Calibrated Eye Dropper

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Abstract

Glaucoma is a disease of the eye that can cause loss of vision and may lead to blindness. Current research in the area tests medications and their effects in the treatment of glaucoma. Researchers at the University of Wisconsin-Madison use animal test subjects for medication testing. Eye drops are delivered to the eyes of the animals via a micropipette or an eye dropper. This method proves to be time consuming and is inaccurate. The researchers hope to have a new eye dropping mechanism developed which minimizes time between drop deliveries, is precise in delivering the exact volume desired, and does not pose any danger to the animals in case of contact with the eye. Innovation of existing products plays an important role in this project.

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Problem Statement

A lab in the Department of Ophthalmology and Visual Sciences needs a device to accurately and efficiently deliver 5μL drops of experimental drugs into the cornea of the eye for glaucoma therapy testing in animals. Currently, the client uses standard micropipettes which deliver exactly 5μL drops. However, this method is time consuming, poses a danger to the safety of the animal, and makes drop placement difficult. The objective is to optimize accuracy, efficiency, and animal safety in optical drug delivery.

Motivation

Glaucoma is a disease of the eye that occurs when the fluid pressure inside the eye slowly rises [2]. This causes damage to the optic nerve and can eventually lead to vision loss and blindness (Figure 1). Glaucoma can be diagnosed by an ophthalmologist. Upon diagnosis, medication is available and is typically administered in the form of eye drops or pills. Current research in the area uses animal test subjects. Dr. Paul Kaufman from the Department of Ophthalmology and Visual Sciences at the University of Wisconsin-Madison focuses his studies on the optic nerve. Research specialists in Dr. Kaufman's lab administer eye drops to the central cornea of the eye in animals in their studies of glaucoma and its effect on the optic nerve. Instead of using a typical dropper bottle, which delivers larger volumes than desired, the researchers utilize micropipettes. Problems are associated with the drug delivery when using pipettes. Although the pipettes accurately deliver the desired volume, their length is a safety hazard to the animal. With the animal's safety in mind, the researchers are looking for a new eye dropper apparatus that maintains the accuracy of the pipette but increases the speed and safety of drug delivery.

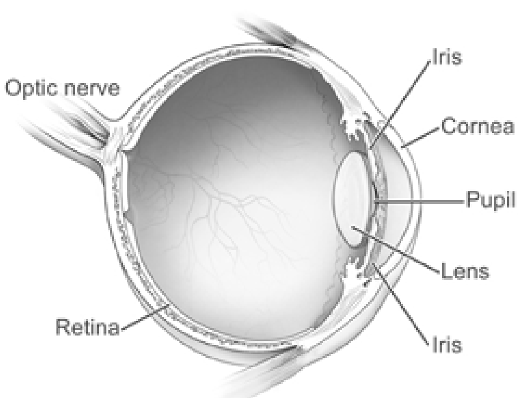

Figure 1: Anatomy of the eye. Drops are delivered to central cornea in glaucoma therapy treatment [2].

Current Devices

Many devices exist that could fit some of the client's needs, but none are exactly what the client would prefer to use in the lab. The MiniFIX Micropipette from Dyna Lab Corporation is a 13cm long pipette which can deliver 5µL volumes (Figure 2). However, these pipettes deliver drops with up to 30% error [3], which is too high by the client's standards. Rainin creates pipettes scaled to 10µL and can be adjusted to 5µL, but and the length of these pipettes exceeds the specifications of the client. MicroZippette Handheld Dispensers from VWR-Jencons are scaled to 1mL and can be used for repeated liquid deliveries. However, the device cannot be scaled to micro liters (Figure 3) [5]. Several US patents (6610036, 7073733, and 5881956) exist that utilize mini ophthalmic pumps, but these are not exactly what the client would like to use in her studies because they are too bulky. The MicropipettePlus from Eppendorf (Figure 4) is a pipette/syringe combination that delivers specified volumes in a continuous fashion [1]. This method saves time between deliveries, but its added length with the specialized tips increases safety hazards, and it costs $485, which is over the client's budget.

Figure 2: MiniFIX micropipettes from DynaLab Corporation [3].

Figure 3: MicroZipette Handheld Dispenser from VWR-Jencons [5].

Figure 4: MicropipettePlus from Eppendorf with syringe tip [1].

Design Specifications

Per the client's request the device must have the functionality of a typical eye dropper and the accuracy of a calibrated 5µL micropipette. The device must be small, but large enough to fit in the average human's hand comfortably, meaning the grip should be approximately 3.5 inches tall. This will allow the user to maintain a steady hand while delivering the drugs and make it easier to control the device if the animal moves. The device should be relatively light, weighing between 50-100 grams; this also adds to the user's level of comfort. The device must accurately deliver 5µL with only 1% error, which is the standard for micropipettes on the market at this time. Not only should the device be able to deliver this specific volume, but it should also be able to deliver liquids with a wide range of viscosities. To improve quickness when using the device and to allow for multiple deliveries in a short time span, an attached reservoir, mechanical parts, or tubing may be incorporated. Depending on how the device is constructed and if there are disposable parts or not, the device should be capable of performing 2000 times each month (B. Gabelt, personal communication). If the tips are disposable, the device should function accurately without calibration for at least a year before recalibration is needed. The target cost for this prototype is $200 or less; this cost should include extra features which make the device ergonomically favorable.

Design Alternatives

Miniaturized Pipette

The current device used by the client to deliver 5µL drops is a calibrated micropipette. The major issue with this method of drug delivery is that the pipette is too long. This makes it hard for the user to stabilize their hand and increases the probability of misplacing an eye drop. In order to improve the current device, the team has incorporated the idea of a shortened micropipette (Figure 5) into each of their design alternatives. This pipette will retain the accuracy needed to deliver a 5µL drop as well as be more efficient and easier to use.

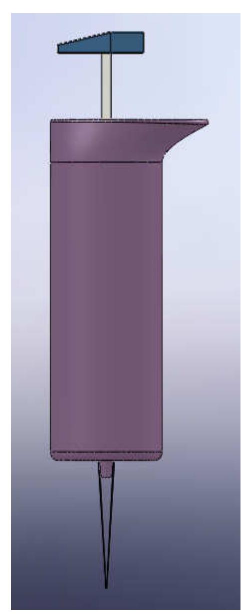

Figure 5: Preliminary external design of the miniaturized pipette.

The concept of the shortened pipette will be achieved by condensing spaces between elements inside the current standard micropipette. The shortened micropipette will use a pre-fabricated spring and piston already calibrated to 5μL because these elements require very tight tolerances and would be difficult for the team to fabricate with accuracy. The shaft through which the piston travels will be shortened to allow just enough space for 5μL of air displacement and an attachment site for the pipette tip. The shaft tip needs to fit with commercially available micropipette tips because fabricating custom tips will not be accurate or cost effective. The gripping area on the shortened pipette will be reduced to 3.5 inches in length to accommodate the average hand size. The pipette will be operated by moving a plunger at the top with the thumb.

The internal elements of the shortened pipette will be the same as those in current micropipettes. With the exception of the positive displacement design, air is displaced by a piston which is connected to a plunger button and is operated by the user's thumb. A calibrated spring ensures the correct piston displacement. The pipette will use 10 μL tips that are commercially available to ensure accuracy, and the pipette tips will be ejected in a similar way to standard micropipettes.

Because this design is calibrated to deliver 5μL drops and is easier for the operator to stabilize, it is incorporated into each of the team's design alternatives. However, each alternative has a different added mechanism to minimize time between dispenses and, overall, make drug delivery more efficient.

Flexible Straw

The flexible straw design incorporates a 5-15mL plastic holding tank attached to the body of the miniaturized pipette (Figure 6). The holding tank is attached on the grip next to the base of the user's palm so it will not interfere with tip visibility and will still be comfortable to hold. At the base of the 5-15mL holding tank, there is a piece of flexible tubing that reaches to the end of the pipette tip. The tubing can be moved into any position and retain its shape, so it can move to the pipette tip when aspirating the drug and then can move away from the tip so it does not interfere with drop dispensing.

At the opening end of the tube, there is a one way valve which can only be opened when the pipette tip pushes through the valve to draw up 5μL of the drug. This valve prevents the drug from being spilled during drop delivery or if the pipette is set down. To aspirate the drug, the user moves the straw to the end of the pipette tip, where the tip pushes through the valve to access the drug inside the tubing. The plunger, operated by the user's thumb, moves the internal piston so that 5μL of air is displaced inside the tip to draw up the drug. The straw is then removed from the pipette tip and moved to the side so the drop can be administered. This process is repeated between each drop. The pipette tips for the flexible straw design would be common 10μL tips that are commercially available. This would ensure accuracy and also be cost effective.

Figure 6: Flexible straw design with reservoir attached to body of shortened pipette and straw reaching to end of pipette tip.

Positive Displacement

The positive displacement design also incorporates a 5-15mL holding tank that attaches to the body of the pipette. However, the tubing from the base of the holding tank does not attach at the end of the micropipette tip. In the positive displacement design, the tubing connects to the end of the micropipette directly above the site where the disposable tip attaches to the shaft.

The main feature of this design is the use of a disposable piston inside the tip, which is used to displace the 5μL volume. As opposed to an air displacement pipette, the disposable piston in this design comes in direct contact with the drug and forces the drop out of the tip when dispensing (Figure 7) [4]. For this reason, this type of pipette is ideal for viscous liquids. When the plunger pulls up the piston, the drug flows due to gravity from the reservoir, through the flexible tubing, and into the positive displacement tip. When the plunger pushes the piston down, the drug is expelled through the tip. When the disposable piston is drawn back up, it displaces a 5μL volume inside the tip. The drug is able to flow into the displaced volume due to gravity to prepare for another drop delivery.

While this design is the most efficient in minimizing the time between drop delivery, the team would need to fabricate custom tips that are calibrated to hold exactly 5μL, which would be time consuming and not cost effective.

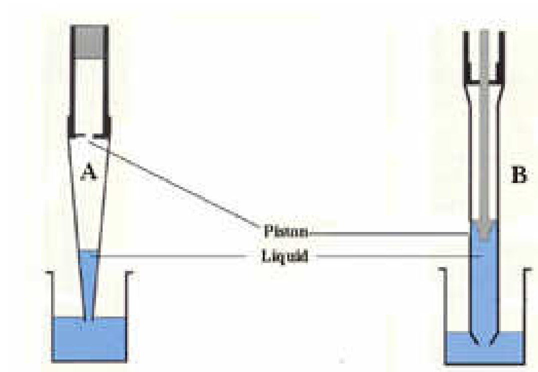

Figure 7: Principle of positive displacement vs. air displacement in micropipette tips. Tip A shows air displacement while Tip B shows positive displacement where the piston comes in direct contact with the liquid [4].

Sliding Reservoir

The sliding reservoir micropipette (Figure 8) includes a reservoir attached to the micropipette by a sliding, vertically oriented track. This track would lock into place when not in use. To refill the pipette, the user would manually slide the reservoir down the track to the level of the pipette tip. Part of the track would also extend in order to allow the reservoir to reach the level of the pipette tip. The extendable portion of the track would be free to rotate so that the reservoir could move from the side of the micropipette into the correct position for liquid intake, directly below the tip. After aspirating the liquid, the user would rotate the reservoir back to the side of the micropipette and raise it to the locked position on the track. The lock mechanism for the track would be a small button that protrudes outward from the body of the pipette when locked. To unlock the track, the user would push the button inward and slide the reservoir down. This design requires the user to hold the micropipette in one hand and to use their other hand to move the reservoir between drug deliveries.

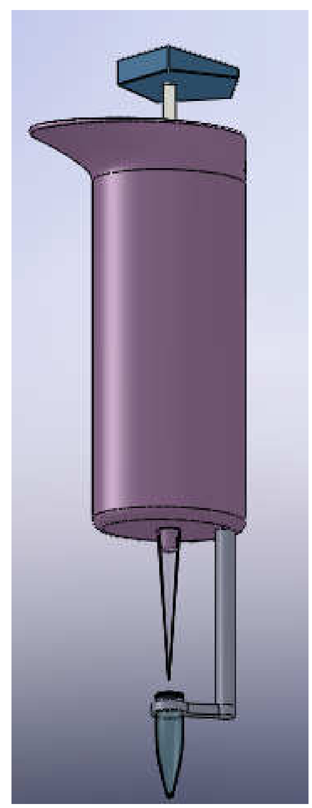

Figure 8: Sliding reservoir design. The track is fully extended, and the Eppendorf is positioned directly under the micropipette tip.

The internal elements of the micropipette would be the same as those in current micropipettes. The pipette would be operated by air displacement, and a calibrated spring would ensure the correct piston position. Furthermore, the pipette tips for the sliding reservoir micropipette would be common 10 µL pipette tips that are available commercially. This would ensure tip accuracy and availability.

Eppendorf Clip

The main feature of the eppendorf clip design (Figure 9) is the ablility to store a removeable Eppendorf on the side of the pipette. A clip with a shape similar to an Eppendorf cap will be attached to the side of the piptette body. This part will be positioned on the body so that it will not interfere with visibility of the tip and can accommodate both left and right-handed users. A normal Eppendorf with the cap removed will be used to hold the drug. The Eppendorf will fit securely on the clip so that no liquid can escape if the pipette is laid on its side, and a reasonable amount of force will be required to detach the clip.

To refill the pipette tip, the user would detach the Eppendorf with one hand and move the pipette tip into the Eppendorf to aspirate the drug. Once the tip is refilled, the user would return the Eppendorf to the clip and dispense the liquid.

The internal elements of the micropipette would be the same as those in current micropipettes. The pipette would be operated by air displacement, and a calibrated spring would ensure the correct piston displacement. Furthermore, the pipette tips for the Eppendorf clip micropipette would be common 10 µL pipette tips, and the design will incorporate standard 1.5mL Eppendorfs, both of which are available commercially. This would ensure accuracy and also be cost effective.

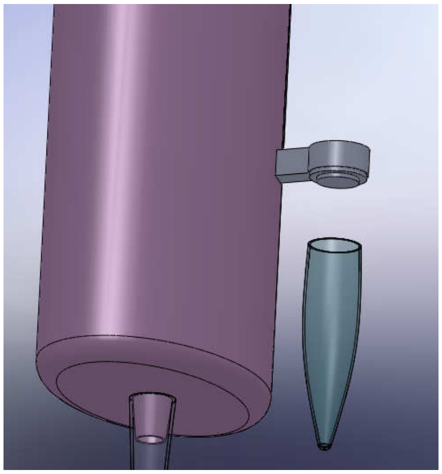

Figure 9: Eppendorf clip design. The Eppendorf is removed from the clip on the pipette body.

Design Matrix

In order to choose our final design, the team created a matrix (Table 1) that rated each design alternative on six different criteria. Higher possible points were given to the more important criteria. The points for all criteria were added to give each design a total score out of 100 possible points. The Eppendorf clip design had the highest total score, so it was chosen as our final design.

Table 1: Design Matrix

Criteria	Flexible Straw	Eppendorf Track	Positive Displacement	Eppendorf Clip
Accuracy (30)	27	30	24	**30**
Speed (25)	20	18	25	**22**
Size/Safety (20)	17	17	17	**17**
Cost (10)	5	8	3	**10**
Feasibility (10)	6	8	1	**9**
Ease of Use (5)	3	4	3	**5**
TOTAL (100)	**78**	**85**	**73**	**93**

Designs were rated out of 100 total points based on the 6 listed criteria. The Eppendorf clip had the highest score.

Final Design

We chose the Eppendorf clip design for our final design because it meets our client's needs, is within our budget, and will be the most feasible of the design alternatives.

The accuracy of the Eppendorf clip design will be sufficient because the pipette will be made using standard parts and will use standard tips. The pipette tips will be filled using the same process as a standard micropipette. Therefore, the necessary ± 1% error will be attainable. The flexible straw design would not be as accurate because the method of refilling the tips from a straw could lead to air bubbles being sucked into the tip instead of liquid. The positive displacement design would also not be as accurate because of the difficulty of trapping and dispensing exactly 5μL.

The speed of the Eppendorf clip design will be acceptable. The amount of time between dispenses will be short because the Eppendorf is attached to the pipette and can be accessed in one quick motion. The positive displacement design would be more efficient because once the user releases pressure on the plunger button, the pipette would be ready for another dispense. Both the flexible straw and Eppendorf track designs would be slower because they require multiple steps to refill the tip. Overall, the four designs would be more efficient than the client's current method of refilling the tip at another location in the lab.

The size and safety requirements for the Eppendorf design and other three designs will be met because all of the designs will be miniaturized pipettes. The pipette will be short enough so that the user can anchor his or her hand on the animal, which will allow for more accurate delivery of the drops and will prevent eye injury if the animal lurches.

The Eppendorf clip design will be the most cost efficient because it will use almost exclusively standard parts and also has the smallest number of parts of the four designs. The only custom part will be the Eppendorf clip, which is small. The other three designs use more custom parts which would increase material and fabrication costs. In addition to being cost effective, the Eppendorf clip design will be the most feasible because it will use mostly standard parts and will be easiest to fabricate. In contrast, the positive displacement design will not be very feasible because it would require very precise fabrication to make a tip whose volume is exactly 5μL.

Overall, the Eppendorf clip design will be easy to use because it will use commercially available Eppendorfs and pipette tips. It will require no cleaning because all of the parts that will come in contact with the drug are disposable. The flexible straw and positive displacement designs would require cleaning before use with a different drug because the drug would come in contact with non-disposable parts.

Potential problems

Although the chosen design represents an achievable goal for the team, some problems may arise, especially concerning the construction of the micropipette. The construction elements that will need the most consideration are the accuracy of the pipette and the ability to use standard size micropipette tips with the device. It is critical for the modified micropipette to be accurate within ± 0.05μL since the client requires an accurate method to deliver liquid medication. To overcome this obstacle, the team will consider the fact that $5mm^3$ of air will need to be displaced in order to intake exactly 5μL of solution. This information will help determine the optimal width of the piston and the necessary distance of piston compression. Also, the accuracy of the device will be increased by the use of pre-manufactured micropipette components.

The second construction difficulty is that the micropipette tips must be a standard size so that the client has the ability to reuse the device in the future. Custom, manufactured tips would not be accessible or cost efficient. The team will solve this problem by constructing the micropipette so that a standard 10 μL tip will form an airtight seal with the pipette shaft. This will require precise fabrication techniques.

Another potential problem is that the micropipette will not be short enough to allow the user to anchor their hand. Animal safety is increased if the user is able to anchor their hand while delivering drugs since the chance of pipette contact with the eye decreases. The team will address this issue by obtaining detailed analysis from the client on the maximum tolerable length for the micropipette.

A fourth potential problem is that the Eppendorf clip would not aid in the efficiency of the medication delivery process. If the attached Eppendorf is not beneficial, then it will be an unnecessary element which may hinder the user. In order to avoid this, the team will construct the Eppendorf clip so that it is as easy as possible to remove and reattach the Eppendorf during pipette use. Also, this potential problem will be evaluated during testing, which will allow time to redesign the device if required.

Ergonomics

The device incorporates many aspects of universal design. The device should fit in the average human hand which is approximately 3.5 inches in width. The gripping area must be at least 3.5 inches tall and should have a diameter that the average hand can grip with minimal effort. The device should be symmetrical to encourage equal use from left-handed and right-handed users. The plunger should be an appropriate distance above the grip to allow any user to comfortably use it, and the plunger should be easy to push down to avoid thumb fatigue during repetitive use. The top of the plunger needs to be large enough to spread the pressure throughout the thumb and decrease pressure points. The tip should be clearly visible during operation to increase accuracy of drop delivery to desired location. All other components of device should be away from the tip so they do not impede tip visibility. The user should be able to attach and remove tips with minimal effort. To increase accuracy, the length of the device should be short to increase hand stability yet be large enough to accommodate all hand sizes. Minimal moving parts will make the device intuitive to use and avoid confusion. To accommodate users of all literacy abilities, there will be no writing on the device except numerical volume indicators. It should also be simple enough that an instruction manual can consist of pictures demonstrating each step of use. The device should consist of simple parts that are easily taken apart and put back together for cleaning and repairing. The materials should consist of neutral colors that will not irritate the eye from prolonged use and should also be light weight, within 50-100g, to minimize human effort during use.

Future Work and Testing

The next steps to complete the project are to finalize design specifics, build a prototype, and test the prototype. The team will need to determine how the Eppendorf cap will attach to the pipette. The Eppendorf cap location has to be decided and designed to accommodate left and right handed users alike. All dimensions need to be finalized. The team also needs to decide on whether an Eppendorf snap cap is connected to the pipette or if the cap is made of a diaphragm containing a slit. The team will also need to determine how to shorten the pipette and what components to eliminate in the standard micropipette design, as well as how to calibrate the prototype to the correct volume. To build the prototype, the correct parts need to be ordered. The parts that are not readily available will have to be fabricated out of the appropriate material. Once all the parts and components are purchased and fabricated, the prototype will be assembled. After the prototype is constructed, it needs to be tested.

Testing criteria and procedure:

- *5µL volume with 1% error*- 1µL of distilled water weighs 1µg. To ensure correct volume delivery and accuracy, distilled water will be dispensed with the prototype, and each drop will be weighed with an analytical scale to make sure each drop is consistently within 1% of 5µg.
- *Comfortable to the user*- The pipette will be used by several different avid pipette users to get feedback on the feel of the pipette and ergonomic design.
- *Assembly and disassembly*- The pipette will be taken apart and put back together by different individuals to ensure that it is intuitive to use as well as to test the durability of its components.
- *Sterilization*- The device will be tested with different types of sterilization solutions to make sure materials do not degrade or diminish in quality.

Material Sources

- Client can supply tips, Eppendorf caps and possibly testing fluids
- Tips - 5µL RC-10 BULK 10UL TIP 1000/PKG $35.00, can be purchased from Rainin and will fit traditional pipettes.
- Rainin Pipette parts can be purchased separately. To find pricing, call company.
- To buy non Rainin parts, pipette.com has many different brands and sizes.
- If raw materials are needed for fabrication, order from McMaster-Carr
- Clint Kisting from VWR International has donated two pipettes and pipette parts to the team

Appendix A

References

[1] *Eppendorf Repeater Plus*. (n.d.). Retrieved March 4, 2009, from Eppendorf North America Web site: http://www.eppendorfna.com/int/index.php?l=131&sitemap=2.3&pb=9ce798080b018b20&action=products&contentid=1&catalognode=9620&productpage=1

[2] *Glaucoma*. (2008, November). Retrieved February 26, 2009, from National Eye Institute Web site: http://www.nei.nih.gov/health/glaucoma/glaucoma_facts.asp

[3] *MiniFIX Micropipettes*. (n.d.). Retrieved March 4, 2009, from Dynalab Corp. Web site: http://www.dynalabcorp.com/news_micropipette.asp

[4] *Technical Info*. (2007). Retrieved March 4, 2009, from Calibration Technology Web site: http://www.calibrationtech.ie/page.php?id=pippete%20technical%20info

[5] *The MicroZipette, Handheld Dispenser*. (2009). Retrieved March 4, 2009, from VWR International Web site: http://uk.vwr.com/app/Header?tmpl=/jencons/microzip.htm

Appendix B

Calibrated Eye Dropper Product Design Specifications

February 13, 2009

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Problem Statement:

A lab in the Department of Ophthalmology and Visual Sciences needs a device to accurately and efficiently deliver 5μL drops of experimental drugs into the cornea of the eye for glaucoma therapy testing in animals. Currently, the client uses standard micropipettes which deliver exactly 5μL drops, but this method is time consuming, poses a danger to the safety of the animal and makes drop placement difficult. The objective is to optimize accuracy, efficiency, and animal safety in optical drug delivery.

Client Requirements:

- Eye dropper mechanism to deliver 5 μL of fluid to central cornea
- Minimizes chance of eye damage in case of contact
- Device accommodates different viscosities
- Apparatus should hold 5-15 mL of liquid
- Minimizes time intervals between dispenses
- Device should be small for stabilization of hand
- Parts easily sanitized or disposable
- Ergonomically favorable

Design Requirements:

1. Physical and Operational Characteristics
    a. *Performance requirements:* The device should deliver 5 μL of liquid to animal eyes with precision and accuracy.
    b. *Safety:* Must not injure the animal eye if contact should occur.
    c. *Accuracy and Reliability:* Must deliver same liquid amount repeatedly during each use and must be calibrated to 5±0.05 μL.
    d. *Life in Service:* The device will be used about 2000 times per month.
    e. *Shelf Life:* If it has replaceable tips, then it should be useable for a year without calibration. If solution is put inside the device, then it would be disposed of after each study. Device will be at room temperature. Components must not degrade.
    f. *Operating Environment:* Used in research laboratory. Chemicals may be spilled on the device in which case, the device should be easily sanitized.
    g. *Ergonomics:* The device will be hand held so it must be comfortable and easy to operate with minimal effort.
    h. *Size:* The device should fit in the human hand (The average hand is approximately 3.5 inches in width). The gripping area must be at least 3.5 inches tall.

i. *Weight:* The target weight is that of standard pipette which is variable between 50 and 100 grams.
j. *Aesthetics, Appearance, and Finish:* The device should be neutral in color with a smooth, cylindrical shape.

2. Product Characteristics
   a. *Quantity:* One prototype device is required for this semester.
   b. *Target Product Cost:* $200, which is similar to the cost of a standard pipette.

3. Miscellaneous
   a. *Standards and Specifications:* FDA approval is not required due to the fact that the device will be considered a "custom device" by the FDA. As such, FDA regulations do not require review and approval for the use of the device.
   b. *Customer:* The device will be used by lab technicians.
   c. *Patient (animal)-related concerns:* The device must be sterilized between uses so cross contamination does not occur.
   d. *Competition:*
      i. The MiniFIX Micropipette is similar to the size constraints desired, but does not have repeated deliveries and the accuracy is 30%.
      ii. RAININ products makes micropipettes calibrated to 10μL with respectable accuracy, but when scaled to 5μL the percent accuracy increases past the desirable amount.
      iii. MicroZippette Handheld Dispensers can be used for volumes of 1mL, but it can be used for repeated deliveries. However, the device cannot deliver the desired volumes.
      iv. The eye drop dispensing system, US patent number 6610036, allows delivery of a predetermined quantity to the eye. It includes a replaceable cartridge with a collapsible bag for ophthalmic liquid.
      v. The microdispensing pump, US patent number 7073733, can be used for ophthalmic applications when an accurate dose is necessary.
      vi. US patent number 5881956 is a microdispensing ophthalmic pump which allows repeated delivery of volumes as small as 5μL.