Disposable Insulin Delivery System
Final report
BME 200/300

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Abstract

Doctor Michael J. MacDonald specializes in type I, juvenile onset diabetes. A great deal of time, money, and research is invested into insulin delivery for insulin dependant diabetics. While extremely intricate systems like Medtronic’s MiniMed can effectively interact with a patient’s daily routine to provide a complex daily insulin diet, these systems are extremely expensive. Our goal is to develop a cheap, disposable drug pump that will deliver the basal rate of insulin for at least eight hours. We developed three designs that could solve the problem and chose one design to pursue for prototyping and further research. Our design will use hydrogels as an actuator and a valve to deliver constant increments of insulin. If prototyping is feasible, we believe we can develop this product for well under $100.00, a dramatic step down from the $6,195 MiniMed Paradigm.

Problem Statement

Our objective is to design a novel method of drug delivery that is disposable, small, light, and inexpensive. The system must be comfortable and discrete while in use. The product should utilize micro-fluidics to deliver a constant flow rate between ten and fifty micro liters per hour with minimal error or fluctuation for no less than eight consecutive hours.

Introduction

The human body uses a complex metabolic system to sustain life and power its everyday actions. It converts complex forms of food into glucose, a type of sugar. Insulin,
a hormone secreted from beta cells of the pancreas, convert glucose into more useable forms of energy. If the body is in need of energy, it aides the movement of glucose into cells for break down into useable energy forms. Surplus glucose is then converted by insulin into glycogen for storage in liver, muscle, or fat cells. Meanwhile, glucagons released from alpha cells of the pancreas break glycogen down from the liver and release it into the blood stream between meals each day. This homeostasis system can be seen in figure 1.

*Figure 1. Flow chart of insulin, glucagon, and glucose in the body.*

Diabetes is a disease that disturbs the body’s use or production of insulin. This disease has three main forms: Type I, Type II, and gestational diabetes. Diabetes II is the most prominent form in the United States. The problem occurs when muscle, liver, and fat cells develop an insulin resistance condition that inhibits glucose uptake into cells. The pancreas responds by creating more insulin to compensate. Over time, the pancreas will become fatigued and will eventually lose the battle with insulin inefficiency; though it is possible to delay the development of diabetes II with a good diet and frequent exercise, the pancreas will eventually fail to secrete enough insulin to adequately respond to glucose intake during meals. A second, less serious form of diabetes is gestational diabetes, which develops temporarily in women in their late stages of pregnancy. Though little is known about the causes of this diabetes type, it is believed that developmental hormones from the mother’s placenta also cause insulin resistance (American Diabetes Association).

Our client Michael J MacDonald, M.D., specializes in Type I diabetes. Type I develops from an autoimmune response in which the body’s white blood cells attack the insulin-producing beta cells of the pancreas. More than 700,000 children and young adults are affected each year. Type I is most commonly developed in children, which is why it is sometimes referred to as Juvenile onset Diabetes. Type I is also called insulin dependant diabetes; because the insulin producing beta cells are destroyed, this type of diabetes necessitates treatment with insulin supplements. Without the constant treatment
with insulin, blood glucose levels will become far too high, which can have fatal repercussions for the diabetic.

Desirable glucose levels in a non-diabetic human are between 70 and 120 milligrams per deciliter (WebMD, Inc.). These levels normally rise after meals, but should return to normal a few hours after. If insulin levels are too low, glucose levels will remain over 180 mg/dL. Immediate responses include blurry vision, frequent urination, and nausea; however, there are many dangerous long-term results of having consistently high levels of glucose. High blood glucose levels cause blood vessels in the eyes to bleed, which can result in blindness. Hyperglycemia can also be hard on the kidneys and can eventually lead to their failure, a loss that would require a transplant or use of a dialysis machine for survival. It can also result in nerve damage, which would most notably be detected by pain or complete loss of feeling in the legs, feet, arms, or hands. Hyperglycemia can provoke gum infections, as well as infections of bones that hold the teeth in place. Finally, long-term high glucose increases the risk of heart disease.

A type one diabetic must supplement the lacking insulin production of their destroyed beta cells with insulin injections. Because insulin is a large protein it cannot be administered transdermally (through the skin), without the aid of ultrasonic frequency vibrations to further open the pores of the skin. It can also not be administered via pills, because the protein would be broken down by the acids and enzymes of the stomach. Although, a great deal of research is committed to discovering alternative methods of insulin delivery, subcutaneous injection is the major method at this time. Insulin is ideally injected subcutaneously into adipose tissue of the abdomen, which requires 9.1 mmHg of pressure. Injection location must be rotated to avoid hypertrophy, a build up of scar tissue
at the injection site. A picture of where subcutaneous tissue is located is shown in figure 2.

Insulin regulation can be broken down into two main components throughout the day: the Bolus injection and the basal rate. Treatment requires the use of two different insulin forms to handle the different components: short acting and long acting insulin. The bolus injection is a large, short-acting insulin dosage given immediately after meals in response to the large amount of glucose being taken into the body in the form of food. The short acting insulin works quickly to lower glucose to safe levels. The insulin injected has three stages of action in the body. First the onset, the span from injecting into the body until it begins working. Next is the peak time, where the insulin is working at maximum strength. Finally the duration is the total length of time that the insulin is working to lower blood glucose levels. Between meals, glucose levels are far lower and much more constant; however, glycogen is slowly broken down and released as glucose from the liver. Because of this steady glucose release between meals and during sleep

Figure 2. Picture of skin anatomy, shows where the subcutaneous layer is
periods, insulin must remain in the blood stream at generally constant rates throughout
the day. Though there are fluctuations based on many factors including exercise, daily
diet, and stress, a constant flow rate called the basal rate can be calculated for any patient.
The basal rate is generally supplied in the form of a few long acting insulin injections
during the day.

It is also extremely important to monitor the amounts of insulin injected by the
delivery system; excessively high levels of insulin and, in response, low levels of
glucose, are also very dangerous for the patient. Hypoglycemia is the condition of having
low levels of glucose in the blood. The patient may initially feel week, irritable, hungry,
or tired. Hypoglycemia is generally less threatening because a patient can simply eat to
raise blood sugars in response to these early symptoms; however, if not dealt with, it may
also induce excessive sweating, headaches, shakiness, fainting, or even seizures. It is
imperative that the basal rate delivery is accurate and correctly calculated for each
patient. In addition to the complex insulin injection routine necessary to regulate the
day’s glucose activities, a diabetic must take frequent readings of their blood to verify the
efficiency of their routine. Glucose levels are measured by running direct tests on small
amounts of blood drawn from fingers in the form of pricks.

While accurate and very safe methods of drug delivery exist currently on the
market, they often cost more than $5,000. Professor MacDonald wants to appeal to a
different market demographic by designing an affordable, disposable, and extremely
small drug delivery system. Ideally the system would cost less than $4.00 and near the
size of a quarter’s diameter, with a thickness less than 2 cm. The system would be
responsible for delivering only the basal rate of insulin throughout the day leaving the
patient responsible for the bolus dosage. Although the patient would still need to make large injections during meal times, this cheap delivery of the basal dosage would reduce the necessity of frequent blood glucose level checks for the patient, making his or her everyday life more convenient without adding excessive cost.

**Competition**

*Minimed*

One of the leading commercially produced insulin pumps is the Paradigm 712 by Minimed, a branch of Medtronic. Their insulin pumps are fairly discreet and can be operated by remote control.

![Minimed's Paradigm 512/712](image)

*Figure 3. Minimed’s Paradigm 512/712*

The Paradigm 512 has a maximum capacity of 176 mL, and the Paradigm 712 carries a 700-unit insulin reservoir. The device is equipped with a glucose monitor that can check blood glucose periodically and check insulin levels in the body. To help
regulate their insulin levels, the pump also includes a bolus calculator that determines the ideal blood glucose and adjusts the flow rate of insulin automatically. The bolus calculator allows the user to input the amount of carbohydrates and sugar in their meal; the calculator would then display the amount of insulin required. MiniMed’s paradigm can be operated by remote control. The remote controlled device utilizes radio frequency (RF) technology, similar to those on mobile phones. RF technology uses radio waves to transmit information instead of infrared (IR) technology. IR technology requires the remote to point directly at the insulin pump, while RF does not. As with most other drug pumps on the market, the Paradigm is rather expensive; it costs around $6,195 (Medtronic-Minimed).

*Microspheres*

In the search for a constant rate of drug delivery, scientists are beginning to look into possible applications of microspheres. Microspheres are small spheres made of degradable polymers as depicted in figure 4. The microspheres can be filled with drugs that are released into the blood system of a patient as the shell disintegrates. The shell is then absorbed into the system, passing through the Krebs cycle and ultimately leaves the body as carbon dioxide and water.

*Figure 4. A picture of a microsphere*
Microspheres show promise in controlled drug delivery because they release their contents fairly constantly over the course of many hours. The rate of drug release depends on the size of the sphere, which can range from 5 to 500 microns. Larger microspheres release more slowly than smaller ones, and the time period of release of larger spheres is also greater.

An obstacle in controlled drug release has been creating uniform size in microspheres. Without this precision in size, constant drug delivery is difficult, as the microspheres would release at different rates. Another problem with microspheres is that they tend to give off large bursts of the drug initially, followed by a more constant release rate. Large peaks of insulin could be very harmful to a patient. Researchers are currently pursuing construction methods that would minimize size irregularities between microspheres.

Microspheres are the future of precision drug delivery, but they do not meet the criteria of this project. Although studies of microspheres delivering proteins have been promising, microspheres are not used in any of the designs because they deliver drugs intravenously over the course of approximately 150 hours, and this project only seeks to deliver insulin to patients over the course of 8-24 hours.

Hydrogel Applications

A microfluidic drug pump currently in the design stage was developed by David T. Eddington and David J. Beebe at of the University of Wisconsin Madison. The device can produce 35 kPa, dispensing 45μL with every stroke of the actuator for up to 24 hours.
Their design utilizes hydrogels, a colloidal gel in which water is the dispersion medium. Hydrogels can be designed to respond to various stimuli to expand, contract, or bend. This design uses pH activated hydrogels, specifically a hydrogel that expands at high pH and contracts at low pH. “Hydrogels respond to a wide variety of stimuli including pH, temperature, light, glucose, antigen, electric field, and magnetic field.” (Eddington & Beebe, 2004). The other material that makes up the majority of the pump is polydimethylsiloxane (PDMS). The drug pump is fabricated in two stages. Four PDMS components are first fabricated separately and then later permanently bonded together. Layers one, two, and three in figure 5 are the three solid layers in the design. Layer two is a 30μm flexible membrane. The hydrogel portions of the device are fabricated by injecting the unhardened polymer into the PDMS frame.

Figure 5. PDMS layer used in fabricating the drug pump. All layers made with 11:1 prepolymer to hardener ratio
UV light is then used to polymerize specific parts of the hydrogel; this is accomplished with a photo mask. The photo mask used to make the actuator has an “array of 2000, 400 μm circles spaced evenly 500 μm apart”. The valve photo mask only has one “300 μm circular hole”. The masked parts of the hydrogel are not polymerized and are flushed out (Eddington & Beebe, 2004).

Both the hydrogel actuator and valve do not come in contact with the substance being delivered; the thin flexible PDMS layer separates them. When either hydrogel expands, it presses down on the PDMS. The actuator forces the PDMS to put pressure on the reservoir, while the valve blocks the disposal path for the insulin. The pump works in

![Figure 6: A cross sectional view of the working device in four steps.](image-url)
three steps as seen in figure 6.

The hydrogel valve is stimulated to close of the opening as the reservoir is filled with the desired drug. Next, the actuating hydrogel is stimulated to create enough pressure to force out the drug while the valve is opened. The valve can either open for a short pulse to release a small amount of drug, or it may open for a longer duration to release the entire contents of the pump, which is 45 μL. This design requires a few modifications before it could feasibly be considered for a drug pump. First, the actuator hydrogel system would most likely have to be triggered electronically. This would simplify the design, as well as quicken the valve response time (Eddington & Beebe, 2004). Also, the reservoir would have to be expanded to hold an adequate volume of drug, so the pump could be used all day.

**Design Requirements**

Our goal is to design an insulin pump that would be able to deliver insulin into the user’s body at a constant flow rate (between 10-50 micro liters) continually for a minimum of 8 hours. Although this is the minimum requirement, it is ideal to have the device function properly for 24 hours; the user can then disposes of and replace the instrument daily. The amount of insulin delivered per hour should have a minimal range of error because a slight fluctuation of the insulin level in the body could have fatal ramifications. This range of error needs to be determined as a percentage of the flow rate of the instrument; since the flow rate is the basal rate of insulin delivered per hour, this value changes for each individual. Hence, the range of error depends on the flow rate of
the device, and should be set to a certain percentage rather than a fixed value of insulin delivered. Our client also requested that the device should be about the diameter of a quarter and should be light in weight to minimize discomfort during continual wear. Currently, MiniMed’s Paradigm 712 is the size of an average pager; it is our goal to produce something smaller than this.

Next, minimizing cost is an integral part of this project; since drug pumps in the market range from $5000-$6000 in cost, creating a device that is less expensive could potentially make insulin pumps more accessible to diabetics. Our client also requested that the device be disposable after use. Hence, the insulin pump must be cost efficient; our client’s ideal cost of production is $35. Although the production cost should be less than a hundred dollars, our client was willing to fund up to $1000 for the prototype. Since the pump carries insulin, and is in contact with the abdomen, it must also be air tight and sterile. The device must be airtight because otherwise, if some fluids are spilled onto the insulin pump, it might contaminate the insulin supply into the body and disrupt the delivery mechanism as well. Therefore, sterility and an airtight seal are key aspects of the design. Furthermore, the driving mechanism will use microfluidics rather than electromechanics because groups from previous years have already explored this area. Previous attempts also indicate that electromechanical mechanisms are often too bulky and cumbersome for the patient to use. The prototype will use hydrogels activated by voltages as the driving force for insulin delivery. Hydrogels allow us to decrease the size of the device compared to the use of piezoelectric or electromechanical actuators.
Rejected Designs

Design One

This next design is a simplified version of the first design. It incorporates many of the same materials and ideas from the first design. Hydrogels and a microprocessor will be utilized for insulin delivery. The hydrogel used will utilize the theory provided in a research using PAA/PVSA (Kim et. al, 2005), which shrinks in response to electric field stimulus. In this research, a PAA/PVSA hydrogel is stimulated with short pulses of three volts as shown in Figure 7 (Kim et. al, 2005). The initial pulse causes the hydrogel to quickly contract. After the voltage is removed, the hydrogel begins to slowly expand back to its initial volume. Before the hydrogel expands to its resting size, an additional voltage pulse is applied, contracting the hydrogel further. With each succeeding stimulus, the hydrogel shrinks a bit more.

Our design would use this principle to actuate insulin disposal. Instead of using a contracting hydrogel, it would use an expanding hydrogel. Short voltage pulses would be applied to expand the hydrogel slowly over the course of the delivery duration. The expansion after each stimulus would be the amount of drug delivered. The pulses will

![Figure 7. Test result from three different mixtures of PAA/PVSA hydrogel with an on/off stimulus of three volts.](image-url)
continue throughout the day until the hydrogel has expanded to its full size and the insulin reservoir is completely expelled.

The voltage will be controlled by a microprocessor. The microprocessor used will be the BASIC Stamp 1 Module (Parallax, Inc) as in design one. The processor will be used to give a simple on/off voltage at a certain time interval. The pulse width and separation will be determined to produce results similar to those in Figure 8. As small voltage pulses are applied, over the course of an extended period the hydrogel growth will approach a linear expansion. The microprocessor only needs five volts to function (Parallax, Inc); because supplying only five volts is difficult without using expensive batteries, our design will use a nine V battery.

Figure 8. Design two diagram
The overall design is shown in Figure 8. The insulin containing reservoir will contain a maximum of 1.2 ml. This allows a 50 µL/hr flow rate for 24 hours. The desired pump rate can be controlled with the voltage pulse width, frequency, and amplitude provided by the microprocessor. The microprocessor will be connected to an anode and cathode immersed in the hydrogel containing aqueous solution. An ideal ionic solution must still be determined.

Dimensions of this design will be dependent on the battery and the microprocessor because the amount of drug that needs to be stored is small. A 1.2 ml reservoir is only 1.2 cm³ in volume. The size of a nine V battery is 1.75 cm by 4.85 cm by 3.56 cm (Duracell Products). The size of the microprocessor is 0.56 cm by 1.52 cm by 0.25 cm (Parallax, Inc). If organized properly, our design should not significantly exceed a volume of 32 cm³.

There are some potential problems with this design. Hydrogels don’t expand in one direction. Our hydrogel will be confined on all but one side; however it is unknown if the hydrogel will direct its expansion linearly. The hydrogel will obviously put pressure on all surrounding walls that restrict its expansion. This poses a problem in finding a material capable of handling this pressure applied by the hydrogel. Also, though our design is relatively small, it is would still be noticeable when used by a person. The pump is still too large and obtrusive for comfort when sleeping. A smaller voltage source than a nine V battery, would dramatically reduce the size of this design.
Design two

Design three has three main components: a fluid reservoir above the device, a J shaped compartment with a plunger, an insulin container, and a driving fluid compartment and a needle at the end of the compartment. Both the driving fluid compartment and the fluid reservoir contain the same fluid such as water. The device relies on the principles of hydraulic pressure and gravity.

![Figure 9. Design three overview](image)

The plunger is driven to actuate the insulin by fluid pressure. The fluid pressure from the driving fluid compartment activates the plunger. The plunger in turn applies pressure on the insulin, pushing it into the body through the needle. As the insulin is displaced out of the tube and into the body, the fluid height in the driving fluid compartment steadily drops. As the fluid level decreases, the pressure on the plunger also decreases; consequently, a constant flow rate into the body cannot be achieved. Since our client requested a constant flow rate, a constant pressure must be applied to the plunger. To compensate for the reducing flow rate of insulin into the body, the fluid height in the
driving fluid compartment must be maintained at a certain height $H$ when the device is in use. The fluid reservoir above the device must add enough amount of the fluid to compensate for the lower pressure on the plunger. The fluid reservoir is entirely reliant on gravity to add fluid to the driving fluid; it also has a narrow microcapillary tube attached to it, which essentially controls the flow rate of the fluid into the J-shaped tube. The inner diameter of the tube and the viscosity fluid will influence the flow rate into the driving fluid compartment and consequently regulates the insulin flow rate. Releasing just the appropriate amount of fluid into the driving fluid compartment will maintain the pressure required to force the insulin out into the subcutaneous layer. Knowing the pressure required (9.1 mmHg), the pressure exerted on the plunger by the column of fluid, the reduction of height of the fluid in the column, and the amount of the unknown fluid in the reservoir released per unit time can all be calculated using the following formulas.

For an incompressible fluid, the pressure is given by the equation:

$$\Delta p = -\rho g \Delta z$$

where $z$ is the height above the arbitrary datum, $g$ is the acceleration due to gravity and $\rho$ is the density of the fluid.

For a manometer difference between the bottom and top of an incompressible fluid column is given by the incompressible fluid statics equation. Since the J-shaped tube acts as a manometer, the following equation can be used

$$\Delta p = \rho gh$$
Using Bernoulli’s principle

\[ \Delta p = p_1 - p_2 = \frac{1}{2}\rho \left( V_2^2 - V_1^2 \right) \]

\( V \) = fluid speed

Changes to fluid flow moving from Point A to Point B along the tube described by Bernoulli’s equation; this equation relates pressure to height of the fluid and the velocity at which the fluid flows

\[ h = z(x) + \frac{p(x)}{\rho g} + \frac{\nu(x)^2}{2g} \]

where \( p \) is the pressure, \( \nu \) is the average fluid velocity, \( \rho \) is the fluid density, \( z \) is the pipe elevation above some datum, and \( g \) is the gravity acceleration constant.

Although this design is relatively simple, and does not involve the use of hydrogels, gears or motors, it does have many setbacks. First, the device is rather large in size and is irregular in shape, which can cause discomfort to the user. Furthermore, any additional forces applied to the fluid reservoir throughout the day could alter the rate at which fluid is delivered to the driving fluid compartment, and ultimately, the flow rate of insulin. Consequently, the margin of error of the flow rate could be large when using this device. As mentioned before, even a slight fluctuation in the amount of insulin delivered to the body causes serious ramifications to the patient’s health. Additionally, since the entire device will be scaled down to a microscale, it would be difficult to rely on such a small amount of fluid in the driving fluid compartment to overcome the subcutaneous
pressure. Perhaps, the most severe of these disadvantages is that the device will not function properly unless the patient is sitting upright or standing. This is a serious limitation since the patient is estimated to use the device for 8-24 hours and it is unreasonable to rely on the patient to stay upright during this period.

Design Matrix

In the design matrix we considered the two rejected designs as well as a third proposed design. The third design was chosen and further developed throughout the semester. The three designs were rated on six categories. Each category was been given a weight; categories of more importance have larger maximum weights. The most important categories were size, reliability and safety. All categories were measured out of five and then multiplied by their respective weights. Final totals were summed and compared to find the optimal design. The last category was a rating done by the four group members. The group rating includes qualitative properties that cannot be quantified. Reliability quantified the probability of failure due to the materials used and the design; it measured each design’s vulnerability to failure over long term use. Versatility measured the effect it would take to change certain aspects of the design, for example, the designs ability to modify flow in response to different patients’ basal rates.
### Figure 10. The design matrix

The first design had the lowest score. The positives about this design were its simplicity and ease in production. The cost of production would have been low, because of the simplicity of the design. The design suffered in all other categories because this design only would have worked while standing up right; its functionality was generally precarious during daily activity. This greatly affected the safety, reliability, and versatility. Our group felt this design would not meet our requirements.

Designs two and three are close in total score. Design two was a simplified version of Design three, but it did not meet the requirements as well as Design three. Design three’s versatility was better even though both designs have the same components. Design three proved more flexible because an adaptable program would be easier to write in future development. Design two would have required a program that would alter the pulse width to rest duration ratio to alter hydrogel growth. Since design three could operate with a program that produced many small voltage surges, which appeared far easier to write. Both designs were safer than design one. This was because they both were not reliant on gravity for operation and they both utilized the addition of a microprocessor. Design two had a lower reliability because of the hydrogel being used. It
is hard to control hydrogels expansion rate; displacement error would be greater than in Design three. The hydrogel in design three didn’t have to expand at a specific rate, but instead achieve a desired bending angle.

Design three was the best solution to our design requirements. Although, the design cost more and seemed harder to produce, the advantages gained by the more complex design out weigh the negatives.

**Design**

*Hydrogels*

The hydrogel acts as the actuating system in our design. A hydrogel is a complex, hydrophilic network of polymers that exhibit response to various stimuli, such as pH, temperature, solvent composition, electromagnetic radiation, Hydrogels are already used for a variety of medical purposes, such as contact lenses. They are made by cross-linking multiple polymers together, although for best results, the maximum number of polymers is usually around three. The polymers are held together by covalent or ionic bonds and “secondary forces in the form of hydrogen bonds or hydrophobic interactions (Qu, Wirsén & Albertsson, 1999).” Hydrogels have captured the attention of engineers due to their remarkable potential of mechanical work in the form of contraction, expansion and bending. Each hydrogel has its own specific

![Figure 11. Interpenetrating network of polymers (Qu, Wirsen & Albertsson, 1999).](image)
characteristics based on its composition and their respective ratios. Possible applications of hydrogels in the future include drug delivery systems, artificial muscles, and sensor systems.

We chose to utilize electrically responsive hydrogels rather than a more common one driven by either temperature change or change in pH; both pH and temperature presented difficulties with repeatability and reversibility given the far less temporary nature of their application. Temperature control could be influenced by the user’s body temperature, making it prone to premature response. pH control would be extremely hard to repeat because it would require constant shift of the pH between each actuation. Applying voltage to a hydrogel is done quite easily, using a battery to provide the voltage and a simple 555 timer or a microprocessor that delivers the voltage to the electrodes. Electrically driven hydrogels tend to bend when a voltage is applied, rather than the expansion/contraction that is seen commonly in the temperature and pH driven hydrogels. This was an important factor to consider in the design that ultimately directed us to final design.

Figure 12. Illustration of a bending hydrogel (Kim et al, 2003).
There are many different polymers that can be used to make an electrically driven hydrogel. The most important aspect to consider when choosing materials is the consistency and repeatability of the results. The design required that the hydrogel bend to the same angle each time a voltage is applied; otherwise the amount of drug injected would be inconsistent. It was also necessary that the hydrogel return to its original shape fairly quickly after the voltage is removed. Because not much is known about electrically driven hydrogels, the team had to depend upon articles published on the subject. After extensive research, the team decided on a hydrogel composed of a semi-interpenetrating network of chitosan and polyacrylonitrile. Published data concerning the behavior of this hydrogel was promising (Kim et al, 2003). The hydrogel bent to the same angle consistently when a constant voltage was applied, and within seconds of the voltage being removed, the hydrogel returned to its original conformation. Although the maximum bending angle was reported when 16 volts were applied, five volts were more appropriate for this project due to the BS1’s output. Research indicated that in a 0.9wt% NaCl solution, the hydrogel would bend to ten degrees in response to an application of five volts (Kim et al, 2003); the pump was designed to create a ten degree bending angle in the hydrogel.

To make the hydrogel we first dissolved PAN in DMSO approximately 1% by weight, as well as chitosan in acetic acid, again approximately 1% by weight. The materials took approximately one hour to dissolve in rapid stirring. Amounts of each solid were chosen so that they would have equal molar concentrations in final solution. Afterwards, the solutions were combined and cooked in a small beaker at 60 degrees Celsius for two days. Next the hydrogel was immersed in glutaraldehyde, which was
responsible for the actual cross linking of the interpenetrating network. After this step, the hydrogel became more turgid and changed to a slightly yellow color. Finally the hydrogel was placed in deionized water for 5 days and then cooked at 40 degrees Celsius for one week. When this process is finished the hydrogel can be placed in saline solution until it reaches equilibrium, a consistent volume level. Finally, the hydrogel was cut into individual rectangles for use in the pump.

**Pump Design**

Our drug pump is design to deliver 200 μL of drug every time the Chitosan and Polyacrylonitrile based hydrogel is stimulated by a five Volt source. The hydrogel bending drives the movement of a plunger. The driven plunger contacts the face of an elastic membrane, which lines the insulin reservoir. When the hydrogel bends, it depresses the plunger, which decreases the volume in the drug reservoir and increases the pressure on the insulin. The increased pressure then drives the insulin into the subcutaneous tissue. The pressure that the pump produces needs to be higher than the 9.1 mmHg pressure in the subcutaneous tissue.

Our main attraction to the Chitosan and Polyacrylonitrile hydrogel was its repeatability in bending. Voltage stimulated hydrogel return to their original shape once the electric field set up by the electrodes is taken away. The ability to make the hydrogel bend

![Figure 13. Graph showing the PAN/Chitosan hydrogel bending angle with successive stimulation, showing the repeatability of movement](image)
and return to its original shape is essential in our design since the pump will deliver small
doses of drug many times through out the day. Also, the reaction time for hydrogel
bending is approximately 0.3 seconds as can be seen in figure 13 (Kim et al.).
Alternatively stimulated hydrogels displayed reaction times on the order of minutes and
even hours, which would hinder the potential of delivering many small doses of insulin.

A couple of problems arise when trying to utilize the movement of the hydrogel.
The bending of the hydrogel cannot be directly used to create the pressure need to deliver
the drug. One reason is that the electrodes can be in contact with the hydrogel. Therefore,
the bending of the hydrogel can directly push on the latex layer covering the drug
reservoir because the electrodes are in the way. Second, the hydrogel must be in an
electrolytic solution, NaCl, in order to apply the proper electric field; the hydrogel must
be separated from the drug to insure the insulin is not diluted. A plunger was designed to
connect the hydrogel to the latex membrane. The surface of the plunger in contact with
the latex membrane is as large as possible to promote even pressure on the latex. The side
of the plunger in contact with the hydrogel was designed minimize obstruction of ion
movement across the surface of the hydrogel while still dispersing the pressure on the
hydrogel surface.

A system was designed with all the properties of the hydrogel accounted for so
the system could deliver 200 µL of drug for every time the hydrogel was stimulated.
First, a box was designed to hold all the components needed for the hydrogel to bend. The
outer dimensions of the box are 28 mm x 31 mm x 11 mm. The outer box has a
rectangular ridge that latches into the top covering. The inside dimensions of the box are
18 mm, x 29.5 mm x 7 mm. Figure 14 depicts the grooves cut to hold a hydrogel in the
middle and an aluminum electrode on each of its sides. Placement of each component that makes up the system can be seen.

**Figure 14.** A picture of the actuator box. Its female port surrounds the actuation system of the pump. A voltage is applied to the electrodes on each face of the hydrogel in the center groove to cause hydrogel bending. The groove on the far right face is used as the male port to the reservoir.

Next the reservoir was created. The reservoir has two functions. First, it contains the insulin in its 7.6 mm x 5.5 mm x 18 mm inner box. Secondly, the 2.6 mm x 8.25 mm x 20.5 mm male port protrudes off the front face of the reservoir to attach to the actuation system. The reservoir can be seen in figure 15.

**Figure 15.** The front face of the reservoir. The inner hole contains the insulin. The open face is lined by an elastic membrane to hold the hydrogel separate from the NaCl. The outer lip of the reservoir is perfectly aligned with the lip of the actuation system so the top covering can fit easily over both of them and hold the system together.
Figure 16 depicts the union of the reservoir and the actuation system.

![Figure 16. Assembly of reservoir and actuation system.](image)

The two aluminum electrodes are placed 9 mm from each side of the hydrogel. Aluminum was used because of its low price and excellent conducting qualities. The electrode on the reservoir side has a small circular cut in its center to allow easy sliding to the plunger. The assembly can be seen in figures 17.

![Figure 17. The full inner assembly. The tan light hydrogel pushes on the dark plunger when it bends in result of voltage application.](image)
The dimensions of the box were determined based on the assumption that the hydrogel would bend 10 degrees and the inner box height would be set to seven mm. Using a trigonometric calculations, we determined that the hydrogel needed to be 18 mm long to produce an adequate plunger displacement when bending ten degrees. The hydrogel is not completely attached to the wall of the box but instead wider than the inner dimensions of the box; it will be held by the grooves cut into the face of the inner wall.

Finally a simple top piece was created to cover the assembly. The inner dimensions of the box are 37mm x 25 mm x 5 mm to join around the outer lip of the bottom assembly. The walls are 1.5 mm thick. Figure 18 portrays the inner face of the cover.

Figure 18. The top piece for the assembly.

Finally figure 19 illustrates the way the top piece would connect to the bottom assembly.

Figure 19. Full assembly with top covering.
Cost

Cost estimations for materials used to produce our prototype are listed in figure 20. Chitosan, gluteraldehyde, acetic acid, dimethylsulfoxide (DMSO), and polyacrylonitrile (PAN) were used to produce the electrically driven hydrogel. With these materials, we were able to make a slab of hydrogel in a circular shape. If the circle is fully intact after production, 46 - 21 mm x 7 mm x 2mm pieces of hydrogel can be cut and placed in an insulin pump. In future work we could use rectangular molds rather than a circular one to maximize production of hydrogel. Thin strips of aluminum were used for electrodes in the container. The table lists the price and the amount of each material purchased in bulk; from this, we calculated the price and amount of each material to produce a single insulin pump. The final cost of production is $4.21; this estimate does not include labor costs, cost for batteries, or needles. The cost of the drug pump will be reduced considerably after mass production since purchasing materials in bulk is much more cost efficient, especially in the case of plastic. Compared to some insulin pumps on the market ranging between $5,000 and $6,000, our product is much less expensive.

<table>
<thead>
<tr>
<th></th>
<th>Aluminum</th>
<th>Chitosan</th>
<th>Glutaraldehyde</th>
<th>PAN</th>
<th>Acetic Acid</th>
<th>DMSO</th>
<th>ABS Plastic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>5.48</td>
<td>30.5</td>
<td>54.4</td>
<td>89.9</td>
<td>29.48</td>
<td>34.7</td>
<td>7.88</td>
<td></td>
</tr>
<tr>
<td>Amount Purchased</td>
<td>12&quot; X 12&quot;</td>
<td>50g</td>
<td>1L</td>
<td>50g</td>
<td>2.5L</td>
<td>100mL</td>
<td>2&quot;X1.5&quot; X2'</td>
<td></td>
</tr>
<tr>
<td>Amount per single box/hydrogel</td>
<td>1.4 X 2.1cm</td>
<td>0.5g</td>
<td>15mL</td>
<td>0.22</td>
<td>3g</td>
<td>75mL</td>
<td>40mL</td>
<td>2&quot;X1.5&quot; X1'</td>
</tr>
<tr>
<td>Cost per box/cut of hydrogel</td>
<td>0.01</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
<td>0.3</td>
<td>3.84</td>
<td>4.21</td>
</tr>
</tbody>
</table>

*Figure 20. Cost table*
**Future Work**

The pump designed this semester is only a potion of a larger and more complex final design that could not be produced in one semester. Our future work would not only involve perfecting the production of hydrogels but also developing all other necessary components and testing of the final product.

In our first trial, the hydrogel was not the proper consistency and the gel broke of into smaller fragments with many cracks, rendering a large portion of the hydrogel unusable. Therefore, further work is needed in developing better methods to crosslink the hydrogel, in order to cut into the slab of hydrogel into smaller pieces. Since the procedure we chose is only one of many in preparing electrically driven hydrogels, experimenting with different materials and methodologies may provide a better ‘recipe’ for preparing hydrogels with the proper consistency. Interpenetrating networks consisting of polyvinyl alcohol (PVA)/chitosan, chitosan/polyallylamine, polymethacrylic acid/poly (vinyl alcohol) may also be used to prepare electrically driven hydrogels. We would also pursue the use of small rectangular molds. We could use PDMS molds to pour the hydrogel solution into the exact dimensions we want. This would minimize waste, as well as make each hydrogel far easier to handle during the production phase.

We must also test the hydrogel to ensure that in a .9 wt% NaCl solution, it bends 10 degrees so that when placed in the insulin pump, accurate amounts of insulin are dispensed (200 microliters). Moreover, testing is needed to measure precision of the instrument; this can be done by taking repeated measurements of the amount of insulin dispensed each actuation. Since all other components of the insulin pump have greater durability, the life of the hydrogel will be the limiting factor for the life of the insulin
pump. Another aspect of the design that needs to be taken into consideration is embedding a rod within the hydrogel. By attaching one end of the rod to the hydrogel and the other to the latex membrane, the force exerted on the hydrogel during bending is directly transferred to pushing insulin out of the insulin reservoir. Insertion of the bar must be done before cross-linking the hydrogel, so that the bar is firmly embedded within the polymer. Further, we must ensure that during regular use of the insulin pump, the rod does not simply break through the back end of the hydrogel. Finally, it is also important to investigate if the bending motion of the hydrogel creates enough pressure to overcome subcutaneous pressure (9.1 mmHg); in other words, it is imperative to ensure that the insulin pump is able to deliver the proper amount of drug into the body.

Our current design is capable of pumping 200 microliters of insulin when a 5-volt electric field is applied to the hydrogel. For this to be useful, the pump must have a controllable source that can give off five volts with precise timing. To do this we have two main options: a 555 timer or a microcontroller. Both offer different advantages to the design. Both sources yield the benefit of reliably controlled timing. A 555 timer is much cheaper, which is especially beneficial when using a disposable device. If the device is to be discarded and replaced daily, it would most likely be our only option. A 555 timer can easily be made to give off brief five-volt pulses every five minutes, allowing us to inject a total of 4 ml of insulin every hour. Its disadvantage is its lack of power in comparison with a microprocessor.

Instead, our future design would encompass the use of a removable microprocessor. We would use the BS1 basic stamp by parallax for our prototype due to its user-friendly interface. The BS1 would be programmed in an alternate BASIC
language called PBASIC. Its software can be written to control when and where voltages are sent down to the millisecond. This will provide intricate control of voltage application as well as expansion and contraction of the hydrogels. The prototype could be designed so that the basic stamp could be easily removed from each pump and inserted in its replacement. This would become even more cost effective than using a 555 timer. The BS1 is ideal for prototyping because it is small (1.4"x.6"x.1") and very cheap. The BS1 costs $29.00 for one chip, but if used in mass production the price would fall to $18.85 per chip. If ordered on a mass production scale, a basic stamp costs only 18 dollars. A user could buy a single microprocessor and large amounts of daily insulin pumps. If a 555 timer were used in the design, each pump would include its own 555 timer.

The main draw back to this chip it requires at least a five volt power source. The prototype will use a nine volt battery, which would be the largest component in the system. The chip draws one milliamp while running; this can run a battery down quickly in constant use. This rapid energy depletion can be slowed with efficient programming, utilizing the timed sleep command which will then draw one quarter of the amperage when not in use (Parallax, Inc.). Though the timed sleep will help the problem, the system will still deplete a battery quickly when in constant use. Our future work would also include searching for an alternative power source. Finding and implementing the use of a small, rechargeable battery capable of yielding at least 5 volts would be essential to the success of the design. Again, a compartment to contain the battery with easy access for the user in the pump would be a main priority in our future work.

The true benefits of using a microprocessor is come from the flexibility derived from a programmable chip. The chip could easily be programmed to use each patient’s
metabolic rate as a variable in the programming. This would allow the pump to have a
controllable pump speed. The chip would be programmed to determine the necessary
duration between voltage pulses to achieve the necessary flow rate in an hour. Secondly,
the microprocessor would allow us to add certain safety checks in the system. Since the
chip has eight I/O pins, we can control multiple hydrogels and transducers at one time.
Transducers could be put in the reservoir to notify the chip if insulin is running low.
Another I/O pin could then be used to control an LED; the LED could be used to notify
the user that the pump needs more insulin.

Our future work would also include devising a system to monitor the hydrogel
efficiency. If the actuation system was working inefficiently due to an ineffective
hydrogel, the microprocessor could again be used to notify the patient with an LED. The
addition of LED’s and transducers would have minimal effects on cost, and would greatly
improve the safety of the product.

As mentioned previously, not all components in the pump have been designed.
The components currently designed were made to fit into a larger model. The
components yet to be designed include any compartments containing circuitry or voltage
related aspects of the design, as well as, a secondary insulin reservoir. The secondary
insulin reservoir (insulin container) is necessary to replenish the insulin volume in the
reservoir. After each plunger depression, the amount of insulin in the reservoir would be
depleted. The plunger would return to its original retracted position and any ensuing
plunger depressions would fail to dispel any insulin without refilling the reservoir. The
purpose of the insulin compartment would be to refill the reservoir between plunger
depressions. The combination of gravity and the negative pressure created by the elastic
membrane surrounding the reservoir would pull insulin into the reservoir. After the reservoir is refilled, the plunger can again effectively push insulin out of the pump. The compartment would be large enough to contain at least eight hours worth of insulin for the user.

Another addition to the pump would be another hydrogel. This hydrogel would shrink in response to voltage stimuli. The hydrogel would act as a valve at the needle exit of the reservoir. The valve would remain closed while the pump is inactive. Immediately before a voltage is applied to the actuating hydrogel, a voltage would cause the valve to shrink; this would allow the insulin to release through the needle during the plunger depression but would not allow the pump to draw any fluids from the patient when the reservoir is refilling. This is also necessary to create the negative pressure in the reservoir. Our future work would include researching and creating a voltage sensitive shrinking hydrogel and designing a component in the pump to hold the hydrogel.

Finally we would need to create a needle, patient interface. A connection from the pump to the patient would include a small diameter tube that could run from the pump to the user’s abdomen. At the abdomen, a small needle protruding from a bandage-like pad would attach to the users skin. This component could most likely be purchased since other drug pumps already use this technology. Our future work would instead focus on making our pump compatible with one of these systems.
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Problem statement:

Our objective is to design an alternative method of drug delivery that is disposable, small, light, and inexpensive pump that is comfortable and discrete while in use. The product should utilize micro-fluidics to deliver a constant flow rate between ten and fifty micro liters per hour with minimal error or fluctuation for no less than eight consecutive hours.

Client Requirements:

- Small, light drug pump-no larger than a pager
- Inexpensive
- Disposable
- Comfortable for patient during long term use
- Constant flow rate
- Minimum eight hour use
- Doesn’t require adjustable flow rates
- Safe range of potential delivery error

Design Requirements:

1. Physical and Operational Characteristics

   a. Performance requirements: The product will be used continually throughout the day. Each individual pump should work for no less than eight hours at a time. The product must provide a known constant delivery rate throughout the tenure of its use.

   b. Safety: Because the pump is delivering insulin to diabetics it is imperative that the flow rate is known by the user and delivered with minimal error. Also the product may use certain gels or chemical reactions that must be biocompatible. The system must be sterile for daily use. Also, needles must be covered while not in use.

   c. Accuracy and Reliability: It is extremely important that the pump delivers insulin within an acceptable range of error.

   d. Life in Service: The product must work for no less than eight hours but is disposable after one use.
e. Shelf Life: The shelf life of the product should be limited by the shelf life of insulin, which is three months if refrigerated. Any chemicals or gels used in the micro fluidic delivery system must not compromise the shelf life of the product.

f. Operating Environment: The product will be attached to the user’s torso. It must be air tight and capable of withstanding the wear and tear of everyday human interaction in a range of all livable temperatures and conditions.

g. Ergonomics: It should remain tightly attached to the user’s torso.

h. Size: It should be extremely small, ideally the size of a quarter.

i. Weight: No specific weight requirements, but it should be as light as possible.

j. Materials: Biocompatible with skin contact as well as capable of containing insulin, and any other chemicals or gels used in the system.

k. Aesthetics, Appearance, and Finish: The product should be unobtrusive and unnoticeable while worn.

2. Production Characteristics
   a. Quantity: It will be mass produced; however, our goal is one working prototype.

   b. Target Product Cost: The product should be as cheap as possible; no more expensive than $35.

3. Miscellaneous
   a. Standards and Specifications: No government regulations exist on a delivery system during testing; however, FDA approval must be gained before commercial use.

   b. Customer: Diabetics are currently our customer of focus, though it could be expanded to any human that needs a constant delivery of any drug throughout the day.

   c. Patient-related concerns: If the device malfunctions the repercussions could be severe to fatal. Delivering too much or too little insulin could induce a coma or even death.

   d. Competition: Because our device will utilize a new method of drug delivery than other systems on the market, we have no competition. There are no cheap, disposable, micro fluidic drug pumps currently on the market.