Engineering World Health

Liquid Medication Delivery System

Midsemester Report

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Abstract

The goal of this project is to create a simple, cost-efficient, and accurate method of dispensing donated medication in a variety of environments in pharmacies around the developing world. Currently there exists a donated kit which is costly and relies on the presence of multiple parts. We present several preliminary design alternatives and analyze them in a comparative matrix weighted to match our product design specifications. We chose a final perforated tube design to be prototyped, tested and submitted to Engineering World Health.

Introduction

The HIV/AIDS crisis has been a growing pandemic since the 1970's. Safer sex practices and better education policies have helped slow the growth of the viral outbreak. Another aspect of HIV transmission that has been largely overlooked until the last decade is viral transmission from mother to child during and after childbirth. HIV positive mothers have a 30 percent chance of spreading the virus to their child during traditional childbirth or during breastfeeding, known as vertical transmission[1]. Between the outbreak of the disease and 1997, 2.5 million children under the age of 15 died of AIDS in sub-Saharan Africa compared to only 300 in the US during that same time[2].

Many medications on the market can reduce transmission rates and, when used in combination, slow the progression of the disease. These medications work in a variety of ways and slow different parts of the infection. One of these medications is Nevirapine (brand name Viramune®), which is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that prevents the HIV virus from transcribing its RNA into DNA. Studies have shown that Viramune® can reduce mother-to-child transmission by 50%[3].

Currently pharmaceutical conglomerate Boehringer Ingelheim donates Viramune® and a dispensing system to developing countries. While the medication is effective, the dispensing system is not. The medication is donated in a variety of bottle sizes, and the system requires multiple parts. Once all parts are delivered to a pharmacy, a trained pharmacy technician can distribute medication to patients. The standard dosing procedure requires a pregnant mother take a single dose of Viramune® before giving birth and then administer a dose to the infant three days after giving birth. In many developing countries pregnant mothers cannot make multiple trips to the hospital or pharmacy, so the medication is usually given to the mother to administer to her child at home.

The current method of dispensing is as follows. First the bottle of medication is uncapped, a dose of medication is drawn into a syringe, and the medication bottle is re-capped (Figure 1). The syringe is then capped and placed in a self-sealing foil pouch with written and graphic instructions for administering the dosage. This method is inefficient and expensive because it requires a new syringe with each dose. Also the medication spends excessive time exposed to air where it can be contaminated. It requires an individual syringe for every dose, and a cap for every syringe. This method has opportunity for spilling. In practice "liquid medications are now given in plastic bags, open syringes or recycled plastic bottles, all of which lead to medication spoilage and loss." [5]

Figure 1: Current dispensing system.[4]

Problem Statement

To design a device that will seal bottles and be able to measure and dispense the proper dosage from a stock supply at pharmacies. The device must be inexpensive, as it will be used in treating HIV/AIDS patients in developing countries.

Design Specifications

As this device is being donated and used in developing countries there are several design criteria that must be met. The device must be able to dispense 4000 doses of medication in its lifetime to make it cost effective and overcome short-term supply chain interruptions. When produced in quantities of 2000, the device has a maximum cost of $2 per unit with a goal of $.50 per device. The device must keep medication from spoiling, and dispense the medication accurately and precisely. The defined dosage is .6 ± .05mL and the device must meet those tolerances. Also, the device must be constructed with materials that will not chemically interact with the medicine. Finally, the device must be easily adaptable so that it may be incorporated into the delivery of medication from a variety of bottle sizes, as donations are made in a number of different bottles.

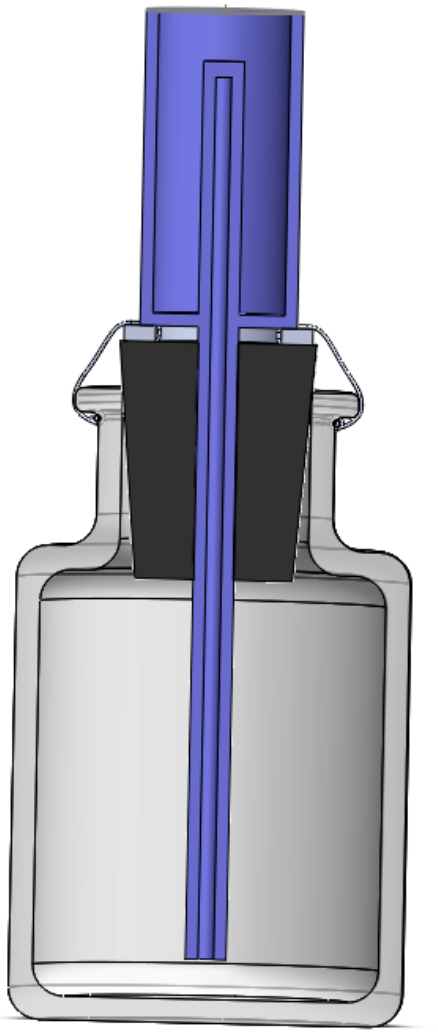

Figure 2: Positive Pressure Device.

Positive Pressure Device

Our first design is similar to the ACT® mouthwash bottles (Figure 2). The pharmacy technician would squeeze on

the sides of the bottle, generating a positive pressure inside the bottle. The increased pressure would force the medication up the straw and into the container at the top. On the sides of the top container there are markings similar to a graduated cylinder indicating how much the container has been filled. A one way valve is incorporated into the straw so that the technician would not have to maintain a constant pressure on the device to keep liquid at the top. Once the container is filled to the correct amount (0.6 ml), the technician would then pour that amount into the foil pouches for distribution.

Connecting the plastic container and straw to the bottle is a rubber stopper and "champagne wire." The use of a rubber stopper allows adaptation to different bottle sizes. The rubber stopper is secured much like a champagne cork (Figure 3). It has a wire ring on top of the stopper, and another wire ring over the neck of the bottle. These rings are pulled tight together with three evenly spaced wire loops that run between them. This design is superior to a stopper simply pushed into the opening, since there is a constant force from the wires holding securing it in place.

Figure 3: Champagne cork attachment[6].

Advantages

This device would be easy to manufacture and inexpensive to produce. Only one mold would be needed, and while it would carry a high initial cost, the cost of producing mass quantities would offset initial costs. The device would also have low maintenance because there are no moving parts involved.

Disadvantages

This device is not applicable for all bottle types. For example, if the medication is given to the pharmacy in glass bottles, the technician cannot generate the pressure necessary to

fill the top container with medication. Furthermore, this design is quite cumbersome to use. It relies on the dexterity of the technician to fill the top compartment with the perfect amount of medication, and then pour this medication into the foil pouches. The technician may not be able to lift the bottle to pour while holding the foil pouch, and if they are able to, the chances of spilling medication during the process are high. Also, without a cover or cap to the top, a large amount of medication is exposed to the open air, compromising the sterility. Finally, as the bottle approaches empty, this design may have difficulty extracting the last doses without bubbles.

Liquid Pour Spout

This design is similar to the measured pour spouts used on liquor bottles (Fig. 4). On the first use, the spout must be primed before liquid can be poured. This is done by tipping the bottle and spout upside down. Liquid flows past the ball bearing labeled 4, and fills up the pink volumetric column. Ball bearing 2 seals the top of the spout so liquid cannot get out. The bottle is then flipped upright, bearing 4 immediately seals the chamber from the bottle, bearing two falls to the bottom of the chamber, thus priming the device. On the next pour, the ball bearing 2 "pushes" out the liquid in the chamber while liquid is flowing past ball bearing 4 and filling up the space that was just vacated. The small vertical column at 1 is present to reduce after drip and eliminate waste. This can occur when the bottle is being set back up right and ball bearing 2 is rolling back down the chamber. Excess fluid can drip down the vertical

Figure 4: Liquid Pour Spout[7]

column and back into the bottle. This feature allows for a more precise pour. This device will also use the rubber stopper and champagne wire for a tighter, more secure seal.

Advantages

This device can be used with any type of bottle, glass or plastic, and it is very easy to use. And unlike the previous design, it does not rely on the precision and accuracy of the technician to administer the correct amount of medication.

Disadvantages

This device would be very difficult to manufacture because of all the moving parts, the wide variety of materials and components needed, and the stringent tolerances. The manufacturing process would be more expensive when compared to the other designs. Maintenance and sterilization would also prove troublesome because of all the parts. Moreover, one dose is always primed inside the volumetric chamber. That chamber is exposed to the open air. It may be days before the next dose is given, and because the sterility of that dose has been compromised, it would need to be discarded, resulting in waste and lost medication.

Syringe and Tubing

This family of related designs is united primarily by the use of a syringe to withdraw and expel the correct dosage. A syringe is a classic method for dispensing precise medication doses. There are many advantages to using a syringe. Nearly anyone who has worked in a pharmacy is familiar with the mechanism and will know how to use the design. Syringes are used so often because they allow a precise and accurate dosage. Another strong point is the ease of adjusting the dose if other amounts are required. Other commonalities between these designs include connection of the functional components with tubing and sealing the device with the bottle by a

wire fastened rubber stopper. The three specific designs are a rotating T-valve, two one-way valves, and a perforated tubing design.

Rotating T-Valve

This design involves a champagne style rubber stopper, tubing connections, a syringe, and a rotating T-valve (Figure 5). When the syringe plunger is pulled out, a negative pressure is created, and the valve is in position such that this pressure is relieved when the medication moves up the tubing and into the syringe. The valve is then adjusted such that when the plunger is pushed in, positive pressure is created and the desired dosage is expelled out of the exit tubing.

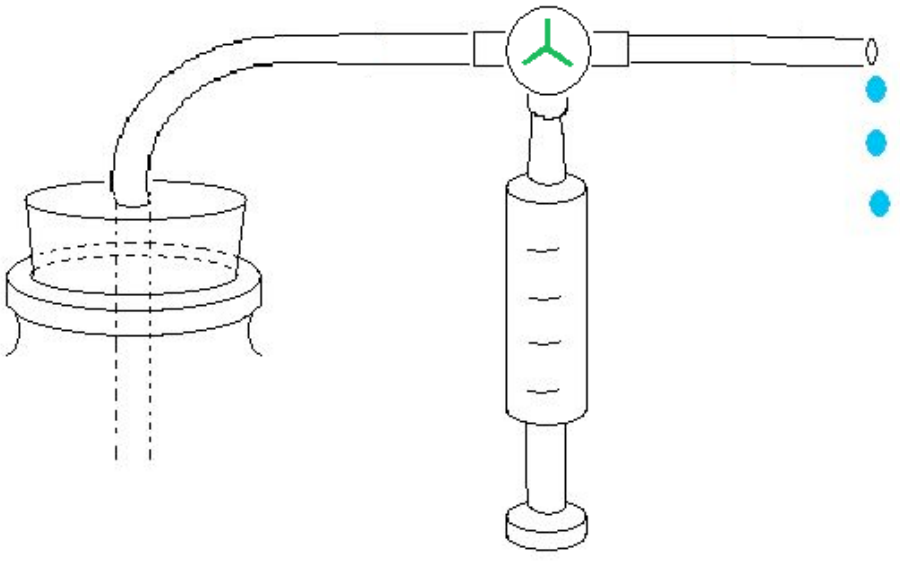

Figure 5: Rotating T-Valve Design

There are many positive attributes of this design. Like all of the stopper and syringe designs, the use of a syringe allows an accurately-measured dose. Another advantage is that the medication spends a short time exposed to the air. On-site assembly of this device is simple; the tubing connections would be secured before shipping, and the technician would only have to tighten the

securing wires. The majority of components are easily obtained and inexpensive. The main setback is the requirement of a rotating T-valve which would be expensive to buy or difficult to manufacture.

Two One-way Valves

This design works much like the rotating T-valve. The main difference is that the T-valve has been replaced by twin one-way valves (Figure 6). When the syringe plunger is pulled out, a negative pressure is created, and the medication moves up the tubing through the first valve and into the syringe. When the plunger is pushed in, positive pressure is created and the desired dosage is expelled out of the exit tubing through the second valve. The advantages and

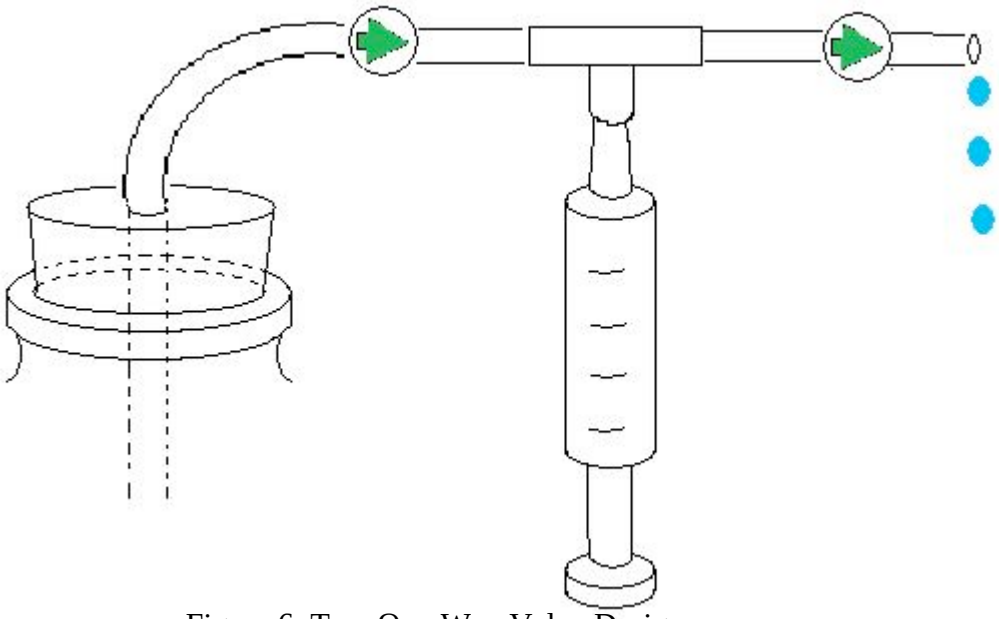

Figure 6: Two One-Way Valve Design

disadvantages are the same as the rotating T-valve with a few exceptions. With automatic one-way valves there is one less step in use, the user need only push and pull the syringe. With manual one-way valves the user must open the first valve, pull the syringe out, close the first valve and open the second, then push the syringe in, then close the second valve. An automatic valve could be a ball check valve, cheaper than a rotating T-valve, but still too expensive. A manual one-way valve would be a simple binder clip over the flexible tubing. The clip would allow liquid to pass when it is unclipped, but stop passage when clipped. The manual valves require more steps in use, but are not exposed to the medication, compared with the automatic valves which are exposed and would be difficult to clean. This design requires the most components and connections-all places for failure to occur.

Perforated Tube

This design involves a rubber stopper, perforated tubing, a binder clip, and a syringe (Figure 8). The tubing is perforated at the point where it rests on the bottom of the bottle. When the syringe is pulled out the clip is in place, and negative pressure is created in the tubing so that medication flows through the tube perforations and into the

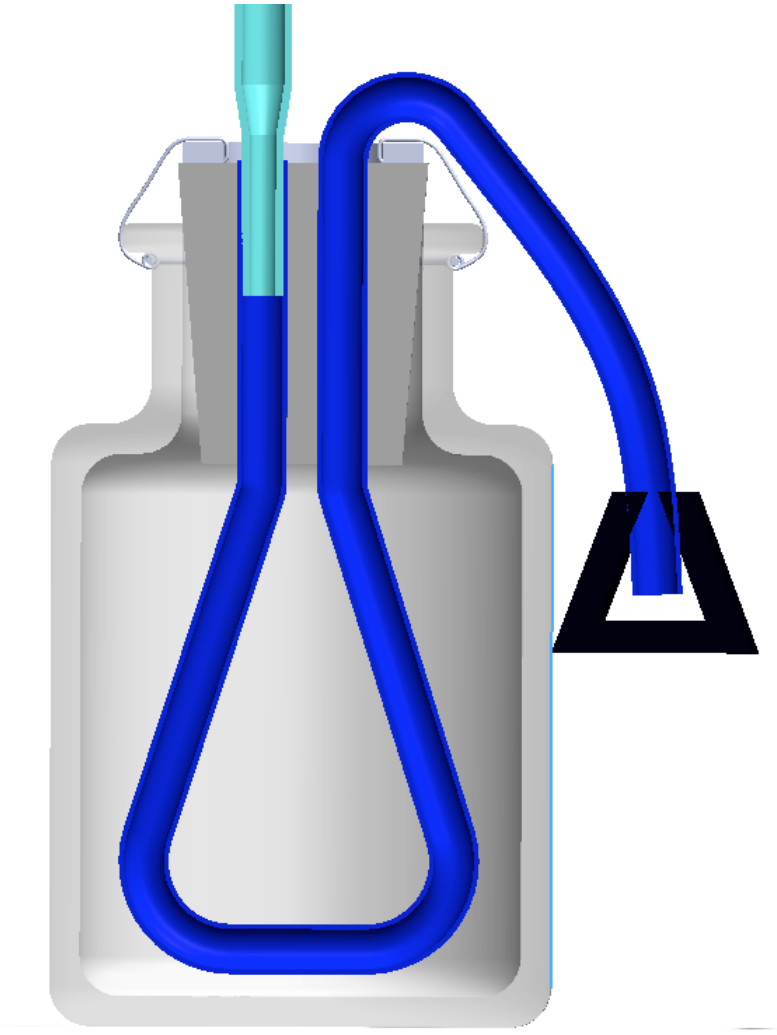

Figure 8: Perforated Tubing Design

syringe. The clip is then removed, allowing the syringe to be depressed so that the medication exits through the exit hole of the tubing. This design relies on the much higher fluidic resistance through the perforations than through the exit to expel the dosage out rather than back into the bottle. This design is the simplest of all syringe designs, involving the fewest components. All of these components are readily available and inexpensive. Use and assembly of this design are basic which allows for fewer user errors and mechanical design failures. One disadvantage of this design is the initial priming which must occur before the device can be used. Long-term testing of this design will be required since minute changes in the perforation size can affect the dosage expelled. Also tests will have to be performed to ensure different pull and push speeds can be accommodated. The optimal amount and location of perforations will have to be determined. As the bottle approaches empty, this design may have difficulty extracting the last doses without bubbles.

Design Matrix

The design matrix includes our three most promising designs: the positive pressure device, the liquid pour spout, and the syringe and tubing design (specifically, the perforated tubing design). Each design is evaluated based upon seven criteria. Three of the criteria are weighted more heavily than the others because they are most important to the design's feasibility and functionality (Table 1). The first of the heavily-weighted criteria is the ability of the design to meet the two dollar cost target. The syringe and tubing design receives the highest score because it uses components that are all off-the-shelf. The positive pressure device receives a lower score due to the fact that it requires a mold. Although making the individual parts is

inexpensive, molds are very expensive and are cost-prohibitive at low quantities. The liquid pour spout receives an even lower rating because it requires more than one mold.

The second criterion is important to the functionality of the design: the ability to dispense an accurate dose of the medication. The syringe and tubing again receives the highest mark because it uses a traditional means of measuring and ejecting the medication. The positive pressure device and liquid pour spout are both dependent on their geometry, and even small variations will multiply to result in large variations in dose size. Furthermore, there is a large surface area, increasing the possibility that the medication will cling to the device.

Sterility is the third important category evaluated. This score is based on two quantities: the medicinal surface area exposed to the air, and the length of time medication is exposed to the air. The syringe and tubing has the lowest overall exposure because the only time the system is open to air occurs when the clip is unclipped and the medication is dispensed. In the positive pressure device, medication sits in the reservoir before being dispensed, which has a significant surface area, hence the lower rating. The liquid pour spout will always have the next dose exposed to the air while it sits in the spout, which introduces a significant possibility of contamination.

Table 1: Design Matrix

	Positive pressure device	**Liquid pour spout**	**Syringe and perforated tubing**
Ability to meet cost target (20%)	14	12	18
Accuracy of dose (20%)	12	12	18
Sterility (20%)	10	6	16
Ease of manufacture (10%)	7	3	10
Ease of assembly (10%)	7	10	7
Ease of use (10%)	10	10	8
Durability	10	9	8
Total	**70**	**62**	**85**

Although the previously mentioned categories are most important to the design, four other significant factors are considered. The first of these factors is the ease of manufacture. The syringe and tubing design is the easiest to manufacture because off-the-shelf pieces require no custom assembly. The positive pressure device and liquid pour spout require molds, which are difficult to manufacture. Furthermore, the molds must hold tight tolerances because the dose dispensed is dependent on the geometry of the design. The liquid pour spout is marked down further because of the several moving parts that are incorporated into the design.

Ease of assembly is also evaluated. The liquid pour spout simply involves inserting the device into the bottle, so it received a perfect score. The other two designs both require that wires are tightened to secure the stopper onto the bottle. Engineering World Health documents specify that significant on-site assembly is acceptable, but our group deemed it less desirable.

Another factor examined is the ease of use. The positive pressure device and liquid pour spout receive perfect scores because each device is filled based on the geometry of the bottle, and then inverted to dispense the medication. The syringe and tubing is slightly more cumbersome because the syringe must be filled, the clip removed, the plunger depressed to expel the dose, and the clip replaced on the end of the tube. These steps must be followed in order, which we assume pharmacy technicians can manage but it is somewhat more involved.

The final factor examined is the durability of the design, meaning the likelihood that the device will dispense the necessary 4000 dosages before failure. The positive pressure device receives a perfect score because there are relatively low stresses placed on the device, and there are no moving parts. The liquid pour spout is downgraded due to the moving parts. The syringe and tubing receives the lowest score because tubing connections wear over time, especially at the

clip connection. This problem could be solved by sending extra tubing to replace worn tubing, but doing so would increase cost.

Future Work

The second half of the semester will be focused on prototyping and testing the syringe and tubing design. First, the design will be submitted to Engineering World Health. They will review the design and if they approve, we will receive $150 to prototype the device. At that point, we will order the supplies that we need and assemble the prototype. The device will then undergo rigorous testing to ensure that the specifications in the PDS are achieved. The tolerances on the dose will be validated by repeated testing using water in place of the medication. Water will be used because it has a known density at standard temperature and pressure, allowing volumetric calculations based upon the mass dispensed. The bottle will be filled with sugar-water and closed by attaching the device. After being left on the shelf for five days, five doses will be dispensed each day for three days. Each of these doses will be incubated at 37ºC and 5% CO_2 for five days, along with five samples taken from the bottle. All samples will be inspected for bacterial growth at the end of the five day incubation period. The final test will examine the durability of the device by testing a limited number of devices by opening and closing the binder clip 5000 times.

References

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[4] Image: <http://pmtctdonations.org/en/products/Syringes.aspx>

[5] Engineering World Health. Available Design Projects. Liquid Medication Delivery System. <http://www.ewh.org/youth/design_projects.php>

[6] Image: <http://www.pastemagazine.com/blogs/images/uploads/2007/02/champagne_cork.jpg>

[7] Image: <http://www.precisionpours.com/pages/pours3.html>