Design of a Large-Dose Drug Delivery Device for Tuberculosis

by

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ABSTRACT

Tuberculosis (TB) affects millions of people all over the world, and in India has an incidence figure of about 2.8 million individuals annually. The TB treatment regime is quite involved, generally requiring six months and multiple medications. A lack of medication adherence can lead to drug-resistant TB. One current method to improve adherence requires the medicine to be dispensed multiple times a week at directly observed treatment (DOT) clinics, a practice which is neither convenient for patients nor completely effective for purposes of adherence.

A suite of technologies is being developed to introduce a large-dose drug delivery device into the gastrointestinal (GI) tract. This device would release a discrete amount of drugs every day over the course of a month. The device would be deployed into the stomach through a short-term nasogastric tube placement, and the device would be removed and replaced with a new device after one month. The medication required for a month of treatment can be transferred into a drug delivery device in the stomach via a standard nasogastric tube. Testing conducted on this medication transportation process has showed that 1 month's worth of medication can be placed into a device in the stomach in 7 minutes. In addition to device design, a series of questionnaires are being implemented to ask TB doctors and patients about the feasibility and acceptability of short-term nasogastric tube usage for TB treatment. This device and treatment method has the potential to assist in eradicating TB and allow millions more convenient and effective TB treatment.

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Title: Walter M. May and A. Hazel May Professor of Mechanical Engineering
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Chapter 1 Introduction

1.1 Tuberculosis as a Disease

Tuberculosis is a widespread and potentially deadly infectious disease. Globally, tuberculosis is the ninth-highest cause of death, above even HIV/AIDS [1]. India is especially affected, with the number of new cases of active tuberculosis in India in 2016 at 2.79 million and a mortality rate of over 400,000 people in India annually [2].

Tuberculosis is a contagious bacterial disease that primarily affects the respiratory system. It is transmitted through the air through tiny droplets in the air, for example by coughs and sneezes. Tuberculosis can be either latent or active. An individual with latent tuberculosis is not contagious and has no symptoms, but the latent tuberculosis has the potential to at some point become active tuberculosis. Active tuberculosis is the contagious and symptomatic version of the disease. This thesis focuses on treating active tuberculosis, and hereafter in this thesis mention of “tuberculosis” refers to active tuberculosis unless otherwise specified. Symptoms of tuberculosis include coughing, chest pain, fever, weight loss, fatigue, and night sweats. While tuberculosis primarily harms the respiratory system, it can spread to affect other body parts such as the kidneys or spine. HIV/AIDS is a significant risk factor for tuberculosis, since HIV weakens the body’s immune system and makes the body more susceptible to other diseases [3].

1.2 Medication Adherence

One of the main barriers to eradicating tuberculosis (TB) is the issue of medication adherence. The TB treatment regime is quite involved; treatment generally takes about six months and requires four different medications. Lack of adherence can lead to drug-resistant TB
such as MDR-TB (multidrug-resistant tuberculosis) or XDR-TB (extensively drug-resistant tuberculosis). According to the World Health Organization [WHO], “Drug-resistant TB is a continuing threat. In 2016, there were 600,000 new cases with resistance to rifampicin (RR-TB), the most effective first-line drug, of which 490,000 had multidrug-resistant TB (MDR-TB)” [1].

There are no large-dose drug delivery solutions for TB currently on the market. The current gold standard for TB treatment requires taking pills through the use of directly observed treatment (DOT) clinics. These clinics require patients to receive their medication at a clinic between 3-7 times every week, so that they can be tracked over time and observed as they swallow the medication. This can be extremely inconvenient for the TB patients and requires significant trained staff on behalf of the clinics. In addition, studies have shown that DOT clinics do not work as well as intended. One study in Mumbai showed that patients with regular drug-resistant TB (DR-TB) do not follow the intended directly observed treatment methods [4]. Some reasons for a lack of proper adherence included: the time commitment, increased stigma with DOT clinics, and missing or overly-busy providers. A review paper about the use of DOT to improve TB medication adherence actually found that DOT was not effective, although specific underlying reasons (or educated guesses) for failure were not given. In fact, the review directly stated, “Given the large resource and cost implications of DOT, policy makers might want to reconsider strategies that depend on direct observation,” an indictment of DOT clinics [5]. It seems clear that the current incarnation of DOT clinics will not completely solve the issues of TB adherence, and different creative solutions should be considered.
Chapter 2 Background

2.1 Health Services in India

There are extreme disparities in healthcare between the rich and the poor in India. In general, the wealthy people pay to access private hospitals, while the much larger, more impoverished population are treated at public hospitals. These public hospitals are of varying quality, and are generally overcrowded and oversubscribed. In India the public hospital system is tiered, with primary, secondary, and tertiary hospitals. The primary hospitals are for general care and patients initially tend to be brought to these. Major surgeries generally do not occur in primary hospitals; if a patient requires specific treatment they are transferred to secondary hospitals. If a patient requires extremely specific expertise, they are seen at tertiary hospitals. Figure 2-1 shows an operating room in a hospital in India.

Figure 2-1: An operating room in a hospital in India.
These public hospitals are generally not “full-service”; a patient needs family or friends to be in the hospital with them. These extra people then attend to the patient when the doctors or nurses are occupied. They are the patient’s advocates in the hospital, as well as the de facto helpers, with the ability to conduct unspecialized tasks (such as holding an IV above the patient’s bed) as necessary.

In addition to hospitals, there are small health clinics in a variety of locations throughout a city, for example inside a slum. A dental clinic that I visited was part of the Swasth clinics, funded through the Swasth Foundation. These clinics offer extremely cheap and accessible medical procedures in impoverished areas of India such as slums. This dental clinic did the basic procedures one would expect to see at a dentist’s office in America, inside a tiny clinic in a working slum. Pictures of this clinic and the information sheet to record procedures can be seen in Figure 2-2.

Some aspects of healthcare in India that could be improved are administrative. Medical records are not computerized, and when patients check in at hospitals, they carry paper folders with their entire medical history. Paper records present clear problems: a patient could lose their entire medical history, or a doctor could be unable to read a previous doctors’ handwriting. In addition, public hospitals in India tend to be overcrowded. Many patients are placed in public wards, sometimes with dozens of beds in a single open-room ward. When another bed is needed, sometimes an extra bed will be quickly placed into the spare floor space, in what had been an aisle. Not only are wards themselves overcrowded, some hospitals have prospective patients or waiting families sitting and lying in the hospital hallways. This creates hallway blockages and induces more germs into the nonsterile hospital environment.
Sanitation is also not to the standards of hospitals in the United States. In one hospital, a red smear on the floor caused us to initially think the floor was bloody (it was not). Sanitary measures are rudimentary—we were asked to take off our shoes to go into a sterile ward and so entered barefoot or in socks.

![Figure 2-2: The dental chair and paperwork inside of a small Swastik dental clinic in a slum within Mumbai.](image)

2.2 Medical Device Design for India

From speaking to doctors at hospitals in India, I realized that many of the doctors there consistently use technologies (such as gynecological hysteroscopes) that are 50-60 years old. However, the doctors also seemed relatively content using this older technology. They indicated that they would switch to new medical devices only if the new devices were extremely cheap and easy to use.

There are several constraints to note when designing medical devices for India and other developing countries. Cost is a major factor; hospitals have a miniscule budget for new medical
devices as compared to US hospitals. Sterilization is a similarly large issue. Devices must be
designed to be sterilized and re-sterilized easily. In India, many devices which are intended to be
disposable are actually re-sterilized and reused. A conscientious engineer should therefore design
a device with the understanding that even if the device in intended to be single-use, it will likely
be reused and must be safely re-sterilizable and somewhat reusable.

Any novel technologies must also be easy to use. One doctor actively mentioned that he
would not switch devices unless the new device was simple. A new device should not require
intensive training, especially if it is intended for use in rural health centers. The time and cost
required for intensive training is prohibitive in India, especially because doctors are already
comfortable with their current devices. In addition, requiring doctors to undergo training at a
central location at some specified time is unrealistic. A new device should be designed with an
ultimate destination and clientele in mind, as rural health centers have different needs from urban
hospitals and clinics. This thesis focuses on a design intended for use in urban health centers.

Furthermore, the Indian government is currently working on a draft of a medical devices
regulation act [6]. As part of this act, there is a push for significant manufacturing to be located
in India. Ideally, new medical devices would be manufactured in India to bring additional
enhancement to the economy in India.

Finally, one specific engineering element of note in India relates to the substantial use of
hard plastic over other materials. One noteworthy medical example is the IV bag. In the United
States IV bags are commonly made of a flexible plastic, for example PVC [7]. These IV bags
distend and deflate like balloons. In contrast, in India many IV fluids are found instead in hard
plastic bottles like those seen in Figure 2-3 [8]. This is because the process of making hard
plastic bottles (likely done with blow molding) is cheaper than the process required to make distending IV bags.

Figure 2-3: IV fluids in India are often contained in hard plastic bottles rather than in flexible IV bags.

2.3 Drug Delivery Inspiration

2.3.1 Drug Delivery Devices

Large-dose drug delivery is an emerging field, as is drug delivery in the gastrointestinal (GI) tract in general [9]–[11]. One major issue is device retention. A given device is expected to stay in the GI tract for a certain amount of time and must be designed in such a manner as to not pass through the pylorus before the medication has been released. One overview on gastroretentive systems puts devices in these categories: bioadhesive, unfolding or expanding, density-controlled (either by sinking or by floating), and a combination of concepts [12]. Note that if a given device is located near the pylorus, the smallest device dimension should be at least 2 cm to ensure it does not accidentally pass through the pylorus [13], [14].
One emerging technology is a star-shaped device meant to treat malaria over the course of about 10-14 days [14]. This device is an unfolding system, as the star is placed within a pill capsule and swallowed, at which point the pill capsule dissolved and the star expands to be retained in the stomach. This device holds approximately 1.2 grams of medication.

In contrast to this star-shaped device, the TB drug delivery device must hold approximately 100 grams of drugs, which is an enormous amount to be held in the stomach. (For comparison, the largest pill capsule size, 000, can hold 1.37 mL. This capsule would hold less than 2 grams of rifampicin, one of the main medications used to treat TB [15].) The TB drug delivery device design is influenced by the unfolding/expanding concept, since the device will enter the GI tract without the drug and then be filled with the drug. Then, while the device is being filled, it will expand to hold the drug. This concept will be discussed in detail in Chapter 4.

Another drug delivery device of note is a device developed at MIT to deliver lidocaine to the bladder [16], [17]. This device was shown to be retained in the bladder in a rabbit study. This device utilizes nitinol wire and a piece of dual lumen silicone tubing in a pretzel shape. This design is flexible enough to allow for insertion and removal, while strong enough that the nitinol returns to its heat-treated shape once in the bladder.

### 2.3.2 Gastric Balloons

In addition to existing drug delivery devices, gastric balloons are a strong source of inspiration. These balloons are deployed into the stomach and then filled, as the device investigated in this thesis for TB drugs is intended to be. One particularly interesting gastric balloon is Allurion Technologies’ Elipse gastric balloon [18]. This balloon is held in a pill capsule and attached to a small catheter. The patient swallows the balloon, a filler fluid is
pumped through the catheter to fill the balloon, and then the catheter is detached and removed. The fluid-filled gastric balloon remains in the body for a number of months, and is comfortably retained in the stomach until the device is directed to pass through the body (according to the Allurion website, this occurs when a release valve opens at the end of the treatment).

Allurion’s patents demonstrate consideration for a variety of engineering design elements of a balloon that remains in the stomach over time [19]-[22]. The Allurion balloon is designed to be a thin film between 0.0005” and 0.004”. It must be made of stomach-safe material that will not irritate the stomach but also must not degrade in the stomach. Additionally, Allurion has determined a variety of different methods of retaining the fluid within the balloon, such as the use of a check valve. Finally, while the focus appears to be on filling the balloon with “filler fluid”, one patent notes the potential for the balloon to “be filled with a gas, liquid or other gel type substance” [19].

2.4 Powder Transport

2.4.1 Literature Review

A literature review was conducted to explore powder transport in both academic research and in industry. Many researchers have studied powder flow, but this research frequently focus on powder in free fall or through a chute, rather than through a pipe or piece of tubing [23], [24]. Significant research has also been conducted concerning powders with fluidized beds [25]-[27], which also has less relevance to the powder transport required for this thesis.

Initially, a pertinent industry example was thought to be loose fill insulation for attics. After further research it was determined that loose fill insulation is a different, highly specific
scenario. Attic insulation generally begins as densely packed material and is then separated and blown out of a machine to fill an attic, whereas this thesis research focuses on powder. In addition, there is a lack of significant technical background about loose fill insulation.

Eventually the appropriate terminology to relate to the powder transport of medication through tubing to a balloon placed in the stomach was found: “pneumatic conveying systems.”

2.4.2 Pneumatic Conveying Systems

Pneumatic conveying systems are frequently used for industrial applications to transport powder. These applications range from chemical production to food processing and even to truck unloading [28]. These industrial applications frequently transport massive quantities of powder, in contrast to the 100g required to be transported for this drug delivery device.

There are two options for pneumatic conveying systems: dilute phase and dense phase. Dilute phase refers to transporting particles while they are suspended in air, requiring high-velocity airflow at low pressure. These particles generally have a low bulk density. In contrast, dense phase transports particles without suspending them in air, requiring low-velocity airflow at high pressure. Dense phase conveying systems are a more careful method of transportation generally used for delicate or abrasive powders [29]–[32].

In addition to dense and dilute phases, pneumatic conveyance is split into two additional categories: pressure conveying and vacuum conveying. Pressure conveying uses a positive pressure pump at the start to push air and powder through the system, while vacuum conveyance uses a vacuum at the end to draw the air and powder along the system to the end. Pressure conveyance is generally used for long distance, while vacuum conveying is usually used for short distances [29].
Pneumatic conveying systems therefore use one of four different methods: dilute phase pressure conveying, dilute phase vacuum conveying, dense phase pressure conveying, and dense phase vacuum conveying. These options can be seen in Figure 2-4 [29], with sample pictorial setups of the various methods in Figure 2-5 [33]-[36].

Figure 2-4: The four types of pneumatic conveying systems and the different use cases for these types.
Figure 2-5: Sample images of the basic setups for the four methods of pneumatic conveying systems. Images courtesy of Powder-Solutions Group.
Chapter 3 Questionnaires

3.1 Background

In addition to the technical engineering design, one must keep in mind the potential for eventual on-the-ground deployment of a drug delivery device. Since this device is focused on India, both the acceptability and feasibility of this idea must be explored in the region of eventual potential distribution. To that end, a set of questionnaires were developed that ask stakeholders about the use of a nasogastric (NG) tube as a deployment method for a drug delivery device for TB treatment. One questionnaire is directed towards TB doctors in India, and focuses on the feasibility of using an NG tube. The other questionnaire is directed towards TB patients, and focuses on the acceptability of using a nasogastric tube to administer the medication as compared to the current gold standard of the DOT clinic. To begin formulating questionnaires, a literature review was conducted to seek out prior similar studies.

To our knowledge, there have not been any prior questionnaires asking about the use of nasogastric tubes in India. One paper describes using a qualitative study to understand TB patients’ and caretaker’s experiences with DOT [37]. Unfortunately, this study format was more of an interview than a questionnaire and therefore does not contain enough specific quantitative information.

One survey in Nigeria did a moderately qualitative survey about oxygen therapy and nasogastric tube feeding for children [38]. This study focused on the feelings of the mothers of sick children, and concluded that most mothers would accept the use of a nasogastric tube for feeding purposes. Unfortunately, this paper did not release the full questionnaires, simply noting that they were “structured and pretested”.

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This area showed a definite lack of literature. Many papers discussing questionnaire results did not show a full questionnaire in an appendix. We found no papers describing nasogastric tube acceptability in India, and the cultural differences between India and Nigeria also add to the lack of clear literature and instructions for running such a survey.

3.2 Pilot of Questionnaires

After initial versions of questionnaires were designed, the questionnaires were piloted in India in Mumbai and Delhi with the help of Operation Asha (Op Asha), an NGO focused on administering TB medicine with a focus on the issue of TB medication adherence [39].

Op Asha uses a specific model they have developed that is meant to improve medication adherence. They have small Op Asha clinics in TB-heavy urban areas where the medicine is distributed. The provider in the clinic distributes medicine to patients in the area. There are many clinics so that a person must only walk a few minutes to reach their clinic. In rural or less population-dense areas, this clinic is actually a mobile clinic consisting of a travelling provider with a bicycle or motorcycle. These providers bridge the gap between TB doctors and patients. They develop the personal rapport with their patients and some counsel their patients. The providers have basic medical knowledge of symptoms and medication side effects. They are literate in the local language, but may not have strong English skills.

This pilot was conducted to assist us in refining and editing the questionnaires for maximal impact in a future intensive study. We spoke to patients and patient families in both the TB DOTS clinic at Safdarjung Hospital in Delhi and in a small Operation Asha clinic in Harkesh Nagar Okhla, Delhi. We spoke to Operation Asha providers at the Operation Asha headquarters in Sarita Vihar, Delhi. Doctors were asked to give feedback on the doctor surveys at the DOTS
clinic and pulmonary ward of Safdarjung Hospital. While the doctors spoke English, an Op Asha staff member was on hand to run most of the questionnaires in Hindi. Overall, to collect feedback on our questionnaires we spoke to 5 providers, 5 doctors, 8 patients, and 7 patient family members for a total of 25 individuals.

This pilot assisted us in editing the questionnaires for a variety of factors we had not considered before coming to India. We took note of when confusion arose on behalf of the potential survey participants while going through the questions. Sometimes individuals were confused because certain questions or options were irrelevant, whereas other times they were confused due to specific issues with phrasing or with translations. To alter the questionnaires for an upcoming survey, some irrelevant or unnecessary questions and answers were removed, others were rephrased, and issues with translations were noted.

Initially, we were under the impression that we would need two separate questionnaires: one for patients and patient families, and the other one for TB doctors and providers. However, while piloting the questionnaires we learned that effectively characterizing each group (i.e. patients, patient families, providers, and doctors) would actually require four separate questionnaires. To ensure a distinct focus and clarity of results, we therefore decided to focus the questionnaires solely on the patients and TB doctors. The feedback from the pilot was used to edit and update the questionnaires to reflect these two populations.

These two questionnaires were planned to be administered differently for doctors as compared to patients. Since the medical training for doctors in India is primarily in English, it was assumed that doctors would generally be comfortable taking the questionnaires in English. They could read and answer the paper-based survey independently, and the survey could then be retrieved.
In contrast, the patient questionnaire would be administered differently. We cannot assume that patients can understand or speak English, nor can we assume that patients are literate in a local language. Therefore, the questionnaire must be administered orally in the local language. Since the full patient survey would be conducted in Delhi, the questionnaires would be translated to Hindi. In addition to this written translation, the survey administrator must speak the local language. The survey administrator can read the survey questions to the patient and the patient can answer, at which point the answers can be marked into a tablet. The survey should be formally translated into Hindi to allow less biasing of results to occur. Instead of relying on the survey administrators’ translation abilities, they can simply read the survey to the patients, allowing for a more generalized survey administration.

This full survey was conducted in Delhi by members of the Langer Lab at MIT and associated hires from August to November 2018. The results and assorted details will be part of Malvika Verma’s PhD thesis.
Chapter 4 Design

4.1 Device Constraints

There are significant constraints to consider when creating a large dose drug delivery device. Since this device is expected to hold 30 days’ worth of medication for the average human during the intensive treatment phase, the amount of medication required is approximately 100 grams.

As the average human weight worldwide is 62 kg [40], a human weight of 60 kg was assumed for the purposes of calculating the amount of medication required. The WHO has released recommendations for the drug dosages in the intensive phase of tuberculosis treatment which can be seen in Figure 4-1 [41]. Note that streptomycin is injected, not swallowed in pill form, and is therefore not included in the medication stack-up. Adding up 30 days’ worth of a daily dose of isoniazid, rifampicin, pyrazinamide, and ethambutol for a 60 kg individual leads to a total dosage about 100 grams for the 30 days.

This calculation was done as follows: A daily dose of isoniazid for a 60 kg individual is 5 mg/kg multiplied by 60 kg, making 300 mg. This daily dose multiplied by 30 days is 9 g. Since the daily dosage of rifampicin is double that of isoniazid, 30 days’ worth of rifampicin is doubled as well, making 18 g of rifampicin. Using similar calculations, 45 g of pyrazinamide and 27 g of ethambutol would be required. Combining the doses of all four medications for 30 days provides
the following requirement: 9 g of isoniazid, 18 g of rifampicin, 45 g of pyrazinamide, and 27 g of ethambutol, for a total of 99 grams of medication.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose and range (mg/kg body weight)</th>
<th>Maximum dose (mg)</th>
<th>3 times per week dose and range (mg/kg body weight)</th>
<th>Daily maximum dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5 (4-6)</td>
<td>300</td>
<td>10 (8-12)</td>
<td>900</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 (8-12)</td>
<td>-</td>
<td>10 (8-12)</td>
<td>600</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 (20-30)</td>
<td>-</td>
<td>35 (30-40)</td>
<td>-</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 (15-20)</td>
<td>-</td>
<td>30 (25-35)</td>
<td>-</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 (12-18)</td>
<td>15 (12-18)</td>
<td>1000</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4-1: The WHO guidelines for drug dosages in the intensive phase of tuberculosis treatment.

Assuming the approximately 100 grams of medication would have a density of 1.34 g/mL, which is the density of rifampicin [42], the volume of medication for 30 days is then ~75 mL (~4.5 in³).

75 mL is quite a large volume to fit into a stomach, and therefore required research to ensure that the volume of the medication would not detrimentally impact the patients’ food intake, causing the patient to lose weight that they cannot afford to lose.

The average adult stomach capacity is about 1 liter [43], so this device can be physically located within the stomach. Gastric balloons, a weight-loss tool discussed above, generally hold between 400-1000 mL of volume, and people begin to perceive the balloon’s presence at around 300 mL of volume (Dr. Giovanni Traverso, personal communication, cgt20@mit.edu). As an additional comparison, people with trichobezoars in their stomachs generally begin to feel the trichobezoars at around 100 grams (Dr. Giovanni Traverso, personal communication, cgt20@mit.edu). To be least invasive, the drug delivery device should not be felt by individuals and should not cause weight loss as a function of its volume and weight. Using gastric balloons
and trichobezoars as a basis of comparison, we expect that the drug delivery device would need to be in the hundreds of milliliters for the average individual to begin to feel the device.

Therefore, the design parameter for the volume of this device is: the volume of the device and the drugs combined should be under 250 mL, ideally less than 200 mL.

4.2 Initial Project

The starting goal of this project was to design a new drug delivery device that would hold 100 grams of drugs. This device would need to be placed into the stomach using a nasogastric tube to be as minimally invasive as possible. The use of a nasogastric tube places significant constraints on the size and shape of such a device. The inner diameter of a nasogastric tube can be assumed to be 0.25". Size 24 French gauge nasogastric tubes seem to be among the largest commercially available nasogastric tubes [44], with an outer diameter of 0.315". Estimating a wall thickness of 0.0325", the inner diameter of this tubing would then be 0.25". Since the nasogastric tube would only remain in the body for a short period of time, it is hypothesized that nasogastric tubes on the larger side could be used for this purpose.

The initial conception of this device was a balloon-like device that could be placed into the body through the nasogastric tube. This balloon would hold 100g of drugs and dispense a certain amount of drugs daily. It was undetermined at the start of the project if the balloon should be pre-filled with drugs or if it should be filled with drugs once it had passed through the nasogastric tube into the stomach. However, some calculations of geometry (namely using the constraint of a large nasogastric tube having an inner diameter of only 0.25") showed that it was more logical to fill the balloon while inside the stomach.
4.3 Drug Delivery Device Strategies

Figure 4-2 shows a chart created to consider the various functional requirements required to strategize on device development. These considerations led to a discretization of the different process components required to use such a drug delivery device.

<table>
<thead>
<tr>
<th>Functional Requirements</th>
<th>Design Parameters</th>
<th>Analysis</th>
<th>References</th>
<th>Risks</th>
<th>Countermeasures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of drugs</td>
<td>Volume of drugs</td>
<td>Volume of drug according to online density=1.34 g/cm^3</td>
<td>Rifampicin density=1.34 g/cm^3 according to: <a href="http://www.guidechem.com/dictionary/en/13242-46-1.html">http://www.guidechem.com/dictionary/en/13242-46-1.html</a></td>
<td>Device becomes too large to insert and/or fit into person's stomach</td>
<td>Expanding device, thin-walled device</td>
</tr>
<tr>
<td>Volume of drugs</td>
<td>Volume of DDD+drugs+volume</td>
<td>Volume of DDD+drugs=250 mL (i.e. 500 mL)</td>
<td></td>
<td>Person loses weight they cannot afford to lose</td>
<td>Very lightweight and small device</td>
</tr>
<tr>
<td>Lacks comfort</td>
<td>Lacks comfort</td>
<td>Lacks comfort</td>
<td></td>
<td>Secondary balloon that remains full to ensure DDD doesn't pass through too early</td>
<td></td>
</tr>
<tr>
<td>Does not pass through</td>
<td>Does not pass</td>
<td>Does not pass</td>
<td></td>
<td>Device degrades, allowing all the drug to be retrieved</td>
<td></td>
</tr>
<tr>
<td>Stomach-safe material</td>
<td>Stomach-safe</td>
<td>Stomach-safe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can be filled with drug</td>
<td>Can be filled</td>
<td>Can be filled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only lets drug out</td>
<td>Only lets drug</td>
<td>Only lets drug</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Figure 4-2: A variety of functional requirements were considered over the course of brainstorming strategies to design a drug delivery device.

4.4 Process Components to Use Drug Delivery Device

The process to use a drug delivery device in the stomach can be broken up into 7 steps:

1. Insertion of drug delivery device
2. Filling (and expansion) of device
3. Sealing of device
4. Detaching of drug delivery device from insertion device

5. Removal of insertion device

6. Retention of device in stomach

7. Retrieval or removal of drug delivery device

Each component will now be described in further detail. While the controlled release of the medication from the device over the course of time is also a crucial factor in drug-delivery, this was considered out of scope for this project and therefore will not be discussed in any detail.

4.4.1 Insertion of Device

The drug delivery device must be inserted into the stomach in a minimally invasive manner. The manner of insertion has been chosen to be through the use of a nasogastric (NG) tube. Minimally invasive methods are preferable for both the doctors and patients, as they have significant advantages for both hospitals and patients. Minimally invasive surgeries, for example, are safer, cause less scarring, and lead to a quicker recovery time and therefore a shorter hospital stay [45]. To avoid cutting into the body to implant a device, minimally invasive routes can use either the mouth or the nose. The nose is a more convenient passage than the mouth, as a tube can be more easily steered to the esophagus and usually leads to less coughing by the patient through the nasal passage as compared to the mouth [46].

Therefore, the drug delivery device must be inserted through a nasogastric tube which can accommodate a 0.25” tube inside of the NG tube. The device must be flexible enough to pass through a curved tube all the way from the nasal passage into the stomach.

Assuming 75mL of drug must be accommodated for, the worst case scenario was calculated. If one conservatively assumes that the inner diameter of a drug delivery device is
0.23” (such that the outer diameter of the tube is 0.25” and the tube thickness is 0.01”), then a completely packed drug delivery device with 100% efficiency would need to be over one foot long (specifically 1.056’ long). We know that a closely packed device would be relatively rigid and inflexible [47], so to be flexible enough to accommodate movement through an NG tube the device would need to be even longer than 1 foot. Once the device entered the stomach, it would need to curl up in some manner as to not puncture the stomach, since the stomach cannot accommodate a foot-long rigid tube. A long cylinder is an extremely inefficient shape to fit inside of a relatively spherical stomach, and in fact a sphere would be a much more efficient shape inside the stomach.

One design considered was a thin-walled spiral that would be inserted as a long tube and would curl up into the spiral shape, seen in Figure 4-3. Assuming the outer diameter of a tube of wall thickness 0.001” was OD=0.25” (such that it would fit into the NG tube), the spiral would be approximately 5.6” wide! This is not a reasonable size to fit in the stomach and so this spiral option was discarded. A second option considered was the use of a cylindrical shape, either hollow or non-hollow as shown in Figure 4-3. St. Venant’s design principle of keeping a 1.6:1 length to diameter ratio was used to calculate the length and diameter. A cylindrical device might be easier to construct than a spherical device, but other than construction there were no especially compelling reasons to prefer a cylinder as compared to a sphere, and it is a less efficient design as compared to a sphere.
With all of the above constraints and explorations in mind, a realization occurred that instead of either creating a tube that curls up or creating a cylindrical shape, why not use the more simplified spherical balloon shape? The decision was thus made that the drug delivery device should be an approximately spherical balloon. Since a pre-filled spherical balloon would not fit into the NG tube, the device would need to enter the stomach empty and "deflated" and then be filled up while in the stomach, similar to how gastric balloons are filled once in the stomach.

4.4.2 Filling and Expansion of Device

The drug delivery device must be filled with drugs, while the device expands to fit the ~75 mL full volume of drugs. This component will be described in significantly more detail throughout the rest of the thesis.

4.4.3 Sealing of Device

The drug delivery device must be sealed after having been filled so that the insertion/filling device can be safely detached from the drug delivery device without any leakage from either the drug delivery device or the insertion/filling device. However, if we assume that the insertion/filling device is empty once all of the drugs have been delivered into the drug
delivery device, then only the drug delivery device must be sealed. The seal might be able to be sealed by the insertion/filling device. The seal could be a one-way valve, or it could be a more permanent adhesive seal.

4.4.4 Detaching of Drug Delivery Device from Insertion Device

After the drug delivery device has been sealed, the insertion device must be detached. Since the detachment is taking place inside the stomach, various creative options must be considered. Some examples of possible inspiration are: a “claw grabber” where the point of attachment is a claw but the grabber can be detached from the drug delivery device, a screw in/out method of detachment, and a pressure-based detachment mechanism, all of which can be seen in Figure 4-4 [48]–[50].

![Figure 4-4: Inspiration for detachment methods included a “claw grabber”, a screw-cap, and a hose quick-connect for a pressure washer.](image)

4.4.5 Removal of Insertion Device

The insertion device must be able to be safely removed from the stomach via the nasogastric tube. A “claw grabber” is envisioned as being able to be safely removed through the nasogastric tube.
4.4.6 Retention of Drug Delivery Device

The drug delivery device must remain in the stomach over the course of the 30-day period of active drug delivery. As described in the background section, this means that the device must not pass through the pylorus, so the smallest device dimension (in the simplest form, this would be the diameter) should be about 2 cm or greater to ensure it does not accidentally pass through the pylorus [13], [14].

One possible method of creating a device with retention is a double balloon. An inner balloon would be filled with air, while the outer balloon would encompass the inner balloon and contain the drugs. The air-filled inner balloon would be large enough not to pass through the pylorus. If the outer diameter of the inner balloon was 2 cm, a completely filled outer balloon’s outer diameter would have to be about 5.33 cm (~ 2.1 in). This is approximately one millimeter greater in diameter than a singular spherical balloon holding 75 mL without an inner balloon which would be about 5.23 cm in diameter. The addition of an inner balloon would therefore cause an almost negligible increase in diameter.

A second possible method would be to have a heat-treated nitinol wire attached to a singular drug-filled balloon, such that the wire would be easily pushed through an NG tube but then would spring into shape when placed into an open space (i.e. the stomach) and would thereby constrain the balloon in such a manner that it could not pass through the pylorus. An example of this can be seen in Figure 4-5.
4.4.7 Retrieval or Removal of Drug Delivery Device

The drug delivery device must either pass through the pylorus after the 30-day drug treatment period or be retrieved through the use of the NG tube. It is not currently clear which method will be more viable, as it is interconnected with the problem of retention and is not the specific focus of this thesis.

4.5 Most Critical Module: Powder Filling

For any design project, the most critical module must be identified as the process or object with the most uncertainties, the module without which the project would completely fail. For this drug delivery device, the most critical module was identified to be the powder filling, or the filling and expanding of the drug delivery device.

The actual design of the device itself will likely be based on existing gastric balloons. Gastric balloon companies such as Allurion have already solved several problems that must be
solved for this drug delivery device: sealing, detaching, removal of insertion/filling device, and removal of gastric balloons.

These companies also have methods for filling a gastric balloon while it is inside the stomach. However, gastric balloons are filled with liquid or gaseous matter. These companies do not fill the device with powder.

The medications needed for tuberculosis patients come in a powder form, and cannot be converted into a convenient liquid form. For example, the liquid form of rifampicin contains 100 mg of drug per 5 mL of liquid [51]. To get the required 100 g of drugs, (assuming that all the other medications have similar liquid conversions,) then 5 L of liquid would be used for the 100 g of medication! As discussed earlier in this thesis, the design parameter for this device is that the volume of the device and the drugs combined should be under 250 mL. We therefore know that the medication will remain in powder form and cannot be liquefied.

Powder transport has completely different requirements from liquid or gaseous transport, and without the ability to insert the actual medication into a drug delivery device, this concept will fail. For this reason, powder filling was chosen as the most critical module of the drug delivery device and is thus the primary focus of this thesis.

### 4.6 Safety Matters: Finding a Drug Alternative

One of the main medications used to treat tuberculosis is rifampicin, so there was a logical desire to use rifampicin as the “test powder” during the design and prototyping stages. Unfortunately, rifampicin is actually a class 2 health hazard which can cause skin inflammation, respiratory irritation, decrease the efficacy of some methods of birth control, and more [52], [53].
For safety purposes, I searched for an alternative to rifampicin that would be usable for safe rapid prototyping.

The specific aspects of rifampicin considered when considering substitutes were density \(\rho\) and particle size (using sphere diameter \(D\)). \(\rho_{\text{rifampicin}} = 83.65\ \text{lb/ft}^3\) and the average \(D_{\text{rifampicin}} = 42\ \mu\text{m}\) [42], [54]. Safe alternatives that were considered included sand, salt, baking soda, flour, potato starch, and corn starch [55]. The alternative ultimately chosen was sodium bicarbonate, or pure baking soda. \(\rho_{\text{sodium bicarbonate}} = 70-80\ \text{lb/ft}^3\) and the typical particle size (for the specific baking soda I ordered for testing that calculated particle size) had a typical \(D_{\text{sodium bicarbonate}} = 44\ \mu\text{m}\) [56]. These properties were considered functionally similar to the properties of rifampicin while being a significantly safer option for use in a mechanical engineering laboratory.

4.7 Pneumatic Conveying Systems

As described in section 2.4.2, there are four distinct types of powder conveying systems. For this drug delivery device, the decision was made to attempt the dilute phase options over the dense phase options. The dilute phase transport is a significantly less complicated setup as compared to the dense phase. Keeping with the principle of KISS (Keep It Super Simple), I attempted to flow powder through the more simplified methods first. Simplified engineering is not only helpful for prototyping, it is especially important when considering the ultimate goal of using this device in Indian hospitals with limited resources. When designing for developing countries, the most useful solution is often among the simplest. In addition, the dilute phase pressure conveying method has been specifically noted to be used for low-density materials such as sodium bicarbonate [31]. Since sodium bicarbonate was my substitute prototyping powder for
rifampicin, it logically followed that I should attempt a method used specifically with that powder.

Within the dilute phase method of powder transport, there are three distinct options: pressure conveying, vacuum conveying, and a combination of the two. This combination of the two methods would include both a positive pressure pump at the front end and a vacuum at the back end. The overall pressure flowing through the system would be positive (such that the pump acts more powerfully than the vacuum), but the vacuum would assist in drawing the powder through the tube system and into the correct location.

Figure 4-6 shows the idealized setup for dilute phase vacuum conveying. A double-lumen tube would be inserted through the NG tube and into the stomach. Inside the stomach, the tube would split and connect to either side of a drug delivery device. An air-and-powder mixture would flow through one side of the double-lumen tube directly into the drug delivery device. A filter at the back end would keep the powder from continuing to flow past the device. The air would then continue flowing through the filter up the other half of the double-lumen tube and through the vacuum.
Air + Powder

NG Tube

Stomach

Filter

Vacuum

Double-lumen tube

Figure 4-6: Idealized setup for dilute phase vacuum conveying. The air and powder would be drawn into one half of the double-lumen tube through the NG tube and into the drug delivery device in the stomach. A filter would then contain the powder in the device and allow the air to flow out of the device and up through the other lumen of the double-lumen tube. A vacuum pump at that end pulls the air and powder through the system and expels the excess indrawn air back out.

Figure 4-7 shows the idealized setup for dilute phase pressure conveying. A single lumen tube would be inserted through an NG tube to the drug delivery device placed in the stomach. A filter would be attached to the other end of the device. In this method, the gas used would not be regular air but would instead be carbon dioxide (CO₂). This is because carbon dioxide can safely be placed into the stomach in relatively large quantities, and then safely be expelled from the body. We can see this from carbonated beverages such as seltzer! Seltzer is water with dissolved carbon dioxide, and is quite safe to consume in reasonable quantities. From a more technical and medical perspective, doctors often use carbon dioxide to insufflate (inflate) the intestinal tract during a colonoscopy. While air has been used for insufflation in the past, carbon dioxide is seen as a potentially more comfortable option [57]. In one study, doctors found that an estimated 8.3
Liters of CO₂ were insufflated in a given procedure, at a rate of about 0.26 L/min during an ~32 minute procedure [58]. Since the time required to flow the medication into the drug delivery device is intended to be significantly less than 32 minutes, it might even be possible to increase the rate of carbon dioxide, thereby increasing the pressure. In addition, since carbon dioxide is commonly used in hospital procedures, it should be available for use in Indian hospitals. For the purposes of proof of concept testing, a positive pressure pump was used with air, but the idealized version is intended for use with CO₂.

![Diagram](image)

**Figure 4-7:** Idealized setup for dilute phase pressure conveying. The pressurized CO₂ and powder would flow into a piece of tubing through the NG tube and into the drug delivery device located in the stomach. A filter would then contain the powder in the device and allow the CO₂ to be expelled from the device and into the stomach, where it would be expelled from the body.

Finally, Figure 4-8 shows an idealized setup for the combined positive pressure pump and negative pressure vacuum. The setup looks similar to the discrete phase vacuum conveying setup, with the addition of positive pressure at the front end. As described earlier, the positive
pressure will be higher than the vacuum pressure, such that the overall pressure effect is more in line with positive pressure vacuum conveyance, with assistance from the vacuum to move the powder smoothly through the tubing.

4.8 Proof of Concept

4.8.1 Lessons from Initial Proof of Concept

Figure 4-9 shows an initial prototype using dilute phase vacuum conveying. This version was able to transport some powder into the powder deposit container that was acting as a stand-in for a drug delivery device. A 3-way adjustable stopcock was used to connect the infeed
section, the powder deposit container, and the air intake. A filter was placed between the powder deposit container and the vacuum pump to ensure that the powder did not leave the powder deposit container.

Several useful lessons were learned from this initial proof of concept. Powder would become stuck in a variety of locations in the system, but especially at the connector joints between different objects/materials, so minimizing connector joints should help minimize clumping. In addition, the use of vibration (tapping or shaking) helped fix some of the powder clumping issues. Finally, the vacuum pump caused the connected tubing to compress inwards and become more closed under the pressure applied by the vacuum, thereby significantly decreasing the efficacy of the vacuum pump.

During these initial proof of concept stages it became clear that both positive and negative pressure were needed to create the most effective option. Quick tests also showed that positive pressure was more effective when pulsed, while the negative pressure could act continuously. In particular, continuous positive pressure was found to be particularly ineffective at moving the powder forwards. Prototyping therefore continued with a dilute phase mixed continuous vacuum and discrete pressure conveying system.
4.8.2 Drug Delivery Device Balloon

I first attempted to create a spherical balloon-like object from scratch to use as the physical device for drug delivery. This balloon would need to be safe for the body, strong enough to withstand a certain amount of pressure, able to be opened and closed easily, and durable enough to stay in the body for a month. In addition, it should likely behave more like a flexible, low elasticity inflatable beach ball than a flexible and highly elastic latex balloon. This is because highly elastic materials require additional pressure to expand as compared to less elastic materials.

I attempted to create this device in a few ways with various materials, including liquid latex paint and heat-sealed polymer sheets. However, these attempts were quite messy and
generally unfruitful, so rather than focusing efforts on the specific design of the device, an alternative was found: a medical balloon from Vention Medical intended for use in balloon catheters. If the concept for this drug delivery device is proven to work, a custom balloon can be easily created by working with an existing medical device company focused on medical-grade balloons.

The Vention Medical balloon (shown in Figure 4-10) is an elliptical balloon composed of low durometer urethane, with an external diameter of 40-55 mm, a length of 55 mm, and a balloon thickness of 0.0292-0.0381 mm. It has two openings consisting of one neck on either side [59]. The volume of this balloon is approximately 65 mL, close to the 75 mL of medication required for a 30-day period. This balloon was therefore chosen to be a useful substitute for a future drug delivery device.

4.9 Proof of Concept Updates

Initially, the proof of concept model was largely horizontal and the powder would often become stuck in the tubes, eventually clogging the tubing. To combat this, the setup was changed to a vertical model (see Figure 4-11). With the assist from gravity, the powder flowed easily
from the powder holding container into the device. This is a reasonable alteration to make because during NG tube insertion, the patient is positioned in High Fowler’s position. In High Fowler’s position, which can be seen in Figure 4-12, the patient’s chest is angled between 60-90 degrees as compared to the legs [60], [61]. In this position, the NG tube is essentially vertical, so the alteration to a vertical setup is logical.

Figure 4-11: A vertical model that allowed the powder to easily flow into the balloon. The balloon’s bottom opening was blocked.

Figure 4-12: The most extreme version of a High Fowler’s position places the chest at a 90° angle as compared to the legs.

The next major adjustments to the proof of concept model were to include the realistic anatomical pathway and miniaturize the setup. A rigid tube was heated and then bent to mimic
the path in the body that the NG tube takes from the nose through the esophagus into the stomach (Figure 4-13). This tube was placed such that the general direction of motion of the powder would still be downwards, as in the extreme High Fowler's position. The tubing was miniaturized such that the tubing inner dimensions would fit within an NG tube. Note that these tubes were used for prototyping; the ideal final version should use a double-lumen tube with similar inner dimensions such that the outer diameter of the double-lumen tube would fit within the NG tube.

![Figure 4-13: A rigid tube was heated and bent to mimic the pathway traveled with an NG tube.](image)

Afterwards, vibration motors were added to the setup. An initial attempt used a small vibration motor that came from a cellular flip phone. This small motor is about the size of a coin cell battery. It was connected to an Arduino and programmed to turn on and off rapidly (for example, change between on and off every half-second). This vibration was found to not be quite powerful enough, so larger vibration motors were acquired.

These larger vibration motors consist of a rotary motor with an attached eccentric weight. The motors were found to be helpful on impact rather than through the use of vibration, meaning that the eccentric weights knocking on the system provided a sharp impact to dislodge the powder from anywhere it might be stuck. Using the vibration motors purely for vibratory purposes was found to be ineffective. One vibration motor was placed into the system as shown in Figure 4-14. Later, a second vibration motor was added around the exit zone of the powder holding container. Motor holders were also designed and 3D printed to be able to easily secure the cylindrical motors onto a flat surface.
Finally, the miniaturized, anatomically realistic version was converted into a test setup using LEGO DUPLO bricks. This setup will be described in detail in a future section.

Figure 4-14: A vertical version of the powder flow setup. One vibration motor is shown knocking against the Y connector.
4.10 Custom Tube Fittings

The next section describes custom tube fitting designs created for use with the test system. While this section does not discuss every single prototype that was designed or created over the course of this thesis, it encompasses the highlights of the created designs.

4.10.1 Venturi Tubes

A custom connector was designed to use the Venturi effect to assist in flowing the powder from the powder holding container into the inflow tube. The Venturi effect is based on Bernoulli’s principle and says that “when flowing through a constricted area of a pipe, a fluid’s velocity increases and its static pressure decreases” [62]. The connector in Figure 4-15 models a pipe with a constriction. These connectors intended to use the higher velocity at the constriction to pull the powder from the powder holding container into the inflow tube. Ultimately, this concept was not effective, and instead other factors to assist with powder flow (such as the vibration motors described earlier) were explored.

![Figure 4-15: A cross-section of a custom Venturi pipe with a diagram over-imposed on the CAD model. The positive pressure pump is meant to push air through the opening and into the tube constriction, where it will pick up powder from the powder holding container. The air and powder mixture will then be pushed through to the inflow tube and eventually to the device in the stomach.](image)
4.10.2 Custom Connectors

A custom connector was designed to allow the air and powder to flow through one tube into the balloon and then air to flow out the other tube. This custom connector went through many iterations, starting as a custom Luer Y connector and ending as a more effective altered design. Designs A-F will now be described, with explanations of the changes implemented when iterating through the design.

A cross-section of design A can be seen in Figure 4-16. The connector was intentionally designed with a divider between inflow and outflow, making it inherently different from regular Y connectors which are open through the bottom half of the Y connector. Due to the vacuum pressure applied through the outflow tube, there was a concern that the powder would flow directly from the inflow tube to the outflow tube, completely bypassing the balloon. As a cautionary measure, the custom connectors were designed with an explicit divide between inflow and outflow. Design A uses a 1:1 ratio of tubing, such that the inflow and outflow tubes are the same size.
Figure 4-16: Design A divides a custom Y connector in half so that air and powder can enter one end of the connector and continue into the device, where the powder falls into the device and the air moves through the other side of the connector and into the outflow tube. The divide in the bottom component is to protect against the powder flowing directly from the inflow tube to the outflow tube without falling into the device itself. The inflow and outflow tubes are inserted into the Y connector in the locations shown by the red dashed boxes.

Design B is a slightly simplified version of design A. In design B the inner tube sections remain the same size throughout the top half of the Y connector, meaning that the inner diameter of the tubes flow smoothly into the diameter of the top section of the Y connector. For example, if a tube’s ID is 0.15”, the diameter of the top section of the Y connector is 0.15” as well. This alteration can be seen in figure 4-17.
In addition, at this stage I began to design the Y connectors for a variety of tube ratios, from ratios of 1:1 to about 7:1 (or 8:1 in later iterations) inflow to outflow inner diameter size. The rationale behind creating a variety of tube ratios was based on the idea that the inflow tube could likely be larger than the outflow tube. The powder has a tendency to become stuck in the inflow tube, but there is little concern of regular air with relatively few particles becoming stuck in the outflow tube. Additionally, the outflow vacuum pressure can be increased when the tube ratios are adjusted. Therefore, a reasonable assumption is that a larger inflow tube and smaller outflow tube would be more and more efficient as the ratio became more and more extreme, up to a certain point. The goal was to be able to empirically test a variety of ratios to find that point (i.e. the most extreme ratio) where the filling efficiency was the highest, before the outflow tube became so small as to be inefficient or ineffective. Figure 4-18 shows design B with a 2:1 tubing ratio.
Figure 4-18: A custom tube fitting was created to accommodate a 2:1 tubing ratio. The top sections of the connector have cross-sections that are equivalent to the internal cross-sections of the tubing, so that the powder flows directly from the tubing into an equivalent size diameter. The bottom section of the connector is divided in half as in design A.

In design C, the bottom half of the Y connectors was modified to have approximately the same inner cross-section ratio as the upper half of the Y connectors. Figure 4-19 shows a cross-section of design C with a 2:1 ratio showing the 2:1 ratio of the bottom half of the Y connector.

Figure 4-19: Design C improves on design B by dividing the bottom section of the Y connector proportionally according to the cross-sectional tubing ratios of the specific connector. In this image a 2:1 ratio is shown.

One issue with designs A, B, and C that became clear was the angle of the Y connector, which was initially a 90° angle. Throughout the connector’s iterations it became clear that I should use PTFE tubing, especially for the inflow tube, as the lubricious properties of PTFE assist significantly in ensuring that powder does not become stuck in the tube. However, PTFE
tubing is not particularly flexible and has a large radius of curvature. This caused the tubes to be unable to bend properly from their straight vertical exit out of a tube mimicking the esophagus all the way into the 90° angle of the connector. (An image of this intended tube trajectory and bend can be seen in Figure 4-20.) To assist the PTFE tubing in completing its intended trajectory without damaging the tubing, the angle was significantly altered to a 40° angle, seen in Figure 4-21 as design D.

Figure 4-20: The intended tube trajectory is only effective with very flexible tubes. PTFE tubes were unable to handle this level of curvature and the design of the custom Y connectors had to be altered to accommodate for these relatively inflexible tubes.

Figure 4-21: Design D significantly decreased the angle between the inflow and outflow sections from 90° to 40°.
Soon after design D was printed, it became clear that the 40° angle was not actually necessary to improve powder flow. Instead, the tubes could descend straight into the connector, rather than coming in at angle. The inflow and outflow sections could then be angled to connect to the outflow tube. Figure 4-22 shows this change as design E.

**Design E**

![Figure 4-22: Design E significantly alters the tubing connector by eliminating the angle between the inflow and outflow tubes. Both the inflow and outflow sections have a small angled section to ensure the barb at the bottom can fit inside the balloon acting as the drug delivery device.](image)

There were several ways to improve upon design E. Design E was taller than necessary—the connector simply needed to be tall enough to fit all of the components properly without requiring harsh angles changes. Additionally, the barb on the end of the connector causes an inherent restriction on width, thereby limiting the cross-sectional areas of the inflow and outflow components in the lower connector section. To combat this, the connector was altered such that the balloon would fit inside the connector rather than the barb fitting into the tube. A glue gun could then be used to create a solid (yet easily removable) bond to hold the balloon to the connector. This is a reasonable change to make, as ultimately the drug delivery device would not need or be expected to have an opening the exact size of the balloon’s opening.
As mentioned earlier, the issue of clogging is a concern primarily in the inflow section of the connector, which contains a mixture of powder and air. To combat this potential clogging, the inflow section of the connector was adjusted to flow directly downwards. The powder can then flow vertically from the end of the inflow tube through the inflow section of the connector and into the balloon. In contrast, the outflow section of the connector was angled to make room for both inflow and outflow tubes to descend straight into the connector. All of these changes were implemented in design F, which can be seen in Figure 4-23. Additional versions of design F were printed to test with silicone tubes as well as the PTFE tubes, but the structure remained the same, with minor dimensional changes to fit the specific silicone tubes.

Design F

Figure 4-23: Design F removes the barb at the bottom end of the connector and is designed such that the connector fits over the balloon entrance, thereby increasing the cross-sectional area at that point. The inflow section is straight to assist the powder in flowing directly into the device without becoming stuck, while the outflow tube is angled, since the directionality of air alone was less of a concern.
4.11 Breadboard Test Setup

LEGO® DUPLO® bricks were used to create an easily modifiable test setup shown in Figure 4-24. The LEGO assembly is clamped to a wooden board, which in turn is clamped to the shelving behind it for a secure vertical setup.

There are two discrete sections of the setup: a powder holding area with the initial powder flow, and the powder flow through the esophageal tract. The first section contains the majority of the hardware, with a powder containment system, two vibration motors with their associated batteries, and the connection to the positive pressure pump.

The powder container system is a modified centrifuge tube with two potential options: a free system and a fixed system. Both can be seen in Figure 4-25. The free system suspends the powder container such that it can shift in response to the discrete impacts from the vibration motor’s eccentric weight while still remaining on the same horizontal plane. The fixed system uses a custom 3D printed support structure such that the tube remains in the same location even with the bumps of the vibration motor. The 3D printed components interlock with the surrounding LEGO pieces to fit comfortably into the LEGO setup.

The two vibration motors are used to assist in the flow of the powder from the powder container system to the inflow tube, eventually leading into the drug delivery device. The upper motor is placed such that the eccentric weight hits around the bottom of the centrifuge tube (which acts as the powder containment system) and the stopcock connected to the centrifuge tube. This motor is an uxxcel 12-volt vibration motor rated for a no-load speed of 3100 revolutions per minute (model number a12101600ux0224 from Amazon.com or uxxcel.com). The second motor is placed lower such that the eccentric motor hits around the tube fittings leading to the main inflow tube. This motor is an uxxcel 12-to-24-volt vibration motor rated for a
no-load speed of 4700 revolutions per minute (model number a14082500ux0138 from Amazon.com or uxcell.com). Note that during the formalized testing described in chapter 5, both motors were run at lower power using 9 volt batteries.

The previous setup used a hard-plastic pipe that had been heated and formed in a shape that approximates the esophageal tract. The rigidity of this pipe created potential distortion of the small inflow and outflow tubes that lie inside the pipe. The tubes can jam or become crushed while being inserted into the pipe. This issue was accommodated for in the LEGO setup. The LEGO test setup uses a flexible plastic tube of similar size that is arranged in an almost identical manner as the original rigid pipe (see Figure 4-26). However, this tube is held in place by the LEGO bricks, and can be easily slipped on and off of the vertical LEGO system. To insert the small inflow and outflow tubes, the larger tube is removed from the LEGO setup and held to be approximately straight. The smaller tubes are then inserted into the tube, whereupon the tube is then carefully returned to the LEGO setup and its esophageal shape. Note that in a real-life scenario, one more robust multi-lumen tube could be used rather than two delicate PTFE tubes. In this case, the tube should be able to be inserted through the winding path of the NG tube and into the stomach, and should not require the straighter path of the prototyped LEGO setup.
Figure 4-24: The LEGO test setup is a relatively modular vertical test setup. The various components are labeled.
Figure 4-25: The two powder container setups are shown from different angles. The free powder container setup fixes the height of the powder holding container while allowing it to move in the horizontal plane. The fixed powder container setup uses custom LEGO-like fixturing to constrain the powder container system and interlock with the rest of the test setup.

Figure 4-26: The rigid plastic tube that was initially used to mimic the esophagus is shown held next to the flexible tube constrained in the LEGO test setup. The curvature of the new flexible tube is almost identical to the original curvature but the flexible tube can easily be removed from the test setup so that the small inflow and outflow tubes can be inserted without becoming damaged.
4.12 Heat-Treating Tubes

As mentioned earlier in section 4.10.2, powder flow was attempted using both silicone tubes and PTFE tubes. PTFE tubes are lubricious and the powder therefore tends to flow more smoothly through the tubes. However, the tubes are not particularly flexible and tend to have large radii of curvature. They also undergo plastic deformation more easily if they are accidentally crushed or jammed during the setup process. In contrast, silicone tubes are generally quite flexible, have small radii of curvature, and undergo elastic deformation. Unfortunately, basic testing found that the silicone tubes were much more likely to clog due to silicone’s limited lubricity, thereby rendering the entire system ineffective. The PTFE tubes were consequently chosen for prototyping purposes.

Note that in a commercial version of this drug delivery setup, PTFE-lined silicone tubes could be used. These tubes would have all of the advantages of silicone tubes, with the tube insides benefiting from PTFE’s low-friction.

The prototyping setup required has certain curvatures that are quite tight, and the PTFE tubing tended to kink when attempting to re-create those curves. These kinks would cause a significant lack of air-and-powder flow. To cause the tubes to be amenable to tight curvatures, they were heat-treated using a heat gun and a track. This track (seen in Figure 4-27) was created using a CNC router and a V-groove bit. The track was designed to have a V-groove to accommodate the various sizes of tubes being tested, and it follows the path required for the air-powder inflow tube, from the lower vibration motor through the esophageal tract into the drug delivery balloon. Note that while the track specifically follows the inflow tube pathway, it was able to be used in heat-treating the outflow tube as well. The outflow tube includes a portion of
the pathway with a larger radius of curvature than the inflow tubes’, which allows the inflow tube track to be used effectively for both tubes.

![Image of a track with tubing](image)

**Figure 4-27:** The track was designed to mimic the approximate curvature (including the curve of the esophagus) required for the LEGO test setup. The tubing is heat-treated using the track to mimic this curvature for use in the LEGO test setup.

To heat-treat the tubing, wire cable was placed inside the tube before the tube was held down and/or taped to the track in small sections. The wire prevented the tube from kinking and/or becoming crushed. A heat gun was then used to heat the tubing in increments along the full length of the track. Heating the tube annealed it so that it would retain its shape when the wires were removed. The tubes with the cables inside are then placed into the flexible esophageal tube (after it has been removed from the LEGO setup and stretched to be somewhat linear). The esophageal tube is returned to the LEGO setup, and the cables are then slowly removed from the inflow and outflow tubes, leaving uncrushed inflow and outflow tubes that can accommodate sharp turns and be connected to the rest of the drug delivery setup.

To test whether tubes could be threaded into the esophagus, two 9 gauge tubes (i.e. the 1:1 tubes) that had previously been placed into the “linear” esophageal tube were used. These tubes were removed from the testing setup and the cables were re-inserted into them. They were simultaneously then successfully placed into the esophageal tube while it remained bent in the
LEGO holder. This shows a potential method for inserting the tubing in a real life scenario. In the ideal scenario, the real-life tubing could be inserted without the need for any internal cable. However, if it becomes clear that the tubing struggles to maneuver through the esophageal pathway or actually kinks during insertion, the method of using a cable as internal support for the tubing can be considered.

4.13 Process Design Takeaways

There are several important takeaways from the design process that can be summarized here. While vibration motors are needed to keep the powder flowing, discrete impacts to the system are required, rather than a semi-continuous vibration. In addition, the vibration motors need to be running the entire time, starting before the pumps are turned on and ending after the pumps are turned off. This helps ensure that the powder does not become clogged in the very start or end of the powder flow. I found that once the test begins, it can be stopped but cannot easily be re-started. The process of powder flow should therefore be a continuous process that takes place in a single attempt.

Using two pumps to introduce both positive and negative pressure elements into the system was found to be necessary. The positive pump needs to be pulsatile, as continuous positive pressure was found to be ineffective. The negative pressure was found to work acceptably as a continuous element. Note that it is possible that pulsatile negative pressure (in addition to pulsatile positive pressure) would be effective as well, but this was unable to be tested at this time due to the materials available.
Finally, having the powder flow be gravity-assisted was found to be of paramount importance. The system requires the use of both lubricious tubing and gravity to allow the powder to flow into the drug delivery device.

4.14 Design for Real Life

The drug delivery test system designed in this thesis is a lab-based system. To use this system in real-life in an Indian hospital, many design changes must be made. This section will describe some such proposed design modifications.

Instead of using separate inflow and outflow tubes, a dual-lumen tube would be used. Some examples of multi-lumen tubes can be seen in Figure 4-28 [63]. This dual-lumen tube would use the inflow and outflow cross-sectional area proportions chosen in the lab-based system. The tubing would be made of silicone, but the inflow (and possibly outflow) internal areas would be lined with PTFE to improve the lubricity of the tubing. Note that lubricity is important for the powder to flow without clogging, and is not necessarily helpful in improving air flow. Therefore, it is possible that the outflow tubing component would not be enhanced by the addition of PTFE lining, while the inflow tubing component would be significantly improved.

The end of the outflow tube component would have a small filter attached to it so that air could escape the drug delivery device into the outflow tube and the medication would remain in the device. The bottom of the dual-lumen tube would be connected to the drug delivery device in a detachable manner that has not yet been determined. The dual-lumen tube would split into two different components near the top of the tubing, i.e. the section of tubing that is in the air and not in the nasogastric tube. (The entire component of tubing that would be in the nasogastric tube
would be the singular double-lumen tube.) This split would be designed so that the inflow tube can be connected to a positive pressure pump and the powder holding container (possibly with the use of a Y connector) and the outflow tube can be connected to a vacuum pump.

The patient would be placed in High Fowler’s position, as described in section 4.9. Since the medication holding container must remain higher than the patient’s body to add the gravity-assist, several different options should be explored. One possible idea is to mount the medication holding container on a helmet that the patient wears during the drug delivery. A second option is to have the medication holding container placed on a high hook (like an IV bag being placed on an IV pole) or a high shelf.

The vacuum and positive pressure could possibly come from the hospital’s wall pressure units, like the commonly seen hospital wall oxygen outlet and vacuum pump. Carbon dioxide is also commonly available in hospitals, either in a tank or through the pipes [64], [65]. Alternatively, the vacuum and positive pressure could come from small, movable pumps that are more similar to the current setup.
In section 4.10.2, a set of tubing ratios are mentioned. The rationale behind different tubing ratios is based on the idea that the inflow and outflow tubes do not necessarily need to be the exact same size. A large inflow (i.e. pressure leg) and small outflow (i.e. vacuum leg) could in fact be the most efficient scenario, allowing a large amount of powder to flow through the inflow and thereby significantly increasing the flow rate of the powder. A variety of tubing ratios were created with the PTFE tubing based on the 0.25" cross-sectional area of the NG tube. Assuming a 0.03" wall thickness for a tube with an outer diameter of 0.25", the inner diameter of such a tube would be 0.19". Note that this is an estimation, where in reality a tube entering an NG tube would have a slightly smaller outer diameter than the NG tube’s inner diameter. The inner cross-sectional area would then be 0.0284 in\(^2\). Further space would be eliminated by the inner walls between multiple lumens of tubing. This estimation contributed to a set of tubing ratios where the total cross-sectional areas were between 0.0184 in\(^2\) and 0.0218 in\(^2\). Table 4-1 shows the various inflow and outflow ratios of the PTFE tubes.

Testing of different tubing ratios is intended to lend insight into which ratio might be most useful in the real-life scenario with a multi-lumen tube.

*Table 4-1 Assorted tubing ratios are shown with the related tube dimensions.*

<table>
<thead>
<tr>
<th>Approximate Tubing Ratio (Inflow:Outflow)</th>
<th>Actual tubing ratio</th>
<th>Gauge &quot;Ratio&quot;</th>
<th>Total cross-sectional area (in(^2))</th>
<th>Inflow cross-sectional area (in(^2))</th>
<th>Inflow ID (in)</th>
<th>Outflow cross-sectional area (in(^2))</th>
<th>Outflow ID (in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>1:1</td>
<td>9G:9G</td>
<td>0.0218</td>
<td>0.0109</td>
<td>0.118</td>
<td>0.0109</td>
<td>0.118</td>
</tr>
<tr>
<td>2:1</td>
<td>1.96:1</td>
<td>8G:11G</td>
<td>0.0210</td>
<td>0.0139</td>
<td>0.133</td>
<td>0.0071</td>
<td>0.095</td>
</tr>
<tr>
<td>3:1</td>
<td>3.09:1</td>
<td>8G:13G</td>
<td>0.0184</td>
<td>0.0139</td>
<td>0.133</td>
<td>0.0045</td>
<td>0.076</td>
</tr>
<tr>
<td>4:1</td>
<td>3.82:1</td>
<td>7G:13G</td>
<td>0.0217</td>
<td>0.0172</td>
<td>0.148</td>
<td>0.0045</td>
<td>0.076</td>
</tr>
<tr>
<td>5:1</td>
<td>5.06:1</td>
<td>7G:14G</td>
<td>0.0206</td>
<td>0.0172</td>
<td>0.148</td>
<td>0.0034</td>
<td>0.066</td>
</tr>
<tr>
<td>6.5:1</td>
<td>6.37:1</td>
<td>7G:15G</td>
<td>0.0199</td>
<td>0.0172</td>
<td>0.148</td>
<td>0.0027</td>
<td>0.059</td>
</tr>
<tr>
<td>8:1</td>
<td>7.82:1</td>
<td>7G:16G</td>
<td>0.0194</td>
<td>0.0172</td>
<td>0.148</td>
<td>0.0022</td>
<td>0.053</td>
</tr>
</tbody>
</table>
Chapter 5 Testing

5.1 Test Setup

A proof of concept test was designed to measure the flow rate of the powder under several different conditions. To have an understanding of the environmental conditions, the temperature and relative humidity near the test setup were measured. To test both the current best-case and worst-case scenarios, the 8:1 and 1:1 inflow to outflow tubing ratios were measured. The best-case scenario refers to the 8:1 ratio, as that would allow for a large inflow and a tiny outflow to help ensure the powder can flow quickly and smoothly into the device. The worst-case scenario refers to the 1:1 ratio, which would prove necessary if the 8:1 and other unbalanced tubing ratios were found to be ineffective. This was considered to be the worst-case scenario because the inflow tube would be the smallest, which would be expected to have the lowest flow rate. The 8:1 and 1:1 tubing ratios were tested with both the free and the fixed powder holding containers, for a total of 4 unique tests.

Testing was conducted for 2 minutes. Before the test began, the vibration motors were adjusted as necessary to accommodate for the free or fixed powder holding container. The vibration motors, vacuum pump, and positive pressure pump were all turned on before the test began. The test was considered to have begun when the stopcock connecting the powder holding container to the rest of the system was opened. After two minutes, the stopcock was closed. The rest of the equipment was kept running for about 15 seconds afterwards to clear out the inflow tubes. While this could add a small amount of powder to the balloon, it is an important step to ensure the tubes remained unclogged for a future test.
After the testing was conducted, the balloon and powder were weighed, and the approximate weight of the balloon was subtracted. The mass flow rate (in grams per minute) of the powder was then calculated, and from the mass flow rate the time required to reach 100 grams of powder (assuming a constant flow rate) was calculated.

5.2 Results

The results of testing can be seen in Table 5-1. Testing of the 8:1 ratio with the free powder holding container was by far the most successful, showing that the device can be filled in 7 minutes.

<table>
<thead>
<tr>
<th>Test Number</th>
<th>Tubing Holding Container</th>
<th>Temp (°C)</th>
<th>Relative Humidity (%)</th>
<th>Weight of powder in 2 minutes (rounded to nearest 0.5 g)</th>
<th>Time to 100 g (rounded up to minute)</th>
<th>Vibration Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Free</td>
<td>25</td>
<td>37</td>
<td>30.5 g</td>
<td>7 minutes</td>
<td>Worked as expected</td>
</tr>
<tr>
<td>2</td>
<td>Fixed</td>
<td>24</td>
<td>33</td>
<td>3 g</td>
<td>67 minutes</td>
<td>Physically held upper motor</td>
</tr>
<tr>
<td>3</td>
<td>Fixed</td>
<td>25</td>
<td>30</td>
<td>11.5 g</td>
<td>18 minutes</td>
<td>Physically held upper motor and near lower motor</td>
</tr>
<tr>
<td>4</td>
<td>Free</td>
<td>25</td>
<td>30</td>
<td>15.5 g</td>
<td>13 minutes</td>
<td>Became caught intermittently, was manually “unstuck”</td>
</tr>
</tbody>
</table>

In contrast, the second test of the 8:1 ratio with the fixed powder holding container was relatively unsuccessful. This is most likely because of an issue with locating the upper vibration motor at the proper location with respect to the powder holding container, and the lower vibration motor at the proper location with respect to the tubing. Due to certain physical constraints within the setup, the upper vibration motor was unable to be moved to the exact correct location, and the lower vibration motor was also slightly off from the ideal. As described
earlier, the vibration motors are crucial to the success of the powder flow process. At the start of
the testing, the upper vibration motor seemed like it might not have been hitting the powder
holding container at all, and I therefore manually held the vibration motor to ensure it made
contact with the powder holding container. It is also possible that the lower vibration motor was
also not contacting the setup at the exact proper location, which would cause an additional
hindrance. Finally, the tubes and the outflow filter were not cleared with compressed air between
the 8:1 free test and the 8:1 fixed test. This likely caused the system to operate significantly less
efficiently. After breaking down the system after the 8:1 fixed test, I noticed significant amounts
of powder in and near the filter, much of which likely stemmed from the 8:1 free test that took
place before it. This clogging almost certainly contributed to the especially low powder flow
rate.

The third test run was the 1:1 fixed test. Since the same tubes were used for both the free
and the fixed test in each individual ratio, the fixed test was run first here as a control against the
8:1 test, where the free test was run first. The outflow filter was cleaned before this third test. For
this test I held the upper vibration motor and a portion of the tubing to ensure that the upper and
lower vibration motors were both hitting the setup. This test was significantly more successful
than the 8:1 fixed test, likely due to the abovementioned factors: clean tubing and vibration
motors hitting the system.

Between the 1:1 fixed test and the 1:1 free test, compressed air was used to clean out the
inflow and outflow tubes as well as the outflow filter. The 1:1 free test was then run. A couple of
times during the 1:1 free test, the upper vibration motor became “stuck” with respect to the
powder holding container, causing the vibration to stop. I used my hands to manually “unstick”
the system. However, it is important to note that these moments likely caused delays, thereby
lowering the average flow rate. Even with these delays, the 1:1 free test was more successful than the 1:1 fixed test. It seems that allowing the powder holding container to move to a certain extent makes the vibration motor more successful.

Of importance is the fact that the vacuum pump was run as different intensities during the testing. For the 8:1 ratio tests, the vacuum pump was run at the maximum negative pressure. For the 1:1 ratio tests, the vacuum pump was run as the minimum negative pressure. The exact pressures were not determined, but the dial indicator on the vacuum pump offered negative pressures from 0-30 inHg. The positive pressure pump did not have any dial to create variations in pressure.

The default was to run the vacuum pump at its maximum intensity. However, a pre-test using the 1:1 system showed that the balloon quickly collapsed under the vacuum’s pressure. A collapsed balloon does not allow for the balloon to fill properly. To combat this, the pressure of the vacuum was decreased to the minimum, which allowed the balloon to remain inflated during the test.

Future testing would be aided by the use of more reliable and more precisely variable vacuum and positive pressure pumps to determine the ideal positive and negative pressure to be applied for a given tube ratio.
Chapter 6 Conclusion

A methodology and process for filling a drug delivery device in a stomach was designed, and a proof-of-concept system was created and tested. The concept miniaturized known larger scale powder conveyance schemes with the addition of critical vibration elements at potential powder jamming junctures to ensure smooth conveyance of powder through a double lumen nasogastric tube into a balloon that would reside in the stomach. In addition, end-of-lumen geometry is critical to enable the air-conveyed powder to enter the balloon, drop the powder, and allow the air to escape back up the tube’s second smaller lumen. Testing showed that a drug delivery device could be filled with 100 grams of medication through a nasogastric tube in 7 minutes. Future work on the process for filling the device would be to design a real-life system that was able to be used in an Indian hospital, as discussed at the end of Chapter 4. More extreme tubing ratios beyond the 8:1 could also be tested, depending on the availability of an extremely high-resolution 3D printer for creating the custom connectors. Testing could also be conducted in a hot, humid environment to mimic the extreme climate that can occur in India. In addition, testing should be conducted with the TB medication itself, which will require testing in a safe environment.

This thesis focused on a small portion of a project with a large scope: the initial “AHA!” Invention phase has been successfully realized with a bench level prototype, but significant future work for this project will be required to optimize elements and package them for animal trials and then human trials. The exact dimensions of the nasogastric tube and multi-lumen tube components should be considered more formally with respect to efficiency, ease of use, ease of manufacturing, and patient comfort. As mentioned in the methods section, other elements of the
project that were not the focus of the thesis are: insertion of drug delivery device, sealing of
device, detaching of drug delivery device from insertion device, removal of insertion device,
retention of device in stomach, and retrieval or removal of drug delivery device. Another major
component is the creation of the drug delivery device itself. In this thesis a catheter balloon was
used, and ideally the continuation of this project would include working with medical balloon
designers to create the device itself. An additional major project component that was not a
function of this thesis was the slow-release of the drugs through the wall of the balloon. The
correct portion of medication must be released daily over the course of the 30 days so that the
individual is treated every day and is never over-dosed.

This device must undergo significant animal testing with swine, and eventually undergo
human subject testing. In later stages of this project, there will also be significant regulatory and
governmental components, to ensure that the process and device are safe and have governmental
approval. While the amount of future work required is significant, the continuation of this project
could eventually lead to effectively treating tuberculosis in millions of people.

In the future, a variation on this project could be used for other diseases that require large
amounts of medication to be delivered to a patient over a large period of time, either
continuously or in discrete amounts. The project could also be expanded in focus to assist in
palliative care or other aspects of pain management, improving the quality of life for millions.
Chapter 7 Appendix

Patient Questionnaire (To be administered in a face-to-face interview in local language (ex. Hindi))

[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.]
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.
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.]
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 of 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?

Rate to take 000 capsule
Ingestion: NG tube more uncom

Ingestion, control of system,
Capsule – quantized version
NG tube – flow system to the gastric cavity

Gastric residence
NG tube rapidly deploy
Evidence – gastric balloons
Allurion eclipse – ingestion

In your clinical
Act of placing the tube – how much time technical portion
Healthcare Professional (To be self-administered)
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
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
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
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?

- 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
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
Bibliography


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