Metered Dose Inhaler Drug Delivery System for Rats

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BME 200/300

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Abstract
Our clients, Dr. Mihaela Teodorescu and Dr. Oleg Broytman from University of Wisconsin - Madison School of Medicine and Public Health, asked our team to create a system that will modify a traditional metered dose inhaler (MDI) for use by rats in a laboratory research setting.

The operation of the MDI should be automatic, and the medicine will be dispensed to the rats in a way that simulates human operation and usage of the device. The modified mouthpiece nozzle and automation circuitry still need to be fabricated, and testing and training of the rats also needs to be completed.

Problem Statement
Research is being conducted on the side effects of corticosteroid medications, in particular the effects on the musculature of the tongue and upper airway because atrophy of those muscles can lead to sleep apnea. The goals of this project are to modify the mouthpiece of a metered dose inhaler (MDI) to allow for use by rats in a laboratory setting and integrate an automated system to dispense the medicine. The mouthpiece may be fitted with a custom nozzle sized appropriately for rat usage, as well as account for the fact that the rats will probably not voluntarily put their mouths around the nozzle. A way to train the rats to voluntarily and correctly use the mouthpiece may also be developed.

1.Introduction

1.1 Background

Metered dose inhalers (MDI) deliver a set amount of medicine through an aerosol mechanism. Dr. Teodorescu's laboratory is currently researching the side effects of corticosteroid medications on the musculature of the tongue and upper airway. Corticosteroid may have the effect of weakening the muscles of the upper airway, such as the tongue muscle.

A detailed illustration of the structures of the upper airway is shown in Figure 1. The muscles of the upper airway may become compromised and collapsible after an exposure of corticosteroids for an extended period of time. Deterioration or atrophy of these muscles can lead to certain diseases such as sleep apnea.

Since corticosteroid medications are often delivered through metered dose inhalers, Dr. Teodorescu is looking to understand if there is a correlation between use of MDI's for delivery of corticosteroids and deterioration of these muscles.

The subject of testing for Dr. Teodorescu's laboratory are rats. Rats are natural nose breathers, unlike humans who are able to breathe through both the mouth and nose. Rats also naturally lick or gnaw to eat. Since rats behave different than human, these details may affect how training is done to have the rats voluntarily and correctly use the nozzles, mimicking the behavior of how a human would use an MDI.

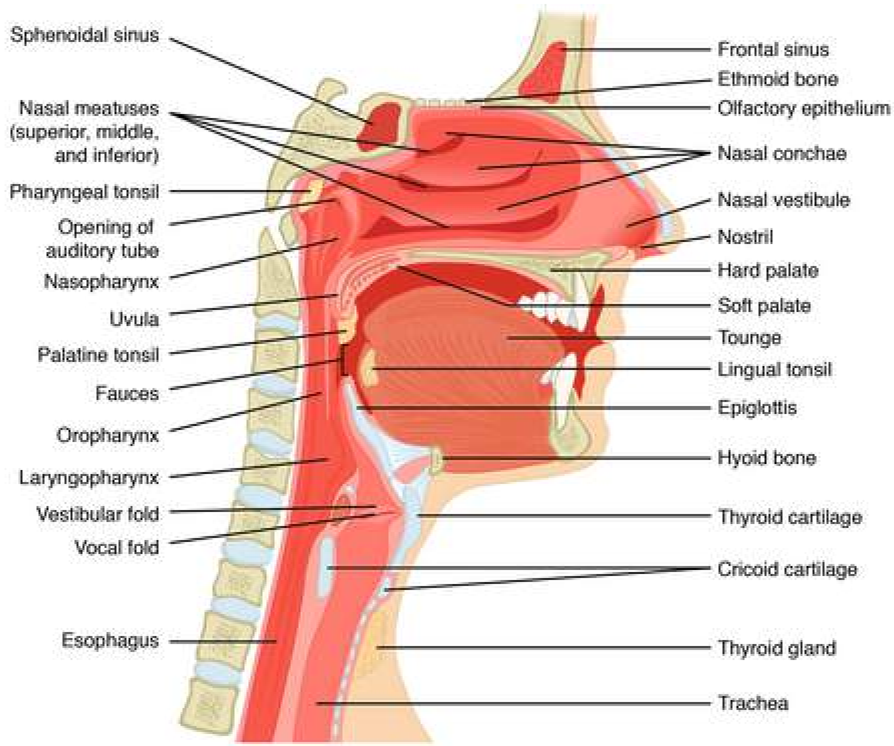


Figure 1. Human Upper Airway

1.2 Motivation

In order to further advance Dr. Teodorescu's research, it is important to develop a method in which rats can mimic the drug delivery system instead of forcing the rats to intake the medications. For this to occur, there must be a way to apply the corticosteroid medication via MDI directly into the rat's mouth, which may improve the accuracy of the replication of such an action a human. In addition, it is time-consuming and inefficient to present the rats with the medications with hands; therefore, an automated dispensing system is desired.

With this specialized MDI for rats, Dr. Teodorescu can further analyze the possible correlation between MDI delivery of corticosteroid medications and atrophy of the musculature of the tongue and upper airway.

2.0 Design Specifications

2.1 Client Requirements

The client specified that the two key components of the design that will aid in their experiments are a fitted nozzle that scales down to a size that a rat can fit its mouth around, and a system that automates the release of the medication whenever a rat puts its mouth around the nozzle. The client would like the system to reset itself after each puff so researchers can test over an extended period of time without having to constantly reset it. For the nozzle, they wanted it to be made out of a material that can withstand multiple uses by rats over an extended period of time. Additionally, it must be safe for the rats and is safe to wash or sterilize. The client was also interested in the possibility of creating multiple nozzle sizes for testing on rats of different ages, as that may be a part of future experiments. In order to ensure that the nozzle's dimensions were accurately proportioned to fit in the average rat's mouth, key measurements were taken on two euthanized rat subjects, which can be seen below in Figure 2.

	Rat 1	Rat 2
Mouth width while open (mm)	2.5	3.1
Mouth height while open (mm)	4.5	4.7
Natural mouth width (mm)	6.0	6.1
Snout length (mm)	12.5	12.6
Snout height (mm)	9.2	10.9
Tip of snout width (mm)	5.7	6.8

Figure 2. Relevant Measurements of Rat Oral Cavity

3.0 Design Alternatives

3.1 Nozzle

For the design of the nozzle piece that will be situated on the existing mouthpiece of the MDI, a few key features are necessary in order for it to function as it needed to. One of the requirements for the design includes that the nozzle fits snug on the mouthpiece to prevent a leak of the medication, as well as to ensure that the nozzle stays on throughout the experiment. Another component necessary to the design is that the nozzle scales down on the outer end to approximately 2 mm in diameter, which is measured to be the distance that a rat can open its mouth. A feature to note about the design is that the narrowed part of the nozzle is about 2 mm in diameter for as much of the length of the nozzle as possible without disrupting the flow of the medication after a puff.

The rat should be encouraged to put as much of the nozzle in its mouth as possible during training, which will ensure that the maximum amount of medication is delivered to the target musculature in the oral cavity. This is a crucial component to the design, due to the fact that rats do not voluntarily breathe through their mouths, so getting the medication released deep into the oral cavity will allow the medication to coat the target muscles as much as possible.

One more key aspect of the nozzle design is that the hole at the end of the nozzle will be as closely lined up to the hole in the mouthpiece that dispenses the puff of medication as possible. This will help deliver the medication in the most consistent puff possible by eliminating potential space inside the nozzle where the medication could get partially blocked.

These constraints and specifications lead to only one feasible option for the design of the shape of the nozzle, pictured in Figure 3.

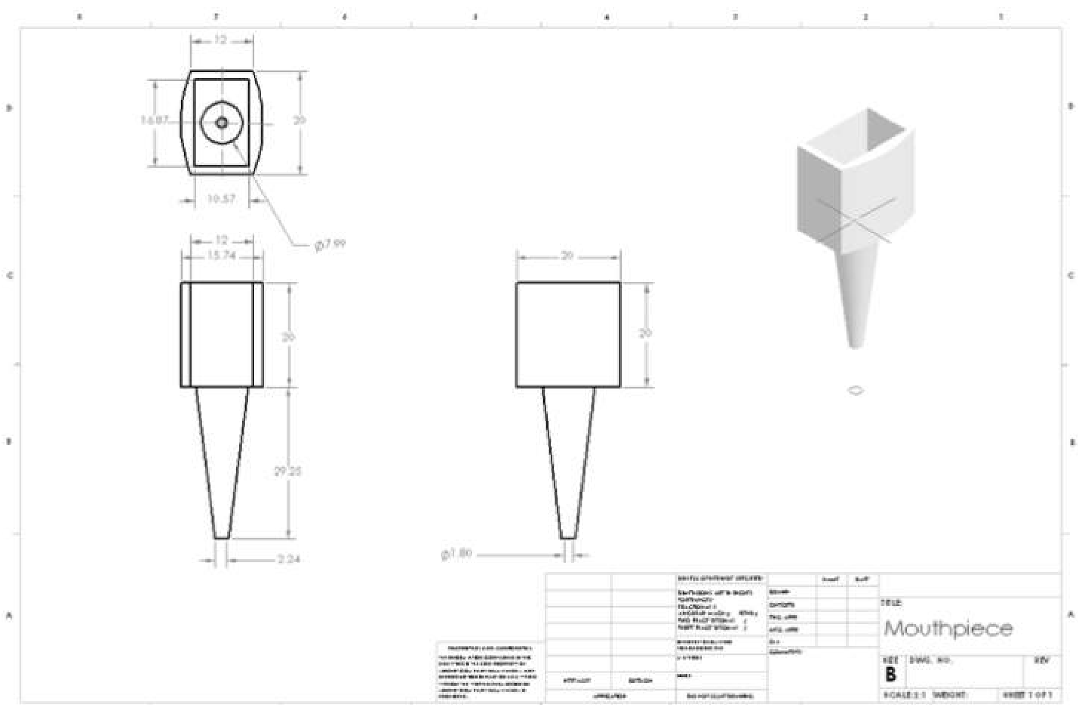


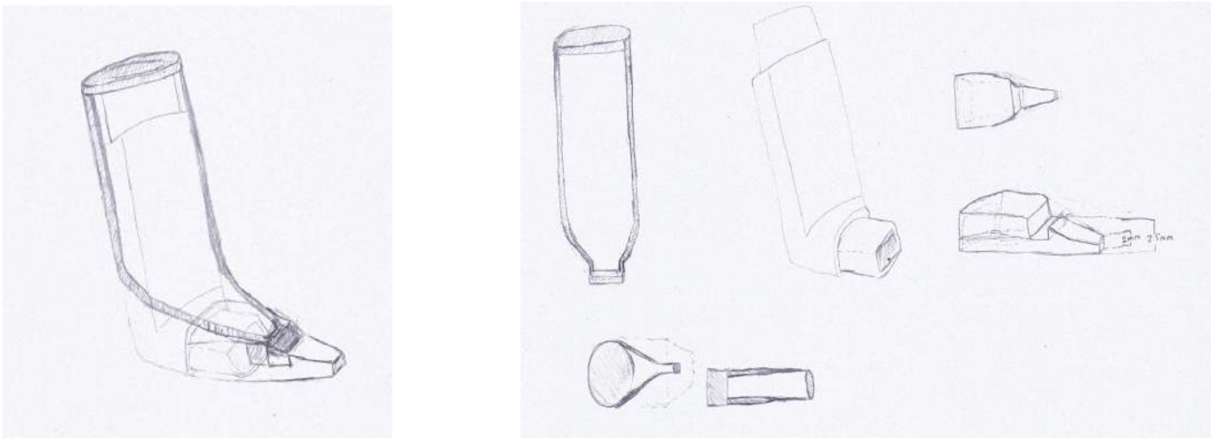
Figure 3. Nozzle Design

There is some option for variability in the material that will be used to make the nozzle. The two options considered were a hard plastic material that would be relatively durable, and a softer plastic material such as rubber or silicone, that would be flexible yet sturdy enough to withstand rat bites.

3.2 Automation System

For the automation system, two possibilities were considered. One option was to create a mechanical system that is activated by the rat biting on the hard plastic nozzle. The second option could incorporate either the hard or the soft nozzle that utilizes a force-sensitive resistor (FSR) and a servo motor run by an Arduino system.

The first system (Design 1) uses the force from the rat's bite and transfers the force up to the canister to release the puff of medication through the nozzle. This is accomplished by creating a solid piece that is situated on the MDI with two plates connected by braces. The first plate is the "bite plate", which is situated on top of the nozzle above a divot, which will allow it to move down when bitten. The braces that run up the side are connected to this plate and another circular plate that is on top of the canister. The goal with this design is that the force applied by the rate bite at the lower plate will shift the entire system downward, with the force transferred to the upper plate pressing the canister down enough to release the medication.



Figures 4. Design 1 - Bite-Activated Automation System

The second system (Designs 2 and 3) is initiated when the rat places its mouth over the nozzle. Since the nose of the rat sticks out further than the mouth, it will push against a small metal plate positioned toward the end of the nozzle. The plate is affixed by a ring to a metal or wire rod, which it will slide along when pushed, until it makes contact with the FSR. The input from the FSR will be sent through an Arduino microprocessor to a servo motor, whose arms will be connected to rods and a weight positioned over the canister of the MDI. When the servo motor receives the input, the arms will be moved down, and this will bring down the rods, pressing the weight onto the canister and dispensing the medicine for a controlled amount of time.

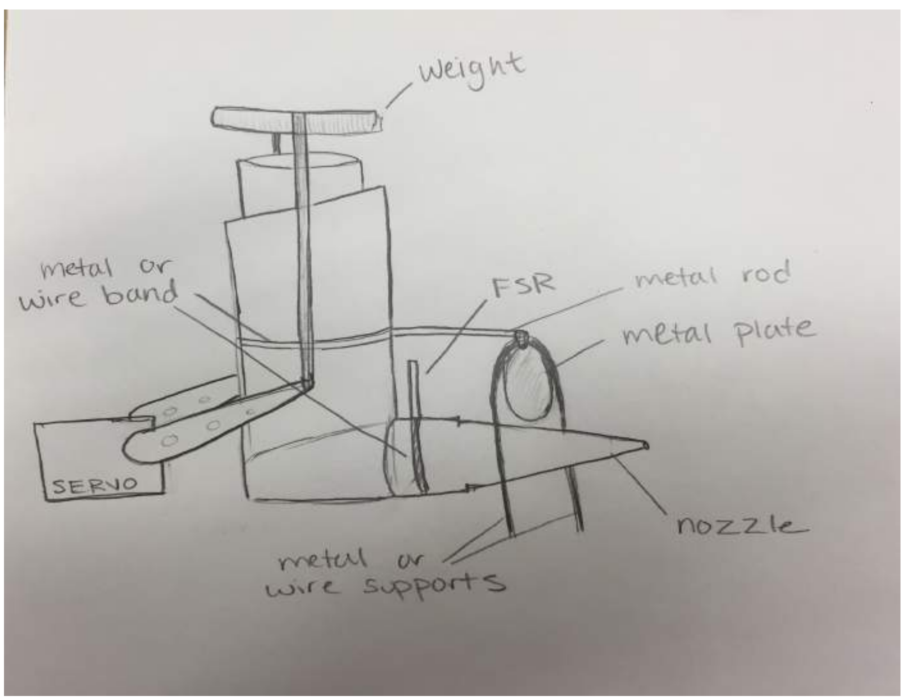


Figure 5. Designs 2 and 3 - Force-Sensitive Resistor Automation System

4.0 Design Matrices

To select a final design from these three potential options, a design matrix was constructed to easily identify which of the options most satisfactorily met the product design specifications. The design matrix may be seen below in Figure 3.

While selecting criteria and assigning their relative weights, accuracy of the simulation was regarded as one of the most crucial considerations. Seeing as our client will be using the product to study the potential adverse effects of inhaled corticosteroids on the upper airway, accuracy is of the utmost importance; the simulation must mimic the drug delivery of a standard MDI to a human subject as much as possible and accurately deposit the medication in the oral cavity to ensure useful and applicable research results. Both Design 2 and Design 3 were ranked higher with regard to this criterion, as the programmed system is expected to deliver the medication more precisely than the mechanically automated Design 1, which could fail to administer the drug if, for example, the rats fail to bite on the nozzle with sufficient force.

Ease of fabrication was also considered to be very important and assigned the same weight as accuracy due to the fact that several replicates must be manufactured for training purposes and for rats of varying ages and sizes. Also, the project duration is only one semester; therefore, we want to be able to accomplish this project in the allotted amount of time. Design 1 was regarded as the easiest to fabricate compared to the Arduino system programming and FSR setup that must be done in Designs 2 and 3.

Durability was considered to be the category of the next most importance. Per client request, the design should ideally last indefinitely, so it was important to select a design that is durable enough to meet these expectations. Design 1 received a lower durability score because the rats must bite down forcefully on the nozzle for the drug to be administered, which could lead to deterioration. However, since the rats are to insert the nozzle of Designs 2 and 3 into their mouths, it is reasonable to assume they will gnaw on it, too, especially if they are trained to use the MDI with food. Seeing as Design 2's hard plastic nozzle would withstand rat bites more effectively than the soft nozzle of Design 3, Design 2 was ranked the highest in terms of durability.

Ease of use for humans was assigned the next highest weight because the product should be straightforward enough that researchers in the lab can be trained to use it without error. The fact that each design is automated contributes to their ease of use; however, none of the designs received a perfect score in this category because they all require some set up by the researchers before they are ready to use in the lab.

Next, safety was considered. Potential safety hazards had been taken into consideration while prototyping the designs to ensure a high degree of safety in each design option. For example, in Designs 2 and 3, the rat's nose pushes a plate into the FSR rather than directly touching it with its nose to increase the distance between the rat and the sensor, eliminating the risk of gnawing on the system's wiring. By taking such considerations into account while prototyping, each design was ranked very highly in terms of safety as a result.

Finally, the criterion of cost was assigned the least weight in the matrix, as the allotted $1,000 budget should almost certainly be sufficient to produce a high quality product. Designs 2 and 3 were ranked lower than Design 1 in terms of cost due to their utilization of FSRs, motors, and Arduino systems.

Design 2 in particular was found to be the most expensive option when the costs of nozzle materials were considered.

After putting each design option through the matrix, Design 2 was found to be the winning design that embodied the product specifications most effectively. However, the designs may have to be reevaluated after testing several training methods on the rats, as our client raised concerns that the rats may try to avoid pushing the metal plate with their noses.

Design / Criteria (weight)	Hard Nozzle with Mechanical System		Hard Nozzle with Force Sensor		Soft Nozzle with Force Sensor	
Accuracy of Simulation (25)	2/5	10	4/5	20	4/5	20
Ease of Fabrication (25)	4/5	20	3/5	15	3/5	15
Durability (20)	2/5	8	4/5	16	3/5	12
Ease of Use (15)	4/5	12	4/5	12	4/5	12
Safety (10)	5/5	10	5/5	10	5/5	10
Cost (5)	5/5	5	3/5	3	4/5	4
Total (100)		65		**76**		73

Figure 6. The Design Matrix

5.0 Conclusion

5.1 Final Design

The final design of the nozzle was chosen to be the same shape as shown in Figure 1, made out of hard plastic. This material was thought to be the most durable and resistant to rat bites. The final design of the automation system was chosen to be the FSR and Arduino system. This design was believed to be more reliable because the same amount of force over a set time would be generated by the servo motor with designated magnitude, rather than a mechanical system that may be hard to standardize the exact and constant force needed to dispense the medicine. With an FSR, a range of pressures can be used as an input for the servo motor, which can filter out pressures that are too high/low, increasing the accuracy of the automated system.

6.0 Future Work

6.1 Rat Training

The first step that needs to be taken before fabrication of the system can take place is to observe the rats using a makeshift nozzle to make crucial decisions for the initial prototyping. Dr. Broytman mentioned that in the past, he had used a soft plastic straw filled with peanut butter to train the rats to use a modified nozzle, so it would be beneficial for the team to see how the rats react to this system before fabrication takes place. Another factor we can test is how the rats react to a small amount of pressure placed on their nose during this process to mimic the sliding FSR plate, since the rat pushing the plate with its nose while its mouth is on the nozzle is imperative to the functioning of the automation system.

6.2 Fabrication

The next step in the project will be starting to prototype our potential designs and testing them in laboratory trials. The two main options we have for fabricating the nozzle are 3D printing or machining using the lathe and mill in the CoE Student Shop. It will be less expensive to use the Student Shop, and it would be much easier to fabricate the hard nozzle design rather than the soft nozzle design in the shop. If, through testing, it is found that the soft nozzle design would work better for training the rats or dispensing medicine, it may be easier to 3D print it or make a mold for the soft nozzle.

6.3 Programming

The materials that will need to be acquired for the programming portion of the design include an FSR, an Arduino Microprocessor, circuitry elements, a servo motor and arms, and potentially an Xbee module if the system is to be wireless. A circuit will have to be set up between the FSR, the Arduino, and the servo motor, taking into account that the rats should have a minimum exposure to the wires. All Arduino code is open source, and can be found on the website.

6.4 Testing

Once our nozzle and automation system are complete and fully functional, we will be able to see how the system does in the laboratory system and address any concerns or shortcomings the design may have. It will be important to test how the rats react to the device, and ensure that they voluntarily and correctly use it. Testing will also have to be done on the accuracy of the medicine dispensed into the rat's mouth. Once the design proves to be at the level our client expects of it, we will instruct them on how to set it up and use it so they can conduct their experiments and utilize our product.

7.0 Budget

Since the clients were given a grant for their research, the budget for the project was not too strict; a cap budget was set at $1000. The team expects to stay well below this budget since the components of the design themselves are relatively inexpensive.

Currently, project expenses include the price of two lab rats at $70.50 each, with a cost of $1.23 per day to house them in the vivarium. At this rate, the project should still stay well below the projected budget. In the foreseeable future, our design should not be restricted by the budget.

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9.0 Appendix A - Product Design Specifications:

Problem Statement: Research is being conducted on the side effects of corticosteroid medications, in particular the effects on the musculature of the tongue and upper airway because atrophy of those muscles can lead to sleep apnea. The goals of this project are to modify the mouthpiece of a metered dose inhaler (MDI) to allow for use by rats in a laboratory setting and develop a way to train the rats to voluntarily and correctly use the mouthpiece. The mouthpiece must be fitted with a custom nozzle sized appropriately for rat usage, as well as account for the fact that the rats will probably not voluntarily put their mouths around the nozzle at first.

1. Client Requirements

- The mouthpiece should be made of a material that can withstand rat bites
- The mouthpiece should be made of a material that propellant medicine will not adhere to
- The nozzle should be detachable and designed in several different sizes
- The material of the mouthpiece should have the capability to be squeezed, similar to the action of getting peanut butter out of a straw
- An automated system should also be designed so that when the rat operates the mouthpiece, a puff is automatically dispensed from the inhaler
- The material needs to be able to undergo sterilization
- The design should cost under $1000
- Replicates should be made for training purposes
- A way to train the rats to use the nozzle must also be devised and tested

2. Design Requirements

2.1. Physical and Operational Characteristics:

a. Performance Requirements:

The design should consist of a detachable piece that fits on the end of a typical metered dose inhaler with a nozzle on the end that could fit in the mouth of a rat. The nozzle must deliver the drug directly into the rat's oral cavity, allowing the medicine to deposit on the tongue and mouth. In this manner, the method of delivery must be as similar as possible to use of an MDI by a human. The nozzle must be able to withstand multiple uses, including wear and tear from rats who will gnaw on the material. It also must tightly fit to the MDI, allowing little to no medicine to escape.

A training system for use of the nozzle by rats must also be devised. The rats must willingly place their entire mouth over the nozzle with their teeth out of the way when the medicine is dispensed. It is crucial for the medicine to deposit on the tongue and mouth of the rat(s).

The system should also be automated so that when the rat places its mouth around the nozzle and bites, the drug will be dispensed into the oral cavity.

b. Safety

Since the product will be used with living rats, it must be composed of a material that is non-toxic to rats. The design of the nozzle must also be durable enough as to minimize the risk of a choking hazard to rats, considering that the rats will bite and gnaw on the nozzle. The nozzle also must be made of a material that is compatible with the medicine and sterilization methods, and not cause any toxic by-products.

c. Accuracy and Reliability
The product must be able to withstand multiple uses and accurately deliver the drug. It must fit tightly on the existing mouthpiece of the MDI and be made of a material that particles will not adhere to so that the majority of the drug is deposited in the oral cavity of the rat.

d. Life in Service
The nozzle will be used multiple times with different rats so it must be durable.

e. Operating Environment
The nozzle and MDI system will be placed in a cage, allowing the rats to operate the system themselves. A researcher will be observing the environment, but will not place the nozzle in the rat's mouth or operate the MDI to dispense the drug.

f. Ergonomics
The nozzle must fit comfortably in the oral cavity of a typical lab rat, but also be available in multiple different attachment sizes, as mouth size varies with age.

g. Size
The nozzle must small enough for the rat to get their mouth around it enough to get a sufficient spray of medicine into it's oral cavity. Several sizes should be manufactured to account for differences in rat size as they age.

h. Weight
The product should be lightweight and remain tightly attached to the mouthpiece.

i. Materials
The nozzle should be made of a material that is similar to the plastic of the existing mouthpiece on a traditional MDI. Specifically, it should be made of a material that the medicine will not easily adhere to and can withstand gnawing by rats.

2.2 Production Characteristics

a. Quantity

Multiple nozzles should be designed and manufactured, incorporating different sizes for use on aging rats. Replicates for use in training and testing should also be created.

b. Target Product Cost

The nozzle and automated system should cost under $1,000.