-TB" (London, United Kingdom, 2015), (available at https://docs.wixstatic.com/ugd/309c93_f0731d24f4754cd4a0ac0d6f6e67a526.pdf).

76. J. Furin, H. Cox, M. Pai, Tuberculosis. *Lancet.* **6736**, 1–15 (2019).

77. ClinicalTrials.gov, (available at https://clinicaltrials.gov/).

78. S. Gupta, V. Kakkar, Recent technological advancements in tuberculosis diagnostics – A review. *Biosens. Bioelectron.* **115**, 14–29 (2018).

79. N. Arinaminpathy, D. Dowdy, Understanding the incremental value of novel diagnostic tests for tuberculosis. *Nature.* **528**, S60–S67 (2015).

80. C. N. Paramasivan *et al.*, Laboratory diagnosis of tuberculosis in resource-poor countries: Challenges and opportunities. *Clin. Microbiol. Rev.* **24**, 314–350 (2011).

81. E. W. Tiemersma, M. J. van der Werf, M. W. Borgdorff, B. G. Williams, N. J. D. Nagelkerke, Natural history of tuberculosis: Duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: A systematic review. *PLoS One.* **6** (2011), doi:10.1371/journal.pone.0017601.

82. L. C. du Toit, V. Pillay, M. P. Danckwerts, Tuberculosis chemotherapy: current drug delivery approaches. *Respir. Res.* **7**, 118 (2006).

83. D. Mitchison, G. Davies, The chemotherapy of tuberculosis: past, present and future. *Int. J. Tuberc. Lung Dis.* **16**, 724–732 (2012).

84. World Health Organization, "Treatment of tuberculosis: guidelines - 4th edition." (Geneva, Switzerland, 2010), (available at

http://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf).

85. M. R. Shaik, M. Korsapati, D. Panati, Polymers in controlled drug delivery systems. *Int. J. Pharma Sci.* **2**, 112–116 (2012).

86. C. Mc Caffrey, O. Chevalerias, C. O'Mathuna, K. Twomey, Swallowable-capsule technology. *IEEE Pervasive Comput.* **7**, 23–29 (2008).

87. P. Y. Kulkarni *et al.*, Non-adherence of new pulmonary tuberculosis patients to anti-tuberculosis treatment. *Ann. Med. Health Sci. Res.* **3**, 67–74 (2013).

88. "WHO Tuberculosis Programme: Framework for Effective Tuberculosis Control" (Geneva, Switzerland, 1994), (available at http://apps.who.int/iris/bitstream/handle/10665/58717/WHO_TB_94.179.pdf).

89. J. Karumbi, P. Garner, Directly observed therapy for treating tuberculosis. *Cochrane Database Syst. Rev.*, 1–56 (2015).

90. M. Gninafon *et al.*, Outcome of tuberculosis retreatment in routine conditions in Cotonou, Benin. *Int. J. Tuberc. Lung Dis.* **8**, 1242–1247 (2004).

91. G. E. Erhabor, O. Adewole, A. O. Adisa, O. A. Olajolo, Directly observed short course therapy for tuberculosis - a preliminary report of a three-year experience in a teaching hospital. *J. Natl. Med. Assoc.* **95**, 1082–1088 (2003).

92. E. Rutta *et al.*, Treatment outcome among Rwandan and Burundian refugees with sputum smear-positive tuberculosis in Ngara, Tanzania. *Int. J. Tuberc. Lung Dis.* **5**, 628–632 (2001).

93. D. K. Lewis *et al.*, Clinical indicators of mycobacteraemia in adults admitted to hospital in Blantyre, Malawi. *Int. J. Tuberc. Lung Dis.* **6**, 1067–1074 (2002).

94. M. R. Joseph, R. A. Thomas, S. Nair, S. Balakrishnan, S. Jayasankar, Directly observed treatment short course for tuberculosis. What happens to them in the long term? *Indian J. Tuberc.* **62**, 29–35 (2015).

95. S. Benbaba *et al.*, Direct observation (DO) for drug-resistant tuberculosis: Do we really

do? *PLoS One*. **10**, 1–14 (2015).

96. A. Asuquo Otu, Is the directly observed therapy short course (DOTS) an effective strategy for tuberculosis control in a developing country? *Asian Pac J Trop Dis*. **3**, 227–231 (2013).

97. M. Z. Imperial *et al.*, A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat. Med.* **24**, 1 (2018).

98. G. Fochsen, K. Deshpande, K. C. Ringsberg, A. Thorson, Conflicting accountabilities: Doctor's dilemma in TB control in rural India. *Health Policy (New. York).* **89**, 160–167 (2009).

99. R. Steffen *et al.*, Patients' costs and cost-effectiveness of tuberculosis treatment in dots and non-dots facilities in Rio de Janeiro, Brazil. *PLoS One*. **5**, 1–7 (2010).

100. C. M. Wright, L. Westerkamp, S. Korver, C. C. Dobler, Community-based directly observed therapy (DOT) versus clinic DOT for tuberculosis: A systematic review and meta-analysis of comparative effectiveness. *BMC Infect. Dis.* **15**, 1–11 (2015).

101. A. Toczek, H. Cox, P. du Cros, G. Cooke, N. Ford, Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta- analysis. *Int. J. Tuberc. Lung Dis.*, 299–307 (2012).

102. World Health Organization, "Implementing the End TB Strategy: The Essentials" (Geneva, Switzerland, 2015), , doi:10.1017/CBO9781107415324.004.

103. R. Prasad, N. Gupta, A. Banka, Rapid diagnosis and shorter regimen for multidrug-resistant tuberculosis: A priority to improve treatment outcome. *Lung India*. **34**, 1–2 (2017).

104. Q. Liu *et al.*, Reminder systems to improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment. *Cochrane Database Syst. Rev.*, 1–59 (2014).

105. E. E. Lutge, C. S. Wiysonge, S. E. Knight, D. Sinclair, J. Volmink, Incentives and enablers to improve adherence in tuberculosis. *Cochrane Database Syst. Rev.*, 1–51 (2015).

106. E. Dolgin, Long-acting HIV drugs advanced to overcome adherence challenge. *Nat. Med.* **20**, 323–324 (2014).

107. R. Pandey, S. Sharma, G. K. Khuller, Oral solid lipid nanoparticle-based antitubercular chemotherapy. *Tuberculosis*. **85**, 415–420 (2005).

108. R. Pandey, G. K. Khuller, Solid lipid particle-based inhalable sustained drug delivery system against experimental tuberculosis. *Tuberculosis*. **85**, 227–234 (2005).

109. J. Cohen, Approval of Novel TB Drug Celebrated-With Restraint. *Science (80-.).* **339** (2013), p. 130.

110. World Health Organization, "Fixed-dose combinations for the treatment of TB in children" (Geneva, Switzerland, 2018), (available at http://www.who.int/tb/areas-of-work/children/).

111. E. Lopez-Varela *et al.*, Adherence to Childhood Tuberculosis Treatment in Mozambique. *J. Trop. Pediatr.* **63**, 87–97 (2017).

112. P. Clayden *et al.*, "2016 Pipeline Report HIV & TB" (2016), (available at http://i-base.info/htb/wp-content/uploads/2016/07/2016-Pipeline-Report.pdf).

113. J. Furin, M. Tommasi, A. J. Garcia-Prats, Drug-resistant tuberculosis: will grand promises fail children and adolescents ? *Lancet Child Adolesc. Heal.* **2**, 237–238 (2018).

114. E. P. Harausz *et al.*, New and repurposed drugs for pediatric multidrug-resistant tuberculosis practice-based recommendations. *Am. J. Respir. Crit. Care Med.* **195**, 1300–1310 (2017).

115. M. Verma, J. Furin, R. Langer, G. Traverso, Making the case: developing innovative adherence solutions for the treatment of tuberculosis. *BMJ Glob. Heal.* **4**, e001323 (2019).

116. Q. Bassat, B. Ogutu, A. DJimde, K. Stricker, K. Hamed, Development of a pediatric formulation for treatment of P. Falciparum malaria: Coartem (artemether-lumefantrine) Dispersible. *Malar. J.* **13**, P7 (2014).

117. S. Salman, D. Bendel, T. C. Lee, D. Templeton, T. M. E. Davis, Pharmacokinetics of a

novel sublingual spray formulation of the antimalarial drug artemether in healthy adults. *Antimicrob. Agents Chemother.* **59**, 3208–3215 (2015).

118. M. F. Gomes *et al.*, Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet.* **373**, 557–566 (2009).

119. N. Ibrahim *et al.*, Artemisinin nanoformulation suitable for intravenous injection: Preparation, characterization and antimalarial activities. *Int. J. Pharm.* **495**, 671–679 (2015).

120. D. A. Margolis *et al.*, Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet.* **390**, 1499–1510 (2017).

121. R. P. Bakshi *et al.*, Long-acting injectable atovaquone nanomedicines for malaria prophylaxis. *Nat. Commun.* **9**, 1–8 (2018).

122. M. Kovarova *et al.*, Ultra-long-acting removable drug delivery system for HIV treatment and prevention. *Nat. Commun.* **9** (2018), doi:10.1038/s41467-018-06490-w.

123. C. Y. X. Chua *et al.*, Transcutaneously refillable nanofluidic implant achieves sustained level of tenofovir diphosphate for HIV pre-exposure prophylaxis. *J. Control. Release.* **286**, 315–325 (2018).

124. E. O. V. Id *et al.*, Optimizing the immunogenicity of HIV prime-boost DNA-MVA-rgp140/GLA vaccines in a phase II randomized factorial trial design. *PLoS One.* **13**, 1–19 (2018).

125. Y. Nakatani *et al.*, Intrathecal isoniazid for refractory tuberculous meningitis with cerebral infarction. *Intern. Med.* **56**, 953–957 (2017).

126. R. T. Ahern, G. P. Arden, Intra-articular streptomycin in tuberculosis of the knee. *Br. Med. J.* **1**, 466–468 (1952).

127. L. Garcia-Contreras *et al.*, Immunization by a bacterial aerosol. *Proc. Natl. Acad. Sci.* **105**, 4656–4660 (2008).

128. A. S. Ham *et al.*, In vitro and ex vivo evaluations on transdermal delivery of the HIV inhibitor IQP-0410. *PLoS One*. **8**, 1–11 (2013).

129. Y. Shahzad, S. Sohail, M. S. Arshad, T. Hussain, S. N. H. Shah, Development of solid dispersions of artemisinin for transdermal delivery. *Int. J. Pharm.* **457**, 197–205 (2013).

130. C. Burger *et al.*, Formulation of natural oil nano-emulsions for the topical delivery of clofazimine, artemisone and decoquinate. *Pharm. Res.* **35** (2018), doi:10.1007/s11095-018-2471-9.

131. J. M. Baeten *et al.*, Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *Obstet. Gynecol. Surv.* **71**, 466–468 (2016).

132. M. Verma *et al.*, A gastric resident drug delivery system for prolonged gram-level dosing of tuberculosis treatment. *Sci. Transl. Med.* **11**, 1–8 (2019).

133. H. Lee, M. J. Cima, An intravesical device for the sustained delivery of lidocaine to the bladder. *J. Control. Release*. **149**, 133–9 (2011).

134. H. B. Gilbert, R. J. Webster III, Rapid, reliable shape setting of superelastic nitinol for prototyping robots. *IEEE Robot. Autom. Lett.* **1**, 98–105 (2016).

135. T. W. Thomsen, R. W. Shaffer, G. S. Setnik, Nasogastric intubation. *N. Engl. J. Med.* **354**, e16 (2006).

136. K.-S. Choi, X. He, V. C.-L. Chiang, Z. Deng, A virtual reality based simulator for learning nasogastric tube placement. *Comput. Biol. Med.* **57**, 103–15 (2015).

137. K. Choi, X. He, V. C. L. Chiang, Z. Deng, J. Qin, A heuristic force model for haptic simulation of nasogastric tube insertion using fuzzy logic. *IEEE Trans. Haptics*. **9**, 295–310 (2016).

138. M. Tarnoff, S. Shikora, A. Lembo, Acute technical feasibility of an endoscopic duodenal-jejunal bypass sleeve in a porcine model: A potentially novel treatment for obesity and type 2 diabetes. *Surg. Endosc. Other Interv. Tech.* **22**, 772–776 (2008).

139. Y. Mintz *et al.*, Hybrid natural orifice translumenal surgery (NOTES) sleeve gastrectomy:

A feasibility study using an animal model. *Surg. Endosc. Other Interv. Tech.* **22**, 1798–1802 (2008).

140. S. C. Becerra, D. C. Roy, C. J. Sanchez, R. J. Christy, D. M. Burmeister, An optimized staining technique for the detection of Gram positive and Gram negative bacteria within tissue. *BMC Res. Notes.* **9**, 1–10 (2016).

141. R. D. Cardiff, C. H. Miller, R. J. Munn, Manual hematoxylin and eosin staining of mouse tissue sections. *Cold Spring Harb. Protoc.* **2014**, 655–658 (2014).

142. E. Machytka *et al.*, Elipse, a procedureless gastric balloon for weight loss: A proof-of-concept pilot study. *Obes. Surg.* **26**, 512–516 (2016).

143. B. Medical, Levin Tubes, (available at https://www.crbard.com/medical/en-US/Products/Levin-Tubes#SpecificationTable).

144. M. D. Hager, S. Bode, C. Weber, U. S. Schubert, Shape memory polymers: Past , present and future developments. *Prog. Polym. Sci.* **49–50**, 3–33 (2015).

145. A. Lendlein, S. Kelch, Shape-Memory Polymers. *Angew. Chem. Int. Ed.* **41**, 2034–2057 (2002).

146. G. L. Fatiha El Feninat M. Fiset, Diego Mantovani *et al.*, Shape memory materials for Biomedical applications. *Av. Eng. Mater.* **2648**, 91–104 (2002).

147. S. O. Ikenberry *et al.*, Management of ingested foreign bodies and food impactions. *Gastrointest. Endosc.* **73**, 1085–1091 (2011).

148. Saint-Gobain Performance Plastics, Tygon ND 100-65 Medical Tubing (2011) (available at https://www.usplastic.com/catalog/files/specsheets/TYGON_ND_100-65.pdf).

149. Zeus, THV, doi:10.1007/978-3-662-03760-7_3.

150. A. Maiguy-Foinard, N. Blanchemain, C. Barthélémy, B. Décaudin, P. Odou, Influence of a double-lumen extension tube on drug delivery: Examples of isosorbide dinitrate and diazepam. *PLoS One.* **11** (2016), doi:10.1371/journal.pone.0154917.

151. M. Winterholler, F. J. Erbguth, Accidental pneumothorax from a nasogastric tube in a

patient with severe hemineglect: A case report. *Arch. Phys. Med. Rehabil.* **83**, 1173–1174 (2002).

152. B. K. Canales, D. Weiland, S. Reardon, M. Monga, Urethral catheter insertion forces: A comparison of experience and training. *Int. Braz J Urol.* **35**, 84–89 (2009).

153. N. Smaby *et al.*, Identification of key pinch forces required to complete functional tasks. *J. Rehabil. Res. Dev.* **41**, 215 (2004).

154. T. Duerig, A. Pelton, D. Stöckel, An overview of nitinol medical applications. *Mater. Sci. Eng. A.* **273–275**, 149–160 (1999).

155. E. H. Hall, On a New Action of the Magnet on Electric Currents. *Am. J. Math.* **2**, 287–292 (1879).

156. E. J. Urrutia *et al.*, Retractable-barb needle for breast lesion localization: Use in 60 cases. *Radiology*. **169**, 845–847 (1988).

157. S. Byun *et al.*, Barbed micro-spikes for micro-scale biopsy. *J. Micromechanics Microengineering*. **15**, 1279–1284 (2005).

158. K. F. Binmoeller *et al.*, Endoscopic snare excision of "giant" colorectal polyps. *Gastrointest. Endosc.* **43**, 183–8 (1996).

159. J. H. Mitchell, Fish hook with retractable barb (1990), , doi:10.1016/j.(73).

160. G. I. Peterson, A. V. Dobrynin, M. L. Becker, Biodegradable shape memory polymers in medicine. *Adv. Healthc. Mater.* **6**, 1–16 (2017).

161. P. T. Mather, X. Luo, I. A. Rousseau, Shape Memory Polymer Research. *Annu. Rev. Mater. Res.* **39**, 445–471 (2009).

162. Q. Zhao, H. J. Qi, T. Xie, Recent progress in shape memory polymer : New behavior , enabling materials , and mechanistic understanding. *Prog. Polym. Sci.* **49–50**, 79–120 (2015).

163. K. Sangeetha, S. Aisverya, J. K. Av, A. Sukumaran, S. Pn, Biodegradable shape memory polymers- A mini review. *Adv. Biotechnol. Microbiol.* **7** (2017),

doi:10.19080/AIBM.2017.07.555722.

164. R. Waksman, R. Pakala, Biodegradable and bioabsorbable stents. *Curr. Pharm. Des.* **16**, 4041–4051 (2011).

165. V. C. Sonawane, M. P. More, A. P. Pandey, P. O. Patil, P. K. Deshmukh, Fabrication and characterization of shape memory polymers based bioabsorbable biomedical drug eluting stent. *Artif. Cells, Nanomedicine Biotechnol.* **45**, 1740–1750 (2017).

166. M. Boncheva *et al.*, Magnetic self-assembly of three-dimensional surfaces from planar sheets. *Proc. Natl. Acad. Sci.* **102**, 3924–3929 (2005).

167. O. Anand, L. X. Yu, D. P. Conner, B. M. Davit, Dissolution testing for generic drugs: An FDA perspective. *AAPS J.* **13**, 328–335 (2011).

168. G. Golomb, P. Fisher, E. Rahamim, The relationship between drug release, particle size, and swelling of silicone matrices. *Scan. Electron Microsc.* **12**, 121–132 (1990).

169. C. Busatto, J. Pesoa, I. Helbling, J. Luna, D. Estenoz, Effect of particle size , polydispersity and polymer degradation on progesterone release from PLGA microparticles: Experimental and mathematical modeling. *Int. J. Pharm.* **536**, 360–369 (2018).

170. W. Chen, A. Palazzo, W. E. Hennink, R. J. Kok, The effect of particle size on drug loading and release kinetics of gefitinib-loaded PLGA microspheres. *Mol. Pharm.* **14**, 459–467 (2017).

171. E. N. & C. GmbH, EUDRAGIT ® RL 30D/RS 30D, 0–1.

172. S. Singh, T. T. Mariappan, N. Sharda, B. Singh, Degradation of rifampicin, isoniazid and pyrazinamide from prepared mixtures and marketed single and combination products under acid conditions. *Pharm. Pharmacol. Commun.* **6**, 491–494 (2000).

173. S. A. Benetton, E. R. M. Kedor-Hackmann, M. I. R. M. Santoro, V. M. Borges, Visible spectrophotometric and first-derivative UV spectrophotometric determination of rifampicin and isoniazid in pharmaceutical preparations. *Talanta.* **47**, 639–643 (1998).

174. Z. Jiang, H. Wang, D. C. Locke, Determination of ethambutol by ion-pair reversed phase liquid chromatography with UV detection. *Anal. Chim. Acta*. **456**, 189–192 (2002).

175. J. S. Nahrup, Z. M. Gao, J. E. Mark, A. Sakr, Poly(dimethylsiloxane) coatings for controlled drug release - Polymer modifications. *Int. J. Pharm.* **270**, 199–208 (2004).

176. L. Brannon-Peppas, Novel vaginal drug release applications. *Adv. Drug Deliv. Rev.* **11**, 169–177 (1993).

177. S. Thakral, N. K. Thakral, D. K. Majumdar, Eudragit®: a technology evaluation. *Expert Opin. Drug Deliv.* **10**, 131–149 (2013).

178. S. Singh, Neelam, S. Arora, Y. Singla, An overview of multifaceted significance of Eudragit polymers in drug delivery systems. *Asian J. Pharm. Clin. Res.* **8**, 1–6 (2015).

179. X. Huang, C. S. Brazel, On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. *J. Control. Release*. **73**, 121–136 (2001).

180. A. Akhgari, A. Tavakol, Prediction of optimum combination of Eudragit RS/Eudragit RL/Ethyl cellulose polymeric free films based on experimental design for using as a coating system for sustained release theophylline pellets. *Adv. Pharm. Bull.* **6**, 219–225 (2016).

181. F. Gonzalo, Ximena; Casali, Nicola; Broda, Agnieszka; Pardieu, Claire; Drobniewski, Combination of amikacin and doxycycline against multidrug-resistant and extensively drug-resistant tuberculosis. *Int. J. Antimicrob. Agents*. **45**, 406–412 (2015).

182. G. J. Fox, C. C. Dobler, B. J. Marais, J. T. Denholm, Preventive therapy for latent tuberculosis infection—the promise and the challenges. *Int. J. Infect. Dis.* **56**, 68–76 (2017).

183. C. Calvori, L. Frontali, L. Leoni, G. Tecce, Effect of rifamycin on protein synthesis. *Nature*. **207**, 417–418 (1965).

184. G. S. Timmins, V. Deretic, Mechanisms of action of isoniazid. *Mol. Microbiol.* **62**, 1220–1227 (2006).

185. M. Stehr, A. A. Elamin, M. Singh, Pyrazinamide: the importance of uncovering the mechanisms of action in mycobacteria. *Expert Rev. Anti. Infect. Ther.* **13**, 593–603 (2015).

186. R. Goude, A. G. Amin, D. Chatterjee, T. Parish, The Arabinosyltransferase EmbC is inhibited by ethambutol in Mycobacterium tuberculosis □. *Antimicrob. Agents Chemother.* **53**, 4138–4146 (2009).

187. E. C. Rivers, R. L. Mancera, New anti-tuberculosis drugs in clinical trials with novel mechanisms of action. *Drug Discov. Today.* **13**, 1090–1098 (2008).

188. N. E. Holmes, P. G. P. Charles, Safety and efficacy review of doxycycline. *Clin. Med. Ther.* **1**, 471–482 (2009).

189. T. Hanas, T. S. Sampath Kumar, G. Perumal, M. Doble, Tailoring degradation of AZ31 alloy by surface pre-treatment and electrospun PCL fibrous coating. *Mater. Sci. Eng. C.* **65**, 43–50 (2016).

190. N. Suharti *et al.*, Effect of bioblend polystyrene/polycaprolactone and polystyrene/starch utilization toward coating thickness and release of active substance from urea granule. *Der Pharma Chem.* **8**, 83–87 (2016).

191. Y. K. Kim *et al.*, Improvement of osteogenesis by a uniform PCL coating on a magnesium screw for biodegradable applications. *Sci. Rep.* **8**, 1–11 (2018).

192. M. Gimeno *et al.*, A controlled antibiotic release system to prevent orthopedic-implant associated infections: An in vitro study. *Eur. J. Pharm. Biopharm.* **96**, 264–271 (2015).

193. J. B. Dressman, G. L. Amidon, C. Reppas, V. P. Shah, Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms. *Pharm. Res.* **15**, 11–22 (1998).

194. J. Dressman, J. Kramer, *Pharmaceutical Dissolution Testing* (Taylor & Francis, Boca Raton, 2005).

195. W. Brown, S. Perivilli, D. Podolsky, E. S. Stippler, S. Walfish, The critical role of the USP

performance verification test in dissolution testing and qualification of the paddle apparatus. *Dissolution Technol.*, 6–12 (2019).

196. B. Brodin, B. Steffansen, C. U. Nielsen, in *Molecular Biopharmaceutics: Aspects of Drug Characterisation, Drug Delivery and Dosage form Evaluation* (London, 2010), pp. 135–152.

197. Y. Fu, W. J. Kao, Drug release kinetics and transport mechanisms from semi-interpenetrating networks of gelatin and poly(ethylene) glycol diacrylate. *Pharm. Res.* **26**, 2115–2124 (2009).

198. G. Dantas, M. O. A. Sommer, How to fight back against antibiotic resistance. *Am. Sci.* **102**, 42–51 (2014).

199. S. Kim, T. D. Lieberman, R. Kishony, Alternating antibiotic treatments constrain evolutionary paths to multidrug resistance. *Proc. Natl. Acad. Sci.* **111**, 14494–14499 (2014).

200. L. Imamovic, M. O. a Sommer, Use of collateral sensitivity networks to design drug cycling protocols that avoid resistance development. *Sci. Transl. Med.* **5**, 204ra132 (2013).

201. C. Pál, B. Papp, V. Lázár, Collateral sensitivity of antibiotic-resistant microbes. *Trends Microbiol.* **23**, 401–407 (2015).

202. V. Lázár *et al.*, Antibiotic-resistant bacteria show widespread collateral sensitivity to antimicrobial peptides. *Nat. Microbiol.* **3**, 718–731 (2018).

203. D. Nichol *et al.*, Antibiotic collateral sensitivity is contingent on the repeatability of evolution. *Nat. Commun.* **10** (2019), doi:10.1038/s41467-018-08098-6.

204. M. Rodriguez De Evgrafov, H. Gumpert, C. Munck, T. T. Thomsen, M. O. A. Sommer, Collateral resistance and sensitivity modulate evolution of high-level resistance to drug combination treatment in staphylococcus aureus. *Mol. Biol. Evol.* **32**, 1175–1185 (2015).

205. A. Fuentes-Hernandez *et al.*, Using a Sequential Regimen to Eliminate Bacteria at

Sublethal Antibiotic Dosages. *PLoS Biol.* **13**, 1–17 (2015).

206. V. Lázár *et al.*, Bacterial evolution of antibiotic hypersensitivity. *Mol. Syst. Biol.* **9**, 700 (2013).

207. M. H. Huang, S. Li, D. W. Hutmacher, J. Coudane, M. Vert, Degradation characteristics of poly(e-caprolactone)-based copolymers and blends. *J. Appl. Polym. Sci.* **102**, 1681–1687 (2006).

208. F. Von Burkersroda, L. Schedl, A. G??pferich, Why degradable polymers undergo surface erosion or bulk erosion. *Biomaterials*. **23**, 4221–4231 (2002).

209. D. S. Muggli, A. K. Burkoth, K. S. Anseth, Crosslinked polyanhydrides for use in orthopedic applications: Degradation behavior and mechanics. *J. Biomed. Mater. Res.* **46**, 271–278 (1999).

210. V. J. Sharma, P. D. Amin, Development of extended release matrices of rifampicin using hot melt extrusion technique. *J. Appl. Pharm. Sci.* **3**, 30–38 (2013).

211. D. R. Jaiswar, J. N. Pawar, P. D. Amin, Hot Melt Extrusion : Continuous Process of Preparation of Sustained Released Matrix Tablet by Using Hydroxypropylcellulose. **6** (2016).

212. D. Simon, A. Holland, R. Shanks, Poly(caprolactone) thin film preparation, morphology, and surface texture. *J. Appl. Polym.* **103**, 1287–1294 (2007).

213. A. Heimowska, M. Morawska, A. Bocho-Janiszewska, Biodegradation of poly(ε -caprolactone) in natural water environments. *Polish J. Chem. Technol.* **1**, 120–126 (2017).

214. H. Kathpalia, A. Gupte, An introduction to fast dissolving oral thin film drug delivery systems: A review. *Curr. Drug Deliv.* **10**, 667–684 (2013).

215. R. A. Khan, D. Dussault, S. Salmieri, A. Safrany, M. Lacroix, Mechanical and barrier properties of carbon nanotube reinforced PCL-based composite films: Effect of gamma radiation. *J. Appl. Polym. Sci.* **127**, 3962–3969 (2013).

216. Y. Xiao, S. Zhou, L. Wang, T. Gong, Electro-active shape memory properties of poly(ε-caprolactone)/functionalized multiwalled carbon nanotube nanocomposite. *ACS Appl. Mater. Interfaces.* **2**, 3506–3514 (2010).

217. A. C. Richards Grayson, M. J. Cima, R. Langer, Molecular release from a polymeric microreservoir device: Influence of chemistry, polymer swelling, and loading on device performance. *J. Biomed. Mater. Res. A.* **69**, 502–12 (2004).

218. A. C. R. Grayson *et al.*, Multi-pulse drug delivery from a resorbable polymeric microchip device. *Nat. Mater.* **2**, 767–772 (2003).

219. L. Lu, C. a. Garcia, A. G. Mikos, In vitro degradation of thin poly(DL-lactic-co-glycolic acid) films. *J. Biomed. Mater. Res.* **46**, 236–244 (1999).

220. A. C. R. Grayson, M. J. Cima, R. Langer, Size and temperature effects on poly(lactic-co-glycolic acid) degradation and microreservoir device performance. *Biomaterials*. **26**, 2137–2145 (2005).

221. H. K. Makadia, S. J. Siegel, Poly Lactic-co-Glycolic Acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers (Basel).* **3**, 1377–1397 (2011).

222. D. G. Anderson *et al.*, A combinatorial library of photocrosslinkable and degradable materials. *Adv. Mater.* **18**, 2614–2618 (2006).

223. D. M. Brey, J. L. Ifkovits, R. I. Mozia, J. S. Katz, J. A. Burdick, Controlling poly(B-amino ester) network properties through macromer branching. *Acta Biomater.* **4**, 207–217 (2008).

224. A. Lendlein, R. Langer, Biodegradable, Elastic Shape-Memory Polymers for Potential Biomedical Applications. *Science (80-.).* **296**, 1673–1676 (2002).

225. H. Kahn, M. A. Huff, A. H. Heuer, The TiNi shape-memory alloy and its applications for MEMS. *J. Micromechanics Microengineering*. **8**, 213–221 (1998).

226. S. M. Mirvakili, I. W. Hunter, A torsional artificial muscle from twisted nitinol microwire. *Proc. SPIE 10163, Electroact. Polym. Actuators Devices* (2017),

doi:10.1117/12.2261712.

227. C. Zanotti, P. Giuliani, A. Tuissi, S. Arnaboldi, R. Casati, Response of NiTi SMA wire electrically heated. *ESOMAT*, 1–7 (2009).

228. C. Hallin, Tablet Dispenser (2005).

229. C. J. Allina, Candy Dispenser (1993).

230. S. K. Acharyya, M. Mandal, Performance of EAs for four-bar linkage synthesis. *Mech. Mach. Theory.* **44**, 1784–1794 (2009).

231. X. Liu *et al.*, Ingestible hydrogel device. *Nat. Commun.* **10** (2019), doi:10.1038/s41467-019-08355-2.

232. D. Collins, H. Lam, F. Hafidz, J. Antipolo, P. Mangao, "Economic Cost of Non-Adherence to TB Medicines Resulting from Stock- Outs and Loss to Follow-Up in the Philippines. Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program" (Arlington, VA: Management Sciences for Health, 2016), (available at http://apps.who.int/medicinedocs/documents/s23230en/s23230en.pdf).

233. D. Collins, C. Njuguna, "The Economic Cost of Non-adherence to TB Medicines Resulting from Stock-outs and Loss to Follow-up in Kenya. Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program" (Arlington, VA: Management Sciences for Health, 2016), (available at http://siapsprogram.org/publication/altview/the-economic-cost-of-non-adherence-to-tb-medicines-resulting-from-stock-outs-and-loss-to-follow-up-in-kenya/english/).

234. A. Heemanshu, K. Satwanti, Determinants of lost to follow up during treatment among tuberculosis patients in delhi. *Int. J. Med. Res. Heal. Sci.* **5**, 145–152 (2016).

235. World Health Organization, "Global Tuberculosis Report 2017" (Geneva, Switzerland, 2017), , doi:WHO/HTM/TB/2017.23.

236. Y. V. Laurence, U. K. Griffiths, A. Vassall, Costs to health services and the patient of treating tuberculosis: A systematic literature review. *Pharmacoeconomics*. **33**, 939–955 (2015).

237. D. A. Scott, C. Reeves, E. M. Russell, M. Napper, "Eliciting public preferences for healthcare: A systematic review of techniques" (2001), , doi:10.3310/hta5050.

238. P. J. Neumann, G. D. Sanders, Cost-effectiveness analysis 2.0. *N. Engl. J. Med.* **376**, 203–205 (2017).

239. P. J. Neumann *et al.*, Future directions for Cost-effectiveness analyses in health and medicine. *Med. Decis. Mak.* **38**, 767–777 (2018).

240. World Health Organization, "Global Hepatitis Report, 2017" (2017), , doi:ISBN 978-92-4-156545-5.

241. G. M. Lauer, B. D. Walker, Hepatitis C virus infection. *N. Engl. J. Med.* **345**, 41–52 (2001).

242. C. W. Shepard, L. Finelli, M. J. Alter, Global epidemiology of hepatitis C virus infection. *Lancet Infect. Dis.* **5**, 558–67 (2005).

243. World Health Organization, "Progress Report on Access To Hepatitis C Treatment: Focus on Overcoming Barriers in Low-and Middle-Income Countries, March 2018" (Geneva, Switzerland, 2018), , doi:WHO/CDS/HIV/18.4.

244. T. A. Brennan, A. Lotvin, W. Shrank, "Analysis of 'Real World' Sovaldi® (sofosbuvir) Use and Discontinuation Rates" (2014), (available at https://cvshealth.com/sites/default/files/styles/SovaldiUseAndDiscontinuation_ResearchArticle_PDF.pdf).

245. J.-M. Pawlotsky, Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. *Gastroenterology*. **151**, 70–86 (2016).

246. J. Velloza, Adherence during antiviral treatment regimens for chronic hepatitis C: A qualitative study of patient-reported facilitators and barriers. *J. Clin. Gastroenterol.* **49**,

e41–e50 (2015).

247. A. Franciscus, "Adherence to HCV Therapy" (2015), (available at www.hcvadvocate.org).

248. R. Gai *et al.*, The role of village doctors on tuberculosis control and the DOTS strategy in Shandong Province, China. *Biosci. Trends.* **2**, 181–186 (2008).

249. N. Awofeso, I. Schelokova, A. Dalhatu, Training of front-line health workers for tuberculosis control: Lessons from Nigeria and Kyrgyzstan. *Hum. Resour. Health.* **6**, 1–9 (2008).