COLLEGE OF ENGINEERING
UNIVERSITY OF WISCONSIN-MADISON

Automated, in-home delivery of inhaled drugs through portable continuous positive airway pressure (CPAP) system

Sara Karle, Michele Lorenz, Emily Maslonkowski, Ashley Matsick

Biomedical Engineering Design 400: Final Report, Fall 2007
University of Wisconsin-Madison, Department of Biomedical Engineering

Clients: **Dr. Mihai C. Teodorescu**
Assistant Professor, Department of Medicine: Geriatrics and Sleep Medicine
University of Wisconsin School of Medicine & Public Health

Dr. Mihaela Teodorescu
Assistant Professor, Department of Medicine: Allergy, Pulmonary & Critical Care Medicine
University of Wisconsin School of Medicine & Public Health

Advisor: **Prof. Mitch Tyler**
Department of Biomedical Engineering, University of Wisconsin – Madison

TABLE OF CONTENTS

List of Figures

1. Abstract

The treatment of concurrent diseases often involves the integration or supplementation of multiple therapies to relieve systemic effects experienced by the patient. The client for this project treats individuals suffering from both obstructive sleep apnea and asthma with continuous positive airway pressure (CPAP) to prevent apneic episodes during sleep. In an attempt to treat the additional airway-related symptoms caused by asthma that occur most often in the early morning hours, Dr. Teodorescu has proposed the design of a device capable of automated in-line delivery of inhaled asthma medication. This semester began with the development of appropriate background knowledge of pertinent disease states, aerosolized medication delivery, and technology included in the proposed device integration. Subsequent work included the design and production of a mechanical prototype capable of vibrating and actuating an asthma inhaler based on work accomplished by a previous design group. The final area of study involves the development of circuitry capable of detecting the onset of inhalation and delivering appropriately timed signals to the circuits responsible for the aforementioned vibration and actuation tasks. The ultimate goal of this project will be a self-contained, automated device capable of fulfilling the client's requirements. Future development of the mechanical and electrical components of the design, including miniaturization and hardware-software integration, are planned for future semesters to achieve the end project goal.

2. Design Problem

Patients living with a combination of asthma and obstructive sleep apnea are currently treated with continuous positive airway pressure (CPAP) to prevent airway obstruction during sleep, but tend to experience inflammation and other asthma symptoms in the early morning hours. In order to address the complications brought on by the patient's asthma without compromising the therapeutic action of the CPAP, a device must be designed to deliver inhaled steroid medication within the ventilation circuit using the flow generated by the CPAP machine.

3. Educational Information: Biomedical Rationale

3.1 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a disorder of the respiratory system that affects over 12 million Americans, and is often coupled with asthma in older, obese patients. Overweight men over 40 are at the highest risk for OSA, but people of all ages are susceptible to developing the disease (ASAA 2007). Obstructive sleep apnea is characterized by chronic airway blockage during sleep due to the relaxation of supporting muscles, inflammation of the tonsils or adenoids, or presence of excessive fatty tissue in the oral cavity and throat.

Negative airway pressure is inherent to the inspiration phase of the breathing cycle and can vary between individuals due to differences in airway dimensions and in the degree of effort used to breathe. Resistance provided by the nasal passages alone can account for 40% of the total resistance to airflow experienced during nocturnal breathing, and patients with enlarged adenoids (Figure 1) or anatomical defects in the nasopharyngeal region of the airway are especially susceptible to complete nasal obstruction.

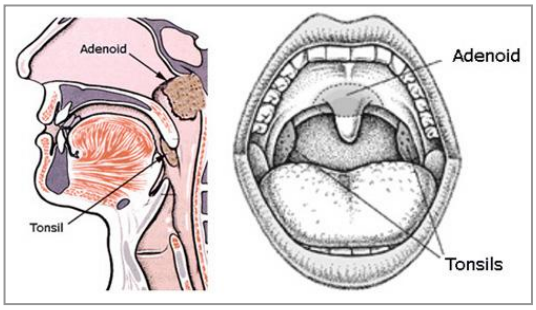


Figure 1. Illustration of relevant lymphoid tissue including the tonsils and adenoid in the nasopharynx region of the upper airway (http://www.kids-ENT.com).

Pressure within the upper airway can increase substantially if there is any existing factor causing constriction (e.g. inflammation secondary to asthma), leaving the individual vulnerable to total airway obstruction if the negative pressure becomes high enough to produce suction and pull the breathing passage anatomy together (Figure 2) (ABFP 2002).

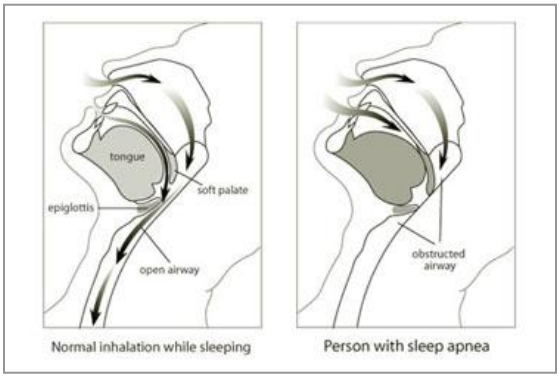


Figure 2. Illustration of OSA effect on airway conformation in which an unobstructed breathing passage (left) becomes fully obstructed (right) due to the relaxation of muscles controlling anatomy in the nasal/oral cavities (cpap.com).

Cessation of breathing triggers the brain to attempt to increase the airflow into the lungs (called increased inspiratory "effort") to maintain a normal tidal volume (Figure 3). The drive to breathe is primarily caused by chemoreceptor activation in the carotid bodies, aortic arch and the medulla of the brain in response to increasing levels of CO_2 in the blood (ABFP 2002). This effort further depletes available oxygen in the system, but is impeded by the original airway obstruction. Severe hypoxia (lack of oxygen in the blood) results from the significant reduction in gas exchange that occurs during this struggle to breathe and results in the individual being fully aroused from sleep (Figure 4).

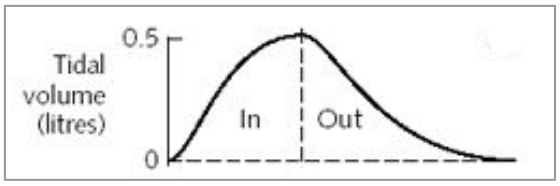


Figure 3. Graph of tidal volume (amount of air breathed in and out during a single respiration) during one cycle of normal breathing (answers.com)

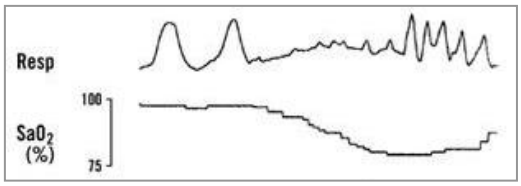


Figure 4. Graphs of tidal volume (Resp) and arterial oxygen saturation (SaO_2) during sleep apnea, demonstrating the negative effects of airway obstruction (medscape.com)

Chronic waking is an inevitable and harmful consequence of the interruption in oxygen delivery to the rest of the body; immediate effects of the disease include fatigue, memory problems, irritability and trouble focusing, while more serious problems such as hypertension, heart attack, stroke, and diabetes can be triggered or worsened by this condition (ASAA 2007).

Obstructive sleep apnea is diagnosed based on the results of a polysomnogram. This test consists of an overnight study in which the patient is instructed to sleep while wearing a variety of electrodes on the head, chest, face, and legs. Data is recorded over multiple channels monitoring the heart rate and rhythm, brain activity, airflow, blood oxygen saturation, as well as chest, abdomen, leg, chin, and eye movements. Results showing cessation of breathing despite the fact that the individual is making an effort to breathe are characteristic of obstructive sleep apnea.

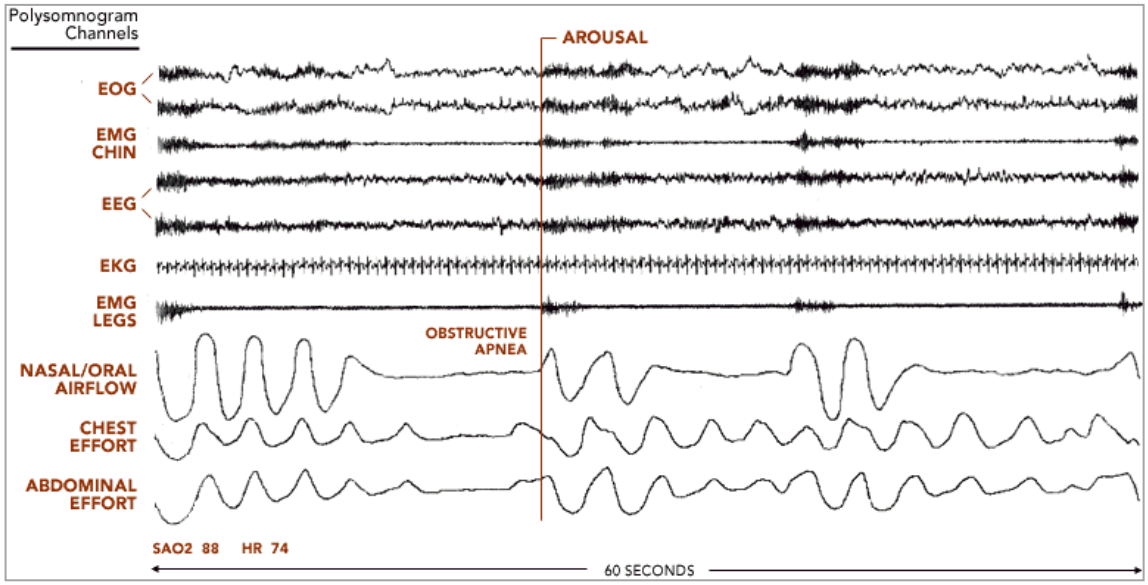


Figure 5. Graphical results of a polysomnogram illustrating sleep study parameters such as muscle movements (denoted by "EMG"), airflow, chest and abdominal effort, and heart rate (EKG). Apneic effect is denoted by the line labeled "Obstructive apnea", followed by indications of arousal and return to breathing that is closer to normal (aaa-studio.com/portfolio/nsdi/default.htm)

3.2 Asthma

Medical conditions rarely manifest themselves in an isolated manner; rather, concurrent development of complications secondary to the original disease often arise and further contribute to the disease state. Patients treated by Dr. Teodorescu experience both sleep apnea and asthma symptoms; understanding of both ailments is crucial to the development of a device providing simultaneous treatment. Asthma is a prevalent disease diagnosed in approximately 20 million people in the United States, and is characterized by chronic inflammation of the airways. Swelling within the airways leads to increased sensitivity to allergens and irritants, such that exposure to these triggers causes further constriction and increased mucus secretion (Figure 6). Air flow to the lungs is reduced by the narrowing of the airways leading to symptoms such as wheezing, coughing, tightness of chest, and trouble breathing. These symptoms are most prevalent at night and in the early morning hours, though the severity and frequency of attacks varies greatly between affected individuals. Treatments for asthma include fast-acting medications for use at the onset of an attack and long-acting medications for prevention of symptoms (NHLBI 2006).

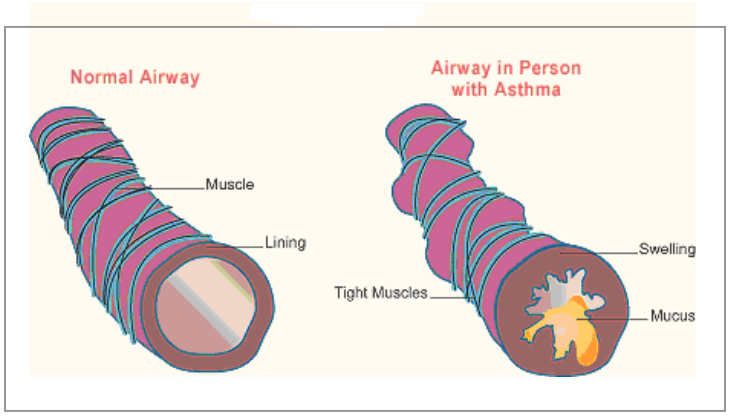


Figure 6: Illustrations of airway in healthy individual (left) and in person with asthma (right). (nhlbi.nih.gov/health)

Yim *et al* (2007) reports that as many as 74% of asthmatic patients are awakened by their asthma symptoms at least once a week. In healthy individuals, lung function varies throughout the day, with peak performance occurring around 4:00 PM and poorest functioning occurring around 4:00

AM (Lafond *et al*, 2007). This effect is exaggerated in asthmatic patients, leading to worsening of asthma symptoms and increasing constriction of the airway in the early morning hours.

Obesity is an increasingly common condition that may contribute to impaired lung function. In obese patients, added weight in the abdominal and chest regions causes a decrease in lung volumes, especially functional residual capacity (FRC). This decrease in capacity seems to partially contribute to an increase in nocturnal asthmatic symptoms. Obesity has also been implicated in making the onset of sleep apnea more likely (Yim *et al.* 2007). Therefore, one treatment option for both the asthma and sleep apnea is desirable.

3.3 Continuous positive airway pressure

Continuous positive airway pressure (CPAP) is one of the many options available for the treatment of sleep apnea and involves the maintenance of a "stent" of air passing through the respiratory system. This effect extends from the primary source of the obstruction – the throat and soft palate – to the alveoli of the lungs, preventing collapse of any respiratory anatomy (MCNC EMS 2002). The exact nature of this stenting action has been suggested by Lin et al. to be a result of the inhibition of "reflex bronchoconstriction." This form of airway constriction is a contractive response of the smooth muscle of the upper airway and occurs when bronchopulmonary stretch receptors are stimulated. Transient stimulation, often due to the presence of "spasmogens" such as histamines, creates a positive feedback loop in the vagal nerve resulting in escalating reactivity of the smooth muscles and thus increasing contraction (Figure 7). It has been proposed that CPAP provides "stiffening" of the upper airway which is sufficient to prevent irritation by external factors and thus reduces the chance that a contractile response will occur. Due to this protective effect, it is reasonable to suggest that CPAP indirectly increases the efficacy of bronchodilator medication administered concurrently (Lin et al. 1995).

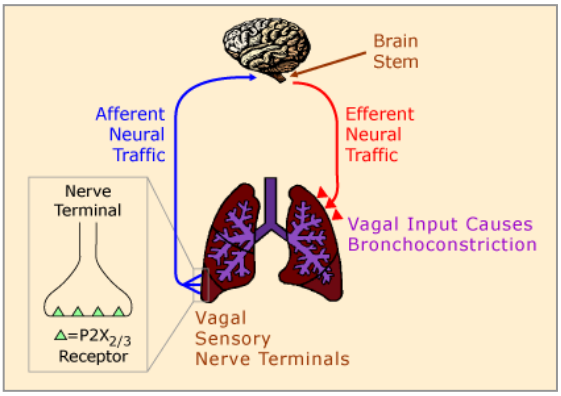


Figure 7. Illustration demonstrating positive feedback loop in vagal nerve stimulated by bronchopulmonary stretch receptors ("sensory nerve terminals") contributing to bronchoconstriction (duskatherapeutics.com.).

Continuous positive airway pressure therapy uses an individualistic approach, whereby a specific air pressure is prescribed for each patient based on the results of an overnight sleep study. Using a fan driven by a variable speed motor, the air pressure delivered to the patient's airway via a nasal or full-face mask (Figure 8) is kept constant by variations in the flow rate of air through the ventilation circuit. To increase patient comfort by reducing damage from dryness to the tracheal mucosa, a humidifier is often integrated into the ventilation circuit as a conduit for the air as it leaves the machine. In patients with asthma complications,

Figure 8. Photograph of full face CPAP mask (cpapusa.com).

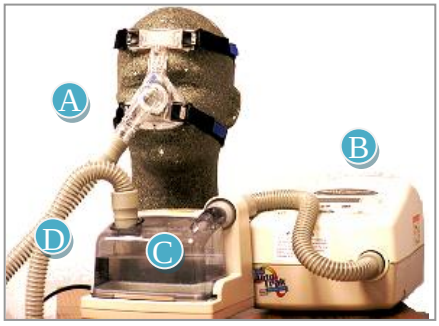


Figure 9. Photograph of CPAP system components, including nasal mask (A), CPAP machine (B), integrated humidifier (C) and flexible helical tubing (D) (njc.org).

symptoms of airway obstruction may worsen in the evening and during sleep, with the most severe episodes often occurring around 4 to 5 am. These patients are often initially treated through in-home use of a CPAP machine, which provides a moderate safeguard against total airway obstruction (Figure 9) (Teodorescu 2007). Ideally, the client of this project would like to administer inhaled steroids in line with the portable CPAP machine in order to prevent airway inflammation before it occurs.

3.4 Metered-dose inhalers (MDIs)

Inhaled steroids may be administered to the respiratory system actively or passively, using either a propellant substance or negative pressure in the oral cavity induced during inhalation. Due to the fact that the patient will not be actively interacting with the device during sleep, the project must focus on delivering aerosolized steroid mixtures containing a propellant. The administration of aerosol medication is typically achieved with the use of metered-dose inhalers (MDIs) that are comprised of a pressurized canister consisting of multiple valves and an actuator/mouthpiece (Figure 10). The dose of drug delivered by an MDI is first metered by the primary internal valve (labeled in Figure 10), which allows a fraction of the drug suspension present in the canister to pass into a small holding space. The actual dose intended for the patient exits the MDI valve into the mouthpiece and is a slightly smaller volume than the initial metered amount. Incorporation of an MDI into the device necessitates the construction or purchase of a substitute for the mouthpiece (see *Aerosolized Medication*, Figure 13) in order to reduce bulk and facilitate canister replacement when necessary.

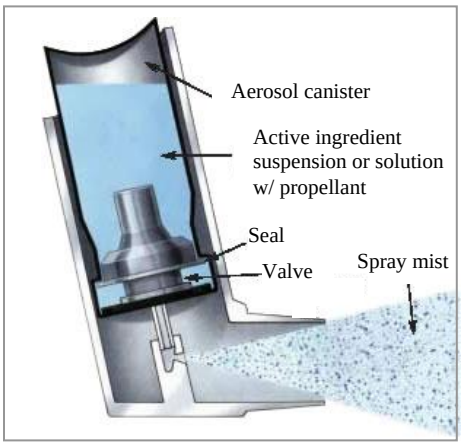


Figure 10. Illustration of internal mechanism of a metered-dose inhaler that first meters a specific dose/amount of drug mixture from the canister and then expels the dose as an aerosol mist during interaction of the valve stem and mouthpiece (solvay-fluor.com).

3.5 Aerosolized Medication & Drug Delivery

The necessity of delivering an aerosol medication usually follows the onset of respiratory distress such as an acute asthma attack, and rapid relief of symptoms allows the individual to continue their normal activity. Patients treated by Dr. Teodorescu experience both acute inflammatory events and chronic airway obstructions complicated by the combined actions of asthma and obstructive sleep apnea. In order to reduce the number and severity of acute attacks during the day, most patients suffering from chronic inflammation are prescribed aerosol medication containing long-acting ingredients. The delivery of medication during sleep using the airflow provided by the patient's CPAP has been presented as a method to passively facilitate this preventative therapy and hopefully reduce asthma symptoms experienced during the remainder of the day.

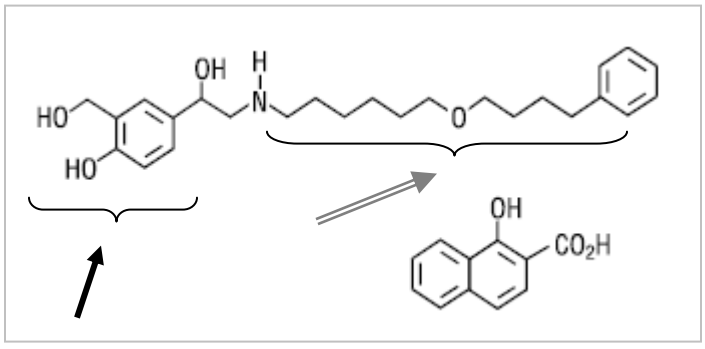


Figure 11. Chemical structure of salmeterol xinafoate, a long-acting beta 2-adrenergic agonist. Hydrophilic side chain indicated by black arrow, lipophilic side chain indicated by gray arrow (us.gsk.com).

Asthma medications such as Advair® and Flovent® prescribed by the client of this project contain long acting beta 2-adrenergic agonists (LABA), which are designed to act up to twelve hours

(compared to the 4-6 hour effect realized by most fast-acting asthma inhalers). The continual stimulation of beta 2-adrenergic receptors found on the luminal surface of the lungs by the hydrophilic portion of the molecule (Figure 11) is assisted by the lipophilic side chain, which binds near the beta(2)-receptor and temporarily anchors the molecule in place. This stimulation results in the relaxation of smooth muscles lining the airways ("bronchodilation") and thus an increase in airflow to the peripheral regions of the lungs (Wishart *et al.* 2006). Delivery of LABA molecules is typically prescribed in conjunction with the introduction of a corticosteroid such as fluticasone propionate. This molecule specifically binds to glucocorticoid receptors on mast cells and eosinophils (a type of white blood cell), two types of cells implicated in the unique host responses that occur during asthma attacks and allergic reactions. Downstream effects of the binding of fluticasone propionate involve the alteration of protein synthesis resulting in many anti-inflammatory actions. The down-regulation of proinflammatory molecules (interleukin-1, 3, and 5) as well as the inhibition of histamines, macrophage recruitment, and complement proteins contribute to the reduction of inflammation in the affected airways (Wishart *et al.* 2006)

Delivery of an administered dose of aerosolized medication through the ventilation circuit of a CPAP machine may be a promising approach to therapy, but it poses a truly multi-factorial problem. Numerous variables associated with each component of both the CPAP and respiratory systems have the potential to improve or inhibit delivery. Studies have suggested that the primary cause of inhalatory treatment failure is the inadequate deposition of drugs in the lungs (Franca *et al*. 2006); in understanding the mechanisms of aerosol administration, the hope is to better tailor a device that will provide maximal drug delivery.

3.5.1 Patient-related factors

Beginning with the nature of the affected individual, it is clear that numerous uncontrollable factors exist, including the tidal volume, length of breathing cycle, mechanism of the airway obstruction and severity of the obstruction in the patient. The final variable in this list adds further complication when taking asthmatic patients into consideration; in the lungs of these patients, aerosol deposition depends on the rate of inspiratory flow, which is a function of the degree of lung tissue inflammation (Franca *et al*. 2006). High inspiratory flow rates, which may be due to either individual patient characteristics or conditions created by a high prescribed CPAP pressure, contribute to a considerable increase in drug impaction in the oropharynx, trachea and proximal airways. Furthermore, in normal patients, deposition in the peripheral regions of the lung has been shown to be relatively uniform and dependent primarily on gravity. The highly inflamed portions of asthmatic lungs prevent uniform distribution by restricting airflow and thus impeding the transport of drug particles to the tissues that need them the most. A heterogenous pattern of deposition occurs in which the majority of the drug is deposited in the healthiest regions of the airway, preventing the drug from exerting its effects properly (Franca *et al.* 2006). Clearly, the problem presented by the combination of airway inflammation and obstructive sleep apnea adds complication to the development of a product capable of providing the most beneficial treatment to the right place at the right time. In the design of a universal device, appropriate functionalities must be developed (e.g. being able to account for breath timing variability with a "smart" circuit) in order to account for such inconsistencies between patients.

3.5.2 Drug-dependent factors

In addition to patient-specific factors, drug characteristics such as intended dose, formulation, aerosol particle size, target site and duration of action also must be considered during the

development process. Particle size, although not easily modified without intervention of pharmaceutical companies, plays an important role in the transport of the drug through both the ventilation circuit and the upper airway of the patient. Most devices that generate an aerosol (e.g. MDIs) produce particles that are 1-5 μm in size, which may be reduced by the integration of a spacing chamber in the ventilation circuit (Dhand 2004). Particles larger than 2 μm usually experience impaction in the walls of tubing, an occurrence that will be minimized by limiting the length of tubing between the MDI and the patient (Dhand 2007). Impaction at the back of the throat is also common, even during normal use of an inhaler with spontaneous breathing (no respiratory assistance by a device), and has been shown to increase with very high (>40 L/min) inspiratory flow rates when an assistive ventilation source (e.g. CPAP or invasive mechanical ventilation) is coupled to medication delivery (Franca *et al*. 2006). While some variables inhibiting drug delivery may be reduced or eliminated, it is important to note that designing for a particular drug or family of medications may limit the future usefulness of the device if and when drug characteristics change.

3.5.3 Equipment-related factors

Several factors that have also been emphasized in literature involve components that are more easily modified for use in this project, including characteristics of MDI integration and the humidity of the air delivered to the respiratory system. The latter issue has an effect on both patient comfort and drug delivery, forcing the group to compromise when making design decisions. Most CPAP machines utilize room air at ambient humidity but include an optional humidifier to reduce drying effects in the nasal and oral mucosa. In previous studies, the use of humidification within a ventilation circuit (tubing) has been shown to reduce drug delivery using MDIs by approximately 50% when compared to dry (relative humidity <30%) circuits (Dhand 2007). Although the use of humidified air for CPAP use of more than 4 hours is often more comfortable, some patients can become distressed during airway emergencies because the hot, humid air causes feelings of suffocation (Parkes *et al*. 1997). The client of this project specified that humidifier use is necessary or requested in about half of his patients, usually when the CPAP pressure prescribed for the individual is high (>10 in H_2O) (Teodorescu 2007). However, in the interest of maximizing drug delivery at the early stages of this project, the application of this device will be restricted to users not requiring room air humidification.

As discussed earlier, particle size decreases following the release of the aerosol when a holding chamber adapter (Figure 12) is used. This effect is due in part to the nature of aerosols as relatively unstable "particles" consisting of both droplet and vapor phases (Parkes *et al*. 1997). The "shrinking" of aerosol particles results from a decrease in the overall speed of the air in the chamber (compared to proximal or distal tubing) that allows for increased propellant evaporation time.

Figure 12. MDI attached to a holding chamber (or "spacer"). (rainbowasthmacenter.case.edu)

Figure 13. Bidirectional in-line MDI adapter. (remotemedical.com)

The aerosol particles become smaller before the airflow carries them into narrower tubing, an effect shown in literature to be correlated with a reduction in drug impaction in the walls of the ventilation circuit (Dhand 2004). A similar effect was observed when a bi-directional inline actuator (Figure 13) was used in place of a holding chamber; for this reason, as well as to reduce the bulk of the ventilation circuit upon integration of this device, the use of an inline actuator will be pursued.

Another component of MDI integration that will have a considerable impact on the success of drug delivery is the position of the MDI in the ventilation circuit. Early in the project, the idea was accepted that actuation would have to occur relatively far away from the patient due to the bulk of the mechanical device for vibrating and actuating the inhaler. The weight of the device was considered as the negative factor most strongly constraining placement, and the assumption was made that the best location for MDI integration would be directly following the exit of air from the CPAP (e.g. perhaps on a bedside table). A brief evaluation of the effect of tubing length (distance of the MDI from the mask during actuation) on the amount of drug delivered to the mask was performed early in the semester; the development of the experiment preceded the discovery of a bidirectional in-line adapter and thus had several flaws preventing the formation of any conclusions about the effect of MDI location on delivery (Appendix C). Previous studies of aerosol generators placed at various distances from the patient have demonstrated that during the use of a positive pressure-based therapy such as CPAP, delivery is more efficient if the generator is as close to the patient as possible (Dhand 2004).

3.5.3.1 Effect of tubing length/method of administration

In order to quantitatively assess the efficacy of placing the MDI actuation device at specific points in the ventilation circuit, samples were collected when the MDI was 1-6" from the end of the CPAP tubing. Ultraviolet spectrophotometry, which measures the transmittance of a given wavelength of light through a sample, was chosen as an indirect measure of the mass of drug which reached the collecting vessel. The previous design group demonstrated that this test method was relatively simple to perform and resulted in sufficiently accurate data (Quinn *et al.* 2004). Due to sampling error caused by the orientation of the MDI with respect to the CPAP tubing (placed perpendicular to the tube and thus the airflow), no correlation between tubing length and amount of drug delivered to the mask end of the tubing was observed (Appendix C). It was probable that no measurable amount of drug reached the end of the tubing due to impaction on the wall due to the positioning of the inhaler (to be fixed by incorporation of the inhaler with an inline actuator) as well as bends in the tubing (to be eliminated by placing the apparatus at the face mask).

Combining the information gained from the pilot experiment and primary literature, a more sophisticated prototype will be developed in future semesters (see *Future Work*) in order to achieve actuation *at the mask* and thus ensure that the device provides the most therapeutic effects possible.

While the patient-related factors mentioned earlier are usually difficult or impossible to control for, understanding the sinusoidal nature of the breathing cycle can make it a much more controllable factor in the development of effective delivery mechanisms. The onset of inhalation has been suggested as the optimal time for actuation of an aerosol generator (Dhand 2004), most likely due to the magnitude of the negative pressure created in the airways during peak inhalation. Assuming that target patients will already have compromised airways due to some inflammation, the coordination of inhalation and MDI actuation will be crucial to the delivery of the maximum amount of drug to the largest possible area of peripheral respiratory tissue.

3.5.4 Effect of CPAP on aerosol delivery

Support for the use of CPAP to help propel inhaled medication deep into the lungs of asthmatic patients is only beginning to emerge due to the limited amount of research performed in this area. However, Fauroux et al. have lent evidence to support the use of non-invasive "pressure support" (PS) ventilation (e.g. CPAP) by demonstrating that total lung aerosol deposition could be "significantly enhanced" when PS was used to drive aerosol transport. Using radio-labeled aerosolized particles, researchers evaluated the spatial distribution of the simulated drug throughout the lungs (Figure 14), finding that the radioactivity count increased 30% from the control session to the PS ventilation session. It is important to note, however, that the particles were delivered as an aerosol through the use of a nebulizer, which acts by a different mechanism than metered-dose inhalers.

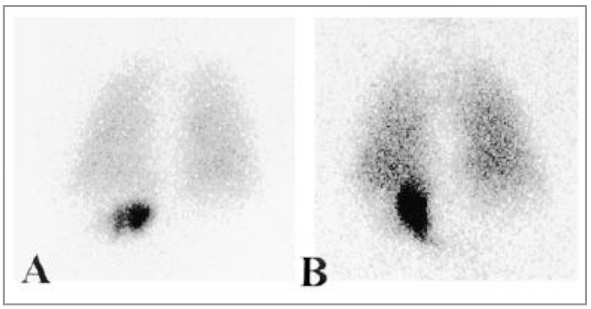


Figure 14. Graphic output of a gamma camera demonstrating the deposition of radio-labeled particles in the lungs: homogenous distribution in control session (A) and PS session (B) (Faroux et al. 2000).

Variation exists in the consensus presented by current studies, making the presentation of solid proof-of-concept challenging until a greater amount of research is conducted. The founding principle of this project, that inhaled asthma medication must be delivered concurrently with CPAP, is still supported by research conclusions. Studies have demonstrated that the beneficial effects on respiratory mechanics provided by CPAP are rapidly lost when it is stopped; it is therefore crucial to deliver aerosolized medication in line with CPAP to ensure that the drug is most effectively delivered to the peripheral regions of the respiratory system.

Suggesting that this concept may be difficult to achieve in reality, certain evidence suggests that positive pressure ventilation may reduce drug delivery. Reychler et al. showed that an aerosol delivered from a "jet nebulizer" (Figure 15) coupled with CPAP led to a significant decrease in drug delivery. Amikacin, a common antibiotic that must be administered intramuscularly or intravenously, was aerosolized and its deposition evaluated by both radio-labeling and renal clearance. The amount of amikacin cleared (excreted in the urine) each day was used to approximate the amount of drug inhaled and thus transported to the bloodstream by capillaries in the lungs. Clearance of amikacin was found to be significantly lower with the CPAP-coupled nebulizer treatment (1.97% of initial dose) than with the use of a nebulizer alone (4.88% of initial dose) (Reychler *et al.* 2007).

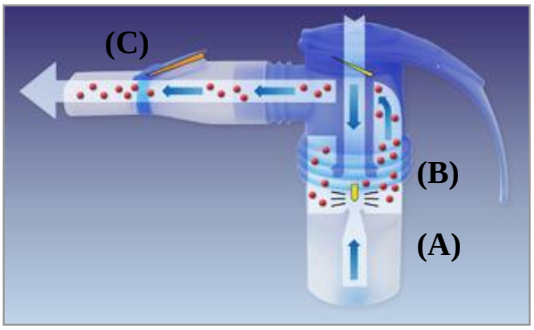


Figure 15. Illustration of a jet nebulizer demonstrating the incorporation of an aqueous solution (B) to aerosolize and escape up through a mouthpiece (pressurized air supply source (A) causing drug particles suspended in an C) (pari.com)

Another study suggested that CPAP significantly reduces the total aerosol delivery from 1.52% to 0.37% to the facemask of a patient receiving nebulized medication. Despite the evidence that suggests that CPAP-coupled drug administration reduces delivery to the patient's lungs, it was also shown that the efficacy of the drug successfully delivered to its target site is not reduced. During stable asthma (airway unrestricted), the delivery of a β2 agonist to its parent receptor was

not altered by CPAP (Parkes *et al.* 1997). It is clear that further investigation is warranted as numerous aforementioned factors related to drug characteristics, delivery mode (nebulizer vs. MDI) and integration of the CPAP may have either opposing or synergistic effects on drug delivery to the lungs.

4. Design Constraints

The design of the device is constrained by the needs of the client of this project and the technical requirements of the project. First, the device must automatically deliver one or more actuations of a metered dose inhaler at a specified time during the night. The time of delivery and number of actuations of the drug should be programmable by the physician but unalterable by the patient. The drug must be delivered into the existing CPAP ventilation circuit and utilize the flow generated by the CPAP to propel the drug into the patient's lungs. Testing has shown that placement of the device even several inches from the mask causes significant drug loss; therefore, the device should be integrated into the ventilation circuit immediately in front of the mask. However, the size of the device should minimize unnecessary bulk near the face to prevent patient claustrophobia and discomfort. The device as a whole should not interfere with the patient's sleeping habits to a greater extent than the existing CPAP equipment.

The release of the drug into the ventilation circuit should be timed with the onset of patient inhalation to maximize drug delivery to the lungs. Prior to actuation, the drug canister must be shaken under the conditions (frequency, duration, and amplitude) necessary to mix the drug and propellant. Additionally, the device should allow for oral delivery through the use of a full face mask. Portions of the device should be easily disassembled to allow for regular cleaning and replacement of the drug canister by the patient, taking into account that some patients may have reduced dexterity of the hands. The device shall have a life in service of at least one year and will be used daily by a single patient.

5. Proposed Solutions

5.1 Mechanical Components

Several actions need to be accomplished by the mechanical components of the design. These include a vibrating/shaking mechanism to effectively mix the propellant and drug, an actuation mechanism to depress the inhaler and release the drug, and an attachment that allows for integration into the CPAP tubing and/or the mask.

5.1.1 Agitation options

Early brainstorming led to the development of 3 different ideas that would accomplish the task of shaking the drug canister. These included a vibrating gear, a double spring mechanism, and rotating cams.

5.1.1.1 Vibrating gear

The vibrating gear idea was developed after examining the mechanics behind the vibration movement found in cellular phones. The motion is accomplished by mounting a weight off- center on a rotating gear (Figure 16). The amplitude of the vibration can be altered by changing the mass of the weight and the distance the weight is mounted off-center. A motor is used to spin the gear which causes a circular vibrating movement. The speed of the motor can also have an effect on the intensity of the vibration (How Stuff Works, 2007). The major drawback to this design is the difficulty in combining it with a depression mechanism due to the fact that the canister would be rotating in a circular fashion and the depression of the canister needs to be linear. It may also require a

significant amount of movement to shake the canister completely which may impede the sleeping state of the patient if placed near the CPAP mask.

Figure 16. Off-center weight powered by gear and motor. Setup creates a vibration that can be adjusted for strength and displacement amounts (electronics.howstuffworks.com)

5.1.1.2 Double spring mechanism

The double spring mechanism accomplishes the shaking of the canister by mounting the canister between two compression springs (Figure 17). When one of the springs is retracted and then released, its recoil will exert a force on both the canister and the second spring, forcing the spring and canister backwards; this adds potential energy to the second spring. This second spring would release and drive the entire system back in the opposite direction, again causing the primary spring to retract. This motion would continue until all of the energy put into the system by the original spring retraction was dissipated. The main issues with using this design would be determining the appropriate spring constant that would ensure complete drug and propellant mixing without damaging the canisters. The back and forth motion of the canister would also require very precise alignment of the springs and inhaler so that the canister could not be rotated and stuck within the cavity of the tube. Additionally, the need to overcome the force of both of the springs would require the canister depression mechanism to be much stronger.

Figure 17. Double spring mechanism (created by author).

5.1.1.3 Rotating cams

The rotating cam idea was developed because it had a number of different options in its shaking abilities (Figure 18). The cam would be mounted to a motor which would rotate the cam at the necessary speed. A custom-made cam that has a number of ridges built on its surface to give many small-amplitude displacements. A single circular cam could be mounted off center a displacement of x so that each rotation would result in one displacement of the canister equal to x. The option of having one cam perform both agitation and actuation was also investigated. This cam

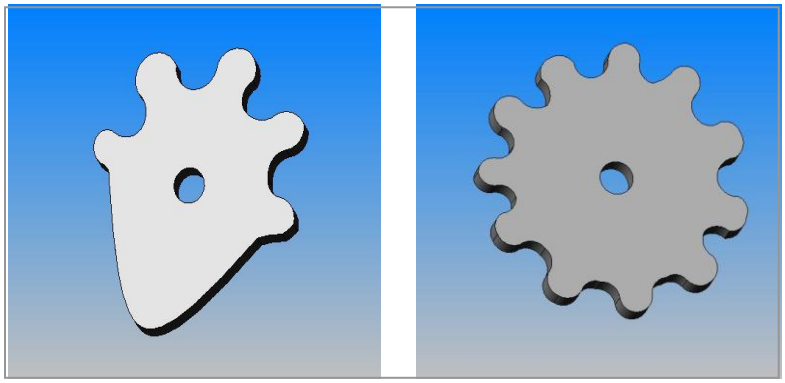


Figure 18. Various cam options to accomplish agitation and actuation. On the left, a cam to shake and depress an inhaler. On the right, a strictly vibrational cam. (Quinn *et al*, 2004).

would have ridges on one side (180°) where the canister would undergo many small displacements. The other side of the cam would have a more oblong shape that would extend beyond the height of the grooves and be able to actuate the inhaler. The major benefit to the cam design is that its movement of the canister is linear, which makes it easier to combine both agitation and actuation mechanisms.

5.1.2 Actuation options

Actuation of the canister is the second motion required of the mechanical design. Again, a number of different designs were developed and analyzed including a linear actuator, an 8-bar-mechanism, and a rotating cam.

5.1.2.1 Linear actuator

The linear actuator is a system that works by combining a threaded shaft and a nut (Figure 19). The nut is spun by a motor which causes the shaft to move through the nut. Using a bidirectional motor, spinning the motor one way would cause the shaft to advance towards the canister, eventually leading to depression of the inhaler. Reversing the direction would bring the shaft away from the canister and allow it to refill with drug and also allow for shaking. The downside to this design is that it would need to be very tall. Mounting a linear actuator on top of the canister in addition to the shaking mechanism could inconvenience the patient.

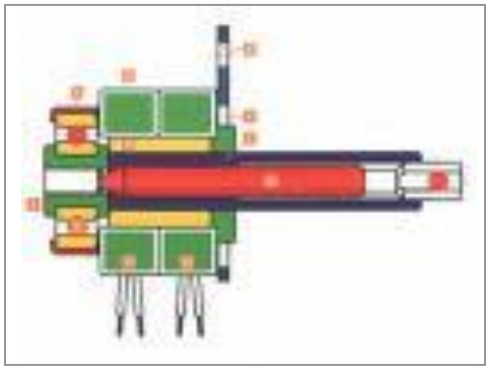


Figure 19. Illustration of components of a linear actuator (acpd.co.uk).

5.1.2.2 8-Bar mechanism

The inspiration for this option came from a boxing-glove punching mechanism (Figure 20). Pulling on one side of the device causes a linear motion on the other side equal and opposite to the input displacement. A solenoid or any other device that causes a fast linear motion could be mounted to one end of the mechanism; this would cause the other end to extend out and actuate the inhaler. Again, the problems with this device include the large size and the need to exert enough power to depress the inhaler.

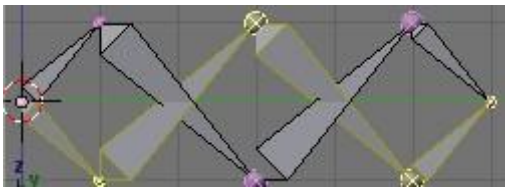


Figure 20. Illustration of an 8-bar mechanism (wiki.blender.org/index.php/BSoD/Introduction_to_Rigging/Some_Beginner_Rigs)

5.1.2.3 Rotating cams

As mentioned in 5.1.1.3, a rotating cam could be used to both shake and actuate the inhaler. Again, a number of different shapes could be used to accomplish the necessary motion. A circular cam could be mounted off center so that one side would have larger amplitude of displacement. Alternatively, an oblong cam could be used where the extended side would be long enough to depress the inhaler (Figure 21). The cam would be driven by a geared-down motor that ensures that the cam only undergoes one rotation in a desired period of time. This guarantees that the patient doesn't receive an unnecessary dosage of the drug.

5.1.2 Actuation options continued

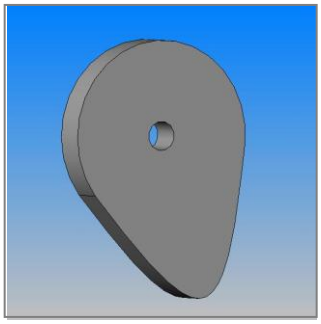


Figure 21. Actuation cam designed to depress a plunger capable of actuating an MDI (Quinn *et al.* 2004).

5.1.3 Background: Spring 2004 BME Design Prototype

In the midst of the process of developing the design options, the fact that a previous design group completed a similar project in 2004 that also involved the shaking and agitation of an inhaler needed to be taken into account (Quinn *et al.* 2004). A significant amount of concept development and testing was completed to determine that the combination of two rotating cams produced the motion needed. The design incorporated the use of two different motors running at different speeds that had different sized cams attached to each (Figure 22). The agitation cam had a smaller amplitude of displacement but rotated at a faster speed. Energy equations and calculations were developed and used to determine the exact height and angular velocity needed to thoroughly mix the drug and propellant. The group also did energy/spring constant calculations that determined the necessary spring constant to hold the inhaler at the desired position, ensuring that the cams could properly agitate and actuate while also allowing the motors to exert enough force to overcome the spring constant and depress the inhaler.

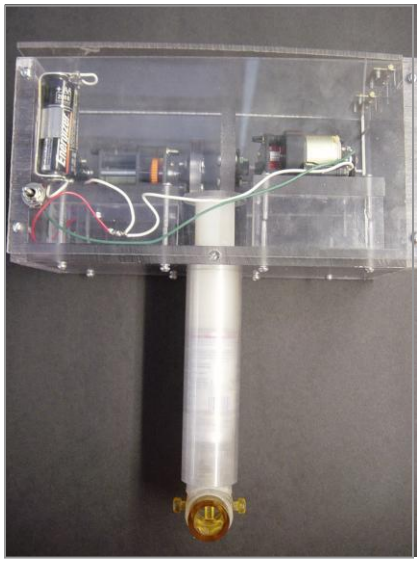


Figure 22. Spring 2004 prototype capable of shaking and actuating MDI for use in mechanical ventilation (Quinn *et al*, 2004)

While the group had done a lot of the legwork needed for the current design, many modifications still needed to be made to fulfill the current clients' needs. However, an advantage to this design was that the 2004 group had proven the concept of using two rotating cams to shake and depress an inhaler.

5.1.4 Evaluating a complete design

The major criteria used to pick a final design (a combination of an agitation mechanism and an actuation mechanism) were based on the ability of the two motions to be integrated, the size, and the manufacturability. The linear actuator and 8-bar mechanism to be used for the actuation movement were eliminated due mainly to their large size. The off center gear idea for the shaking motion was discarded due to its difficulty to combine its circular motion with the vertical motion needed to actuate the inhaler. The final design decision was between modifying the previous design group's project to meet the current needs and developing an entirely new project. Modifying the previous project would allow for the exploration and development of electrical components (to accomplish such tasks as detecting breathing patterns and timing drug agitation/release with inhalation), but developing a novel device would delay work on the electrical requirements until a later semester.

In the end, the Spring 2004 group's project was used as a starting point to modify in order to meet the current requirements. The alterations would include miniaturization, improved ease of canister removal, and integration with needed electrical components.

5.1.5 Final mechanical design

The rotating cam design involves the use of two separate cam and motor combinations to drive a plunger/canister/spring system. The plunger, canister and a spring are placed in-line in a tube to ensure that the force applied to the plunger via the cams is directed to the canister in a purely linear fashion. This aids in both agitation and actuation. An in-line actuator, a device currently used for mechanical ventilation equipment, is used to replace the usual mouthpiece included with an MDI (Figure 23). This device is open on both ends, allows for connection to CPAP tubing on either side, and directs spray into the tubing upon actuation of the inhaler. Therefore, it is placed at the bottom of the canister/spring tube to allow for continuous flow of the CPAP air through the mechanical device. The delivery of the drug is then in the direction of the CPAP air flow which may help to more effectively propel the drug to the patient.

Figure 23. Photograph of bidirectional in-line actuator used in this project (iimedical.com).

5.1.5.1 Motors

Two motors were purchased to drive the cam systems: one to drive the agitation cam and one to drive the actuation cam. The actuation cam needed significantly more torque to overcome the 11 lb force needed to depress the inhaler (Quinn *et al*, 2004). Both motors were purchased from a hobby shop and are typically used to power small electronic equipment such as robotic cars or airplanes. This allowed the motors to have significant power while remaining small in size. The agitation motor has an un-geared speed of 10,500 rpm when run off of 3 V. The actuation motor runs at about 20,000 rpm and needs to be run off of 12 Volts in order to produce the torque needed. Gear boxes were purchased to gear the motors down to go at the speeds needed. The agitation motor was geared down at a ratio of 5:1 to produce a speed of 2100 rpm. For the actuation motor, it was more important that the motor produced enough force to actuate the canister. Therefore, the gear ratio was determined by experimentation instead of calculations and was found to be 625:1. At an original speed of 20,000 rpm, the motor needed to be powered for 0.533 sec to complete one full revolution. This number can be used as the lag time between the motor initiation and inhalation making it possible to coordinate actuation of the motor with inhalation.

5.1.5.2 Agitation and Actuation Cams

For ease of manufacturing reasons, it was decided to make the cams circular and mount them off center to achieve the displacement needed. This means that the plunger system will only get activated one time for each cam rotation. To achieve the desired amount of displacement, an original cam diameter d_i was chosen with the axis of rotation located in the center of the agitation circle. The distance of the desired displacement for actuation, D, should be added onto the original cam diameter (Figure 24). With the axis of rotation located at the center of the original circle, the cam will under go a displacement equal to D with each rotation.

Using these ideas, it was found that the inhaler displacement needed for activation with the use of the in-line actuator was .125 in (from a resting position on top of it). Therefore, the actuation cam displacement distance needs to be at least .125 in longer than the agitation distance, assuming that the agitation distance is great enough to bring the canister to a resting position on top of the actuator.

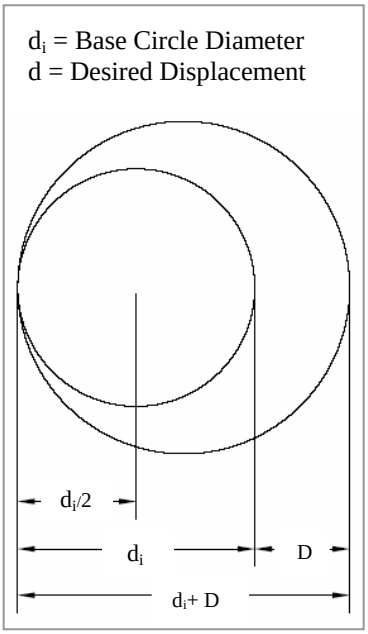


Figure 24: Method for determining cam sizes and axis of rotation location (Quinn *et al*, 2004)

To determine the agitation distance, calculations were performed to determine how much energy was put into the system during manual shaking of the inhaler. The components of the design could then be altered to find the appropriate angular velocity, time, and amplitude required to achieve an equal amount of energy using the cams.

Assuming harmonic motion, the energy of the system is equal to the power input over a specified amount of time (Eq. 1). When power is found with Eq. 2, and force with Eq. 3, the equations can be combined to formulate a final energy equation (Eq. 4).

$$E = \int_0^t P(t)\,dt \qquad [1]$$

$$P = Fv(t)\,t \qquad [2]$$

$$F = ma(t) \qquad [3]$$

$$E = \int_0^t m\,a(t)\,v(t)\,dt \qquad [4]$$

Because of the harmonic motion assumption, Equation 5 will lead to the formulation of Equations 6 and 7 to further substitute into the energy equation.

$$d(t) = A\sin(\omega t) \qquad [5]$$

$$d'(t) = v(t) = A\omega\cos(\omega t) \qquad [6]$$

$$d''(t) = a(t) = -A\omega^2\sin(\omega t) \qquad [7]$$

Assuming a mass of 12 g for the canister, a frequency of 3Hz for manual shaking, and an amplitude of displacement of 10 cm, the energy of shaking was calculated as 1.05×10^{-9}J. With a gear ratio of 5:1, the agitation cam was runs at an angular velocity of 219.91 rad/sec. Using this information, the canister displacement was determined to be 0.26 mm for a duration of 5 seconds in order to absorb enough energy to mix the drug and propellant. This displacement was increased to 3 mm (0.118 in) to both ensure mixing as well as allow for easier manufacturing and mounting. The actuation cam displacement distance needed to be an additional length adequate to depress the inhaler, and therefore the agitation cam was created with a diameter of 1.35 in and the actuation cam with a diameter of 1.75 in. The axes of rotation were placed according to the previous measurements.

5.1.5.3 Spring

Because the current design's canister requires the same amount of force to actuate as the previous group's (Spring 2004) inhaler, the equations derived in Quinn *et al* (2004) were utilized and the resulting spring constant was found to be 4.75 lb/in.

5.1.5.4 Platform, tube and base

The material used to make the cams, the plunger and the base of the system was .125 in thick polycarbonate. It was chosen due to its light weight relatively easy machinability. It can also be cleaned and doesn't rust or weather easily.

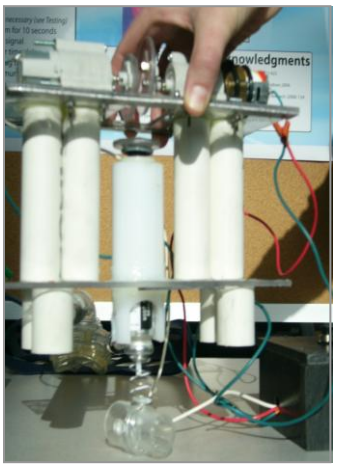


Figure 25. Prototype showing removable in-line actuator that allows for easy disassembly.

The previous group's design did not allow for easy canister replacement or removal of the in-line actuator. In order to replace the canister, the user would have to loosen bolts near the motors/cams and remove the entire tube. Knowing that many of the people using the device may have limited dexterity, the setup of the tube system was redesigned so that the user would only have to remove the in-line actuator, slip out the old canister, and slide a new one in. The spring could be fixed to the actuator to minimize any possible complications or confusions during reassembly. Because of this, a custom-milled agitation tube was chosen to allow insertion and holding of the in-line actuator but also allows for its removal when desired (Figure 25). The spring and canister are inserted into the agitation tube and the in-line actuator is contained on the bottom.

The height of the agitation tube was determined by summing the distance of displacement of the actuation cam, the height of the canister, and the height of the in-line actuator for a total 4.25 in. The spring height was considered but not included due to the fact that it was longer than the 0.4688 in of displacement created by meaning the spring would be partially compressed when placed in the tube. The agitation tube is made out of UHMWPE with a 0.9 in inner diameter. The canister has a 0.878 in diameter to provide a pathway for the canister that has enough clearance for linear movement but also keeps the canister vertical. A plunger made out of a wooden dowel with two nylon guides was fixed with epoxy to a circular polycarbonate disc that acted as the plunger platform. PVC tubing was cut to act as feet holding the base platform up off of the table (to allow the in-line actuator to sit below the platform while still being removable for canister replacement) and as the platforms for the motor/cam systems (Figure 26).

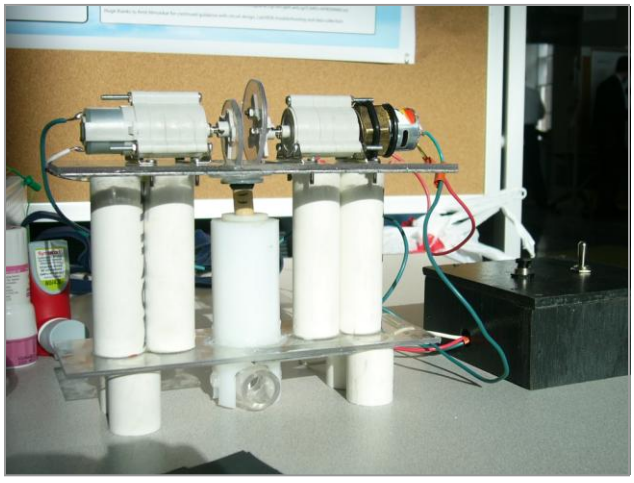


Figure 26. Final assembled prototype.

The current device allows for access to the cams and motors, however, ideally a box would enclose the system to aid in soundproofing the device as well as reduce the risk of damage in the patient's home.

5.2 Electrical Components

In order to engage the vibration and actuation motors at the correct time so that drug delivery is most efficient, it was determined that actuation must occur concurrently with peak inhalation. During early brainstorming meetings, a list was created of measurable parameters relevant to the physiological changes that occur during the different stages of the breathing cycle. To incorporate these individual variables into the circuit, the merits of each associated sensor were investigated, considering the unique needs of this project. Given the high number of component-based decisions made early on in the project with limited background knowledge, the majority of the sensors were eliminated simply based on complexity or cost.

5.2.1 Sensor rationale

Humidity and gas (CO_2 or O_2) sensors that would be most accessible (w.r.t. cost, size) to a bioinstrumentation application such as this project typically had very long response times and would thus not meet the need for synchronous detection and output; one example of a CO_2 sensor small enough to integrate into the circuit design had a response time listed only as "<60 seconds," a value not specific or fast enough for this project. Another factor related to the use of a gas sensor that caused its elimination was the short lifetime suggested in primary literature, as well as signal drift over time (Zhou *et al*. 1993)

The option of using a pressure sensor was eliminated because it was believed that analysis of the resulting signal would be complicated by the nature of the CPAP. Assuming that the sensor would have to be very sensitive to detect the change in pressure between inhalation and exhalation, it was postulated that the high, steady pressure generated by the CPAP would saturate the sensor and be difficult to account for in signal processing. For a similar reason, the possibility that an in-line flowmeter could detect the transition between phases in the breathing cycle was eliminated. Correspondence with a product support representative from Respironics© elucidated how most CPAP machines work; in order to maintain a steady pressure, the flow rate of the compressed air fluctuates during the breathing cycle (Product Support 2007). Due to constantly changing conditions at the mask with respect to air flow, it was assumed that inclusion of a flowmeter would not offer a definitive indication of the onset of inhalation. Yet another option briefly explored during the design process was the use of a mechanical sensor to detect chest expansion during inspiration. This proposal was not pursued further because it was assumed that the motions of the patient during sleep such as tossing and turning would cause unwanted input to the sensor. Variable patient size and comfort level with an additional piece of equipment also led to the elimination of the chest expansion sensor as an option.

Temperature sensors were also considered for the detection of respiratory cycle phase. An abundance of data concerning the temperature profile of breathing stages in both normal and diseased subjects offered support that distinguishing between the stages would be feasible. Several sensor options meant for small applications were explored, including RTDs (resistance temperature detectors), thermocouples and thermistors. All three sensor types involve a relatively simple relationship between temperature and resistance (RTDs, thermistors - linear) or electric potential difference (thermocouples - nonlinear), thus facilitating downstream signal processing. However, other important characteristics varied widely between the three groups. Thermocouples are inexpensive and have standard connectors, but can only detect changes ≥ 1

°C. RTD technology offers an improvement in response time and precision, but those that provide sensitivity similar to thermistors are generally expensive (OEI 2007).

Thermistors were chosen as the most appropriate temperature-sensing element for this design due to their sensitivity, low cost, durability, small size and weight, and fast response time. These characteristics are realized in such simple component due to the unique nature of the materials used to construct them. Thermistors have semiconductor properties because of their thermally resistive ceramic materials, allowing a nearly linear conversion of changes in temperature to similar changes in resistance across the element (Figure 27). The sensitivity of this product is especially appealing in biomedical applications because temperature fluctuations relevant to physiological processes can cause the resistance to range from 0.1 to 100 Ωm, a large enough span to accurately detect target activity. Although not anticipated in this project, high temperatures can skew the output generated by a thermistor because self-heating that occurs at a certain threshold will cause the R/T relationship to become nonlinear; this phenomenon will not occur under 125 °C (257 °F) in the thermistors purchased for this project. Another favorable characteristic of thermistors mentioned earlier is their small size and durability; offered types range from washers and rods to glass-encapsulated beads (Figure 28), where the latter is most commonly applied to biomedical applications due to exposure to physiological conditions (Webster 1999).

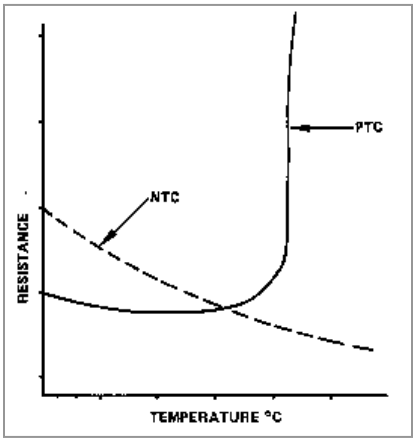


Figure 27. Relationship between T° (x-axis) and resistance (y-axis) in NTC (negative temperature coefficient) and PTC (positive temperature coefficient) thermistors (usmotors.com)

Before development of the circuit began, the parameters of the purchased thermistors had to be taken into account. The primary variable that had to be carefully controlled was the maximum current permitted by each thermistor, denoted in company literature as 1.05 mA at ambient temperature. It is expected that the thermistors will be powered by ≤ 5V because such a low voltage can be easily reproduced with several small batteries; minimal current will be drawn by the first stage of the circuit, so it is not anticipated that battery use would hinder performance of the device. Because of the variable resistance afforded by thermistors, it was necessary to perform calculations at both room temperature (approx. 23 °C or 296.15 K) and assumed exhalation temperature (35.75 ± 0.6°C or approx. 308.9 K) (Paredi *et al.* 2002).

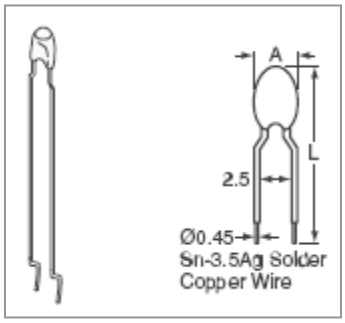


Figure 28. Illustration of the NTC encapsulated bead thermistor purchased for the project (digikey.com)

Resistance can be calculated given the B constant value for the thermistor (3500 for the 2 kΩ thermistors purchased from Digi-Key) and the following equation (Wikipedia 2007):

$$R = R_0 e^{B(\frac{1}{T}-\frac{1}{T_0})} \qquad [8]$$

Under baseline (room T°) conditions, the thermistor provides a resistance of 2000 Ω, necessitating the use of a voltage divider with an R_A value of ≥ 2.7 kΩ (if V_S = 5V) or ≥ 860 Ω (if V_S = 3V). When the thermistor is exposed to exhaled breaths, the resistance will increase to approximately 1228 Ω, requiring R_A to be ≥ 3.5 kΩ (if V_S = 5V) or ≥ 1.6 kΩ (if V_S = 3V). To

incorporate a safety factor into the design of this circuit, 10 kΩ resistors were chosen for R_A when R_B is a 2 kΩ NTC thermistor (Figure 29).

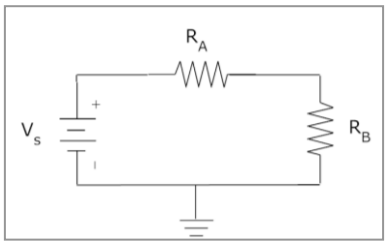


Figure 29. Circuit diagram illustrating components of a voltage divider, where the source voltage (V_S) is distributed between the two resistors R_A and R_B based on the ratio of the resistor in question to the sum of the two resistance values (Appendix A).

5.2.2 First draft of circuitry

The development of the circuit was based on a bioinstrumentation lab involving a difference amplifier comparing the voltage across the thermistor to ground (Figure 30). Initial testing was performed with the thermistor placed on the lab bench and exposed to random exhaled breaths (no extensive testing with the mask was performed at this point). Resistor values were extrapolated from the aforementioned lab and scaled down so that R_1 would match the room temperature resistance of the thermistor. In this situation, the circuit was set up with R_g = 10 kΩ, R_1 = 2.2 kΩ, R_2 = 10 kΩ and R_g ~ 2 kΩ.

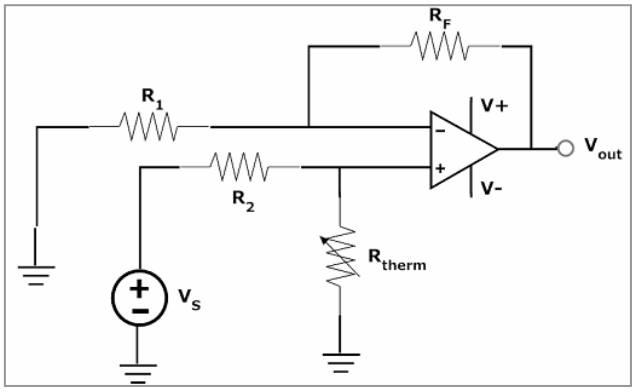


Figure 30. First draft of circuit designed to deliver an amplified voltage (V_{out}) proportional to the voltage across the thermistor (R_{therm}).

5.2.3 Final circuit

Following multiple iterations of the initial circuit to improve gain and reduce noise, a completely novel design was pursued. The new circuit was proposed to maximize universality and generate an output positively correlated with breath temperature. In order to begin minimizing the variability associated with the circuitry and its environment, a multi-stage difference amplifier was developed for the detection of breathing cycle changes. The first stage (Figure 31) consists of a simple voltage divider that provides power to the thermistor and produces the voltage across the thermistor as its output. During the development of this stage, the permissive operating current of the 2 kΩ thermistors during use at both room temperature and maximum exhalation temperature had to be accounted for in the choice made for R_1 and R_2 (Figure 31).

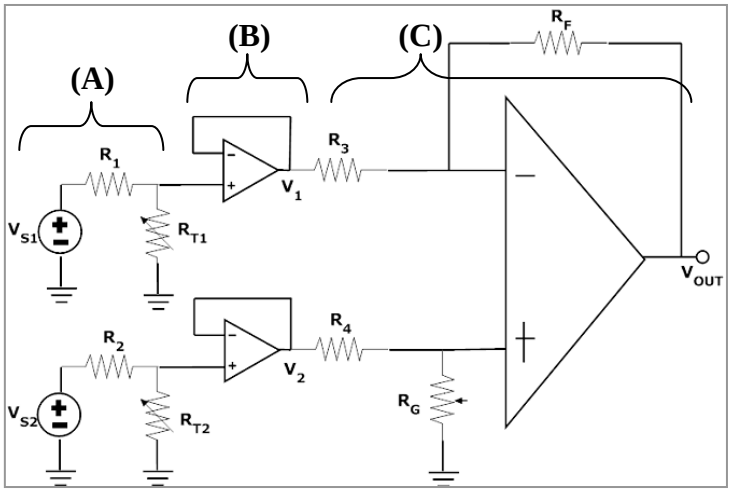


Figure 31. Next-generation difference amplifier circuit designed to deliver an amplified voltage (V_{out}) proportional to the difference between the voltage (V_1) across a reference (room T°) thermistor (R_{T1}) and the voltage (V_2) across the thermistor exposed to the patient's breathing cycle (R_{T2}). First stage denoted by (A), second stage by (B), third stage by (C).

The anticipated universal nature of this design depends on the use of two thermistors in stage one, where R_{T1} serves as a reference representing the voltage associated with ambient temperature while R_{T2} produces a voltage that fluctuates in response to temperature changes during the breathing cycle. A unity gain amplifier (Figure 31) follows the first stage in

order to prevent complications (unwanted voltage changes) due to loading in subsequent stages, where V_{in} (V_+) = V_{out} ("V_1"). The final stage of the circuit represents a general difference amplifier, governed by the following equation:

$$V_{out} = \frac{(R_f + R_1)R_g}{(R_g + R_2)R_1} V_2 - (\frac{R_f}{R_1})V_1 \qquad [9]$$

The determination of the resistor values for this stage of the circuit involved two main ideas: the desired gain for the final amplifier and the characteristics of the individual thermistors. An R_f value of 47 kΩ was arbitrarily chosen to maintain a low current through the system. The use of a potentiometer for R_g provided an opportunity to determine the best resistance value for R_g given the assumption that the two 2 kΩ thermistors had inherent minor differences in material characteristics and thus response to temperature changes.

Following further development with the circuit, it was determined that in order to achieve a suitably high gain, a higher ratio of R_f and R_g to R_1 and R_2 would have to be established. The original amplifier output using old resistor values (e.g. R_f = 47 kΩ) had units of millivolts, with a relatively small signal amplitude. To create a more defined signal with a higher output voltage, R_f and R_g were changed to 81 kΩ, while 3.9 kΩ resistors were chosen for R_1 and R_2; this change resulted in a final gain of ~20.

5.2.4 Testing

Difference amplifier testing was conducted using a 21 year old female in good health as a test subject. The subject was lying down on the floor of the lab and instructed to relax and breathe normally, although she did not fall asleep. The lab was a comfortable room temperature.

Initially, the temperature-sensing thermistor was taped outside one of the mouth ports (Figure 32) of the mask while the reference thermistor was resting on the lab bench approximately 5 feet away from the subject. The CPAP tubing was attached to the mask, but the CPAP was initially not turned on for the comfort of the test subject. The subject was instructed to raise her index finger when she began exhalation, and lower her index finger when starting inhalation. The physical indication used by the subject to signal the beginning of inhalation and exhalation exactly corresponded to the peaks and valleys on the oscilloscope voltage trace, respectively, and the subject was not allowed to watch the oscilloscope. To confirm this result, the subject was instructed to stand up near the oscilloscope and the rising and falling of her chest was observed as an indication of inhalation and exhalation. Within the limits of human visual observation, the relative maxima and minima of the voltage trace corresponded to the switch between rising and falling of the subject's chest.

Figure 32. Full face CPAP mask showing position of mouth ports and nasal leak ports (cpapworksllc.com).

The second test was conducted with the same setup over a period of 30 minutes for the purpose of observing the response of the thermistor during extended exposure to rising and falling temperatures at physiologically relevant levels. The thermistor output was viewed on the

oscilloscope for the duration of the test while the supine subject breathed steadily into the mask. Data viewed on the oscilloscope showed an initial rise in the baseline temperature as the thermistor warmed from contact with the subject's breath. However, after approximately 2 minutes there was no further drifting of the waveform, evidence of self-heating, or saturation of the circuit. This test was repeated on two other test subjects, both 21 year old females in good health, for a reduced duration of 5 minutes (Figure 33). It should be noted that the maximum and minimum voltages vary from one breath to the next, and there is considerable variation between test subjects.

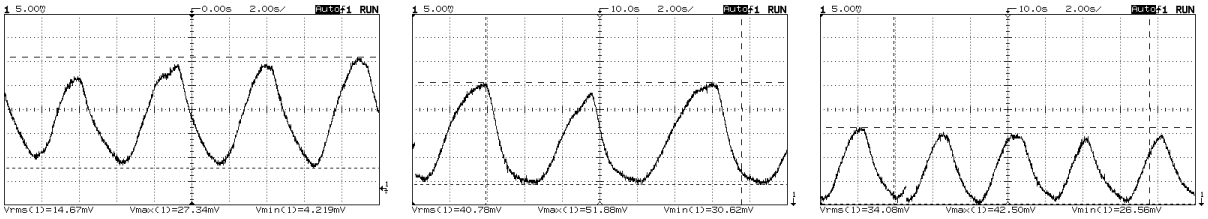


Figure 33. Voltage vs. time traces for 3 different subjects captured for 20 seconds with thermistor at mouth port after ≥5 minutes of subject breathing into mask without CPAP. Voltage is indicated at 5 mV per division, time at 2 sec/division.

Next, the thermistor was moved from its position outside a mouth port of the CPAP mask to a position outside the nasal leak ports. Both of these trials involved placing the thermistor outside the mask rather than inside because it was reasoned that the temperature inside the mask would show less variation as the exhaled air becomes trapped. The position outside the nasal ports was tested because the mouth ports have caps that can be screwed on to prevent air from escaping, while the nasal leak ports are always open and thus have a reduced chance of negatively affecting the pressure in the system. Positioning the thermistor at the nasal leak ports would give the patient the flexibility to open or close the mouth ports. The subject was again instructed to breathe normally while the CPAP was left off (Figure 34).

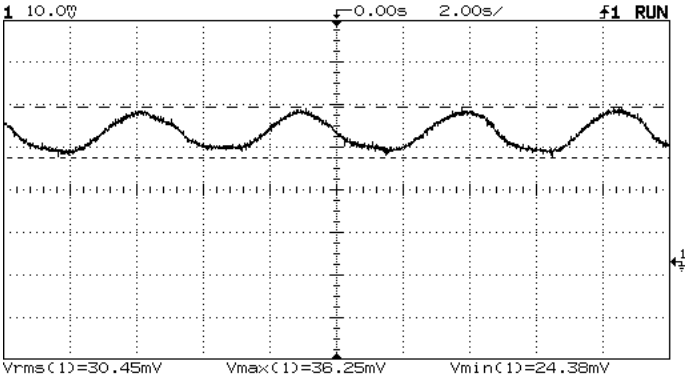


Figure 34. Voltage vs. time trace captured for 20 seconds with thermistor at nasal leak port and subject breathing into mask without CPAP. Voltage is indicated at 10 mV per division, time at 2 sec/division. Output voltage ranged from 24.38 mV to 36.25 mV.

The peak to peak variation observed when the thermistor is positioned outside the nasal leak ports is significantly smaller than that observed when measurements are made at the mouth port. This may be due to the fact that the mouth ports are located directly in front of the user's mouth in the path of the exhaled air. Exhaled air must travel upwards from the mouth to the bridge of the nose in order to reach the nasal leak ports and may cool along the way, especially if it mixes with fresh air delivered by the CPAP machine. For this reason, the decision was made to proceed with the thermistor located at the mouth port. Additionally, it was assumed that positioning the thermistor at the mouth port would allow for a more immediate response to

changes in breathing since the exhaled air travels a shorter distance to the thermistor at this location.

Finally, the response of the thermistor was tested while the CPAP machine was on and therefore forcing air into the ventilation circuit. A voltage trace was captured with the thermistor located at the mouth port (Figure 35). Both the maximum and minimum voltage values were decreased by the addition of CPAP, likely due to the cooling effect of the room air flowing past the thermistor. Although the entire waveform was shifted and the peak to peak amplitude decreased slightly, the overall response of the thermistor to the subject's breathing was unchanged. The switching of the voltage trace from a positive to negative slope still corresponded exactly to the transition from exhalation to inhalation. Likewise, the initial rise in baseline temperature stabilized after approximately two minutes.

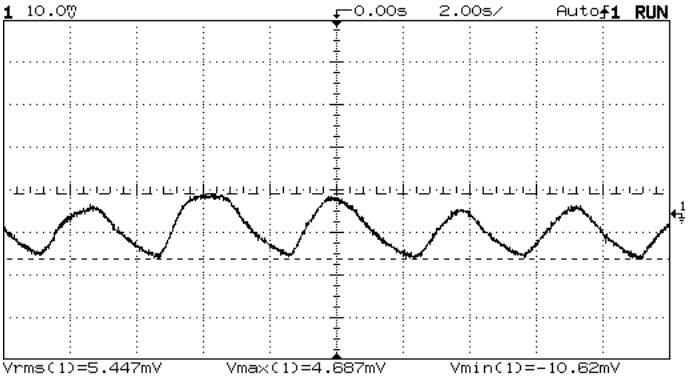


Figure 35. Voltage vs. time trace captured for 20 seconds with thermistor at mouth port and subject breathing into mask during delivery of continuous positive airway pressure (CPAP). Voltage is indicated at 10 mV per division, time at 2 sec/division. Output voltage ranged from -10.62 mV to 4.687 mV.

5.2.5 Signal Processing

In order to deliver the maximum possible amount of drug to the lungs, the inhaler should be actuated at the start of inhalation. As discussed in the testing section, the beginning of each inhalation corresponds to a local maximum on the voltage output from the thermistor, but the value of this local maximum varies from breath to breath and between different subjects. Using a comparator to trigger actuation of the inhaler was previously considered, assuming that a particular output voltage from the thermistor would be seen at the beginning of each inhalation. However, due to the variability in voltage output, it was determined that a circuit involving a set threshold would not cause actuation at the same point in the breathing cycle for all individuals and all breaths. This led to the conclusion that some signal processing needs to be involved in determining the appropriate time to actuate the inhaler.

The rotating cam mechanism responsible for depressing the inhaler also contributes to the idea that signal processing is a necessary step in timing drug delivery with inhalation. Due to the design of this system, the motor driving the cam needs to rotate 180˚ from its resting position before the inhaler is fully depressed and the drug is released (Figure 36). Approximately 0.533 seconds elapse between the time that the motor receives power from the battery and the time of actuation. Due to this lag time, the idea that detection of a relative voltage maximum could immediately trigger

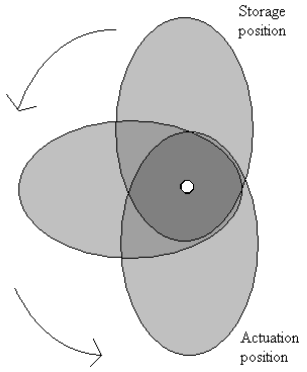


Figure 36. Illustration of actuation cam rotation responsible for time delay between powering of motor and actuation of inhaler.

powering of the motor was disregarded. Instead, it was determined that the signal processing program should calculate the period of the breathing pattern so that time, rather than voltage, is the variable that determines when the motor receives power.

LabVIEW was chosen as the programming language for accomplishing the necessary data acquisition and signal processing. This decision was made based on the functionality of the program and the availability of National Instruments equipment belonging to the UW-Madison Biomedical Engineering department. An algorithm for controlling both of the cam motors was developed and partially implemented. However, the implementation is not completely finished, so the full algorithm is explained below.

The LabVIEW program shall begin running at the start of each evening. The program periodically checks for the current time stamp, and at 4:00 am it turns on the agitation motor for the necessary duration. After the agitation motor is turned off, the difference amplifier circuit containing the thermistors shall receive power. The output from the difference amplifier is recorded by the LabVIEW program for analysis.

Initially, the voltage output is passed through a low pass filter to remove noise from the signal. The signal processing portion of the program utilizes peak detection in order to determine the time at which three consecutive voltage maximums occur. The elapsed time between peaks is stored as the period, and the average period is calculated. Using real-time data processing, a voltage maximum is detected and the time of detection is saved. The actuation cam receives power and begins to rotate t = (period – lag time) seconds after the voltage maximum is detected. This ensures that the cam rotates 180˚ and actuates the inhaler at the next voltage maximum, corresponding to the onset of inhalation. The actuation motor receives power for 0.533 seconds, during which one full rotation is completed and the cam is returned to its storage position (Figure 36).

The proposed algorithm assumes that the individual breathing into the CPAP mask produces breaths which are large and frequent enough to cause periodic fluctuation of the voltage output from the thermistor circuit. Testing conducted on healthy subjects clearly demonstrated such oscillations in the signal. Individuals with obstructive sleep apnea are unable to breathe for intervals during sleep and would therefore fail to produce a clear signal during an apneic episode. However, the addition of CPAP maintains an open airway and removes the apneas that would interfere with the temperature sensing algorithm.

In order for the LabVIEW program to turn the cam motors on and off, relays or transistors will be used (Figure 37). A relay is an electronic switch that utilizes a magnetic field to change the location of the switch contact (Figure 38). The magnetic field is produced by current flowing through a coil within the relay. For the purposes of this project, the switch would typically be in contact with the Normally Closed (NC) connection when the relay coil is off.

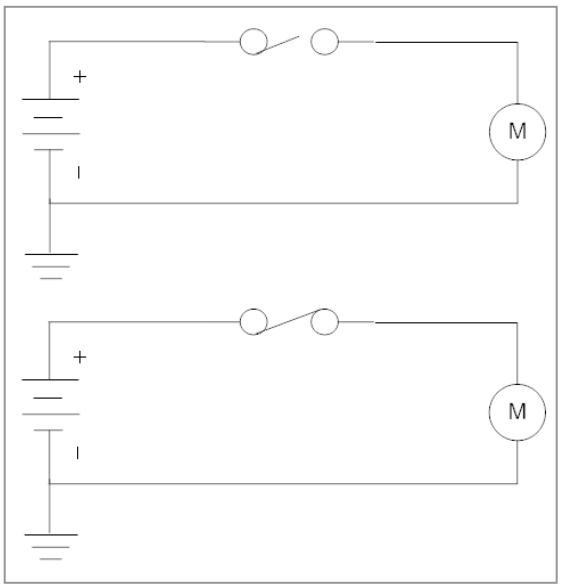


Figure 37. Theoretical circuit diagram illustrating the effect of using a relay or transistor in series with a voltage source and motor, creating either an open or closed circuit depending on input delivered to relay/transistor circuit element.

When the program signals that the relay coil should receive current, the coil is turned on and the switch contacts the Normally Open (NO) connection. The Common (COM) is the moving part of the switch which is always in contact with the remainder of the circuit. A transistor is another circuit element that acts as an electronically controlled switch (Figure 39). For this project, an NPN transistor switch would be used to switch on the load when the chip output is high (Hewes 2007).

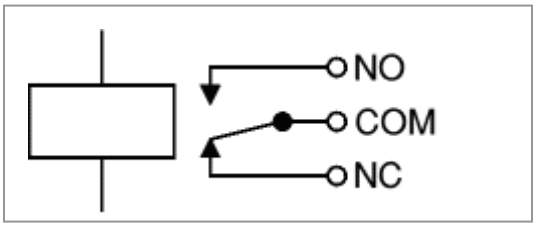


Figure 38. Circuit symbol for a relay showing Normally Open (NO), Common (COM), and Normally Closed (NC) positions. kpsec.freeuk.com

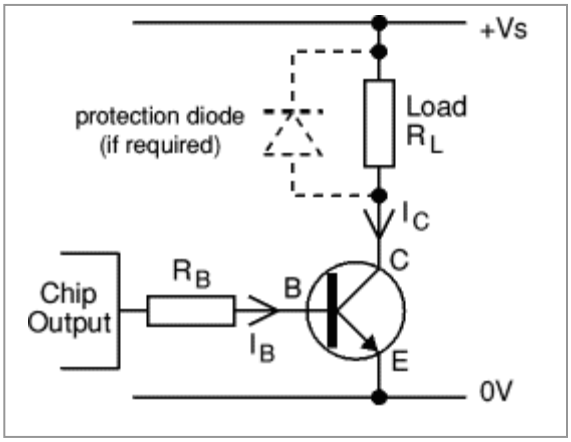


Figure 39. NPN transistor switch (kpsec.freeuk.com).

6. Ethical Issues

There is currently no method available for treating asthma and sleep apnea concurrently, and as biomedical engineers, it is our duty to design a device to improve the quality of life of individuals with these diseases. In designing such a device, a number of ethical issues must be considered, particularly those involving patient comfort and safety. Since the device will be used during sleep, the noise of the motors and the vibrations caused by agitation and actuation should be low enough so as to not interfere with the patient's sleeping patterns. Bulk near the user's face may cause a claustrophobic reaction and should therefore be minimized. Maximizing the comfort of the device will increase the odds that patients who benefit from the device will comply with the prescribed use.

Safety is another important issue to consider during the delivery of medications. The use of a nasal CPAP mask was initially considered because it is preferred by most patients; however, inhaling the medication through the nose may cause burning due to the differences in pH of the medication and the nasal mucosal membranes. To avoid inflicting pain on the patient, a full facemask was selected to facilitate oral drug delivery. Additionally, the physical components of the device, especially the moving parts, must not endanger the patient during sleep. To reduce the risk of injury, the motors and cams should be placed in a self-contained housing. Also, the signal processing algorithm used to trigger drug delivery should be validated to ensure that the intended number of doses is delivered to the patient. Under or overdosing may deprive the patient of necessary therapy, or conversely, endanger the patient due abnormally high levels of drug.

The device should allow for the widest possible range of users, including those of varying financial status, physical abilities and mental capacities. For these reasons, the device should not be designed specifically for use with one type of drug. New drug formulas are continually being introduced to the market with varying levels of effectiveness and affordability. Therefore, the device should fit the standard MDI canister in order to allow for use with multiple drug formulas. Also, individuals with physical limitations, such as reduced dexterity, should be able to perform the necessary maintenance activities on the device. Similarly, a counting mechanism should be implemented to alert the patient when the drug canister requires replacement. If the drug canister

were to be empty without the patient's knowledge, the patient would not receive the prescribed therapeutic treatment. This concern is increased with patients suffering from memory deficiency.

7. Future Development

A considerable amount of work remains to be done in order to complete this design project. First, the mechanical device needs to be miniaturized for incorporation into the CPAP ventilation circuit close to the face mask. This will likely be done through a "helmet" onto which the device is attached or a platform integrated onto the bed near the pillow. An oral pressure appliance (OPAP) is a mouthpiece that will also be considered for use with the device in order to direct the drug into the mouth and eliminate the possibility of drug loss in the nose (Figure 40). Although not as readily used as the nasal and full face CPAP masks, such mouthpieces are currently in use with positive pressure systems. Testing still needs to be performed to determine if the canister can provide an accurate dose of the drug when displaced from the vertical position. Additionally, testing will be done to determine the effects of the delay between agitation of the MDI and the delivery of the drug. It may be possible for the patient to shake the canister prior to going to sleep and still receive an accurate dose of the drug, in which case the agitation motor is unnecessary.

Figure 40. Oral pressure appliance (OPAP) used to direct airflow and drug into mouth (apneadocs.com).

The new mechanical device components must allow for a reduction in the noise levels during operation. In addition, the motors responsible for cam rotation currently drain the batteries relatively fast. An extended battery life or modifications to allow operation using a common wall outlet would reduce frequency at which the device must be serviced. Ideally, a stepper motor would be used to control the actuation cam to ensure that exactly one rotation is completed each time the motor is powered. The actuation cam would therefore return to the same starting position after each use, eliminating the drift in starting position that may be seen when timing alone is used to stop the cam's rotation. A strap must be added around the base of the device to prevent the in-line actuator from being ejected from its position each time the cams apply force to the canister. Finally, an enclosure should be constructed surrounding the mechanical device to prevent injury from moving parts, reduce noise levels, and decrease possible damage resulting from patient interaction.

The circuitry of the device is still in the early stages of development. The peak detection algorithm must be fully implemented and tested in order to accurately calculate the period of the patient's breathing and trigger cam rotation at the appropriate time. Determining the lag time of the actuation motor is crucial to timely release of the drug from the canister. Furthermore, the program must be able to turn on the motors through the use of electrical switches such as relays or transistors. In addition, the thermistor on the patient's CPAP mask needs to be secured in place using a surface mount, perhaps involving an adhesive similar to that used on electrodes. Once the algorithm is implemented and tested with the circuit, the programming should be written on a microcontroller and the circuit printed. Miniaturization of the electronics and mechanics of this project will allow for final incorporation into the ventilation circuit near the CPAP mask. The completion of this device will ultimately lead to human testing to determine the therapeutic effects of delivering inhaled steroids using CPAP.

References

American Board of Family Practice. "Sleep Apnea: From the Nose to the Heart." *Journal of the American Board of Family Practice*, 15.2 (2002): 128-141.

"Asthma." National Heart Lung and Blood Institute. 2006. 9 Dec 2007. <http://www.nhlbi.nih.gov/health/dci/Diseases/Asthma/Asthma_WhatIs.html>

Dhand R. "Basic Techniques for Aerosol Delivery During Mechanical Ventilation." *Respiratory Care*, 49.6 (2004): 611-622.

Dhand R., "Inhalation therapy in invasive and noninvasive mechanical ventilation." *Current Opinion in Critical Care*, 13 (2007): 27-38.

"Encapsulated RTD Sensors." Omega Engineering, Inc. 2007. 5 Oct 2007 < http://www.omega.com/ppt/pptsc.asp?ref=RTD-809&Nav=temc12>

Fauroux B, Itti E, Pigeot J et al. "Optimization of Aerosol Deposition by Pressure Support in Children with Cystic Fibrosis." *American Journal of Respiratory and Critical Care Medicine*, 162 (2000): 2265-2271.

Hewes, John. Relays. The Electronics Club. 2007. 1 Dec 2007. <http://www.kpsec.freeuk.com/index.htm>

Lin HC, Wang CH, Yang CT et al. "Effect of nasal CPAP on methacholine-induced bronchoconstriction." *Respiratory Medicine*, 89 (1995): 121-128.

Macon County North Carolina EMS. "Emergency Medical Services – CPAP Use and Operation." 2002. 16 Oct 2007 <http://www.maconnc.org/ems/CPAP.html>

"NTSD1 Series – NTC Thermistors for Temperature Sensing." Digi-Key Corporation. 2007. 31 Oct 2007. <http://dkc3.digikey.com/PDF/T073/P1792.pdf>

Paredi P, Kharitonov SA, Barnes PJ. "Faster Rise of Exhaled Breath Temperature in Asthma." *American Journal of Respiratory and Critical Care*, 165 (2002): 181-184.

Parkes SN, Bersten AD. "Aerosol kinetics and bronchodilator efficacy during continuous positive airway pressure delivered by face mask." *Thorax*, 52 (1997): 171-175.

Product Support (Respironics©). Personal communication. 31 Oct 2007.

Quinn K, Lam Y, Vanderpool R. "Metered Dose Inhaler Vibrational Device." Madison, WI: University of Wisconsin – Madison, 2004.

Reychler G, Leal T, Roeseler J, Thys F, Delvau N, Liistro G. "Effect of continuous positive airway pressure combined to nebulization on lung deposition measured by urinary excretion of amikacin." *Respiratory Medicine*, 101 (2007): 2051-2055.

Shneerson JM, "Handbook of Sleep Medicine" Blackwell Science Inc., Oxford (2000).

"Sleep Apnea Information." American Sleep Apnea Association. 08 Oct 2007 <http://www.sleepapnea.org/info/index.html>

Teodorescu, Mihai. Personal Interview. 13 Sept 2007.

"Thermistor." 2007. Wikipedia: The Free Encyclopedia. 31 Oct 2007. <http://en.wikipedia.org/wiki/Thermistor>

"The CPAP Basics." CPAP.com. 21 Sept 2007 <http://www.cpap.com/cpap-faq/CPAP-and-Sleep-Apnea-Basics.html#4>

Webster, John. "Medical Instrumentation: Application and Design." New York: John Wiley & Sons, Inc., 1999.

Wilder, N. "Overnight Sleep Study." 2007. American Academy of Sleep Medicine. 1 Dec 2007 < http://www.sleepeducation.com/Topic.aspx?id=12>

Wishart DS et al., "DrugBank: a comprehensive resource for in silico drug discovery and exploration." *Nucleic Acids Research,* (2006) 1;34

See: "Salmeterol." http://redpoll.pharmacy.ualberta.ca/drugbank/cgi-bin/getCard.cgi?CARD=APRD00277.txt
"Fluticasone Propionate." http://redpoll.pharmacy.ualberta.ca/drugbank/cgi-bin/getCard.cgi?CARD=APRD00065.txt

Yim S, Fredberg JJ, Malhotra A. "Continuous positive airway pressure for asthma: Not a big stretch?" *European Respiratory Journal,* (2007) 29.2: 226-8.

Zhou R, Vaihinger S, Geckeler KE and Göpel W., "Reliable CO_2 Sensors Based with Silicon-based Polymers on Quartz Microbalance Transducers," *Sensors and Actuators B* (1993): 18-19, (1994): 415-420.

Resistance for thermistors under different conditions:

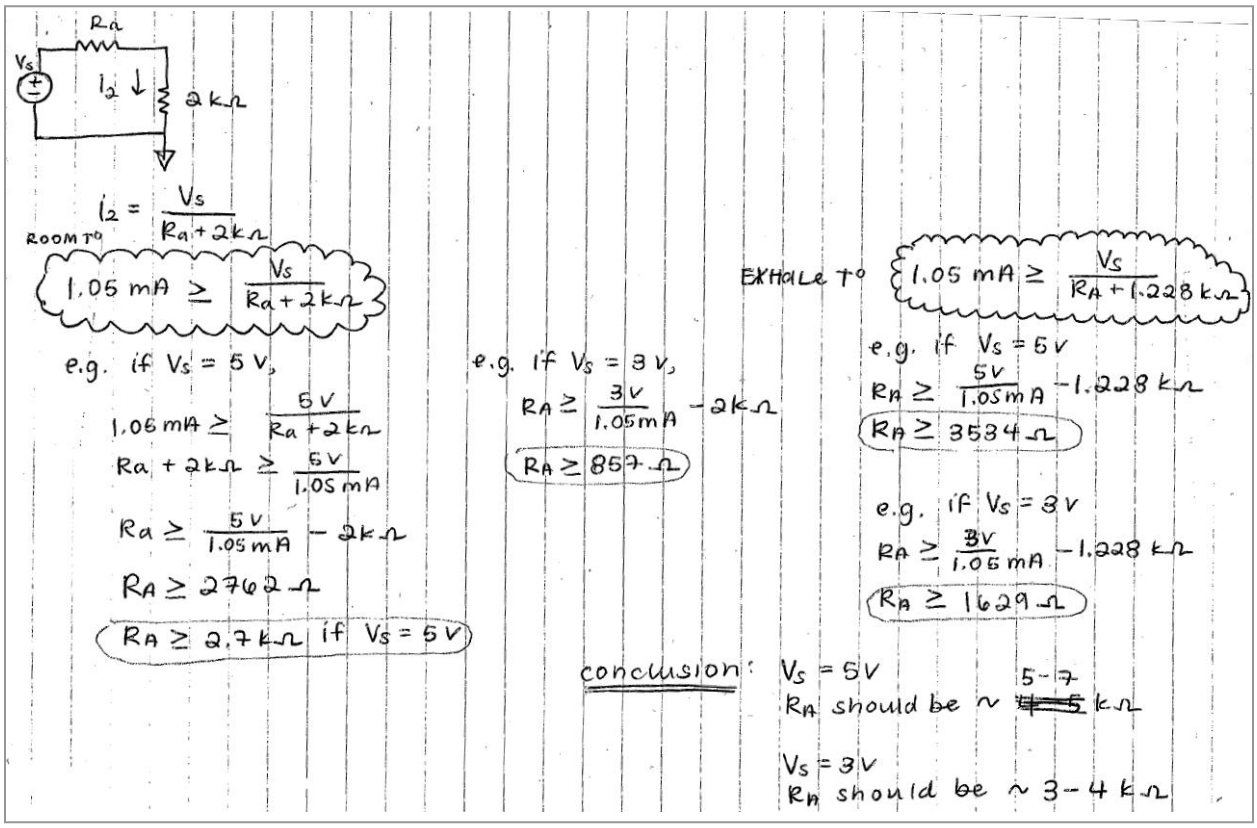
R_{therm} @ room T° = 2000 Ω (indicated by manufacturer) (Digi-Key Corp. 2007)

Using the B parameter equation (Wikipedia 2007):

$$R = R_0 e^{B(\frac{1}{T}-\frac{1}{T_0})}$$

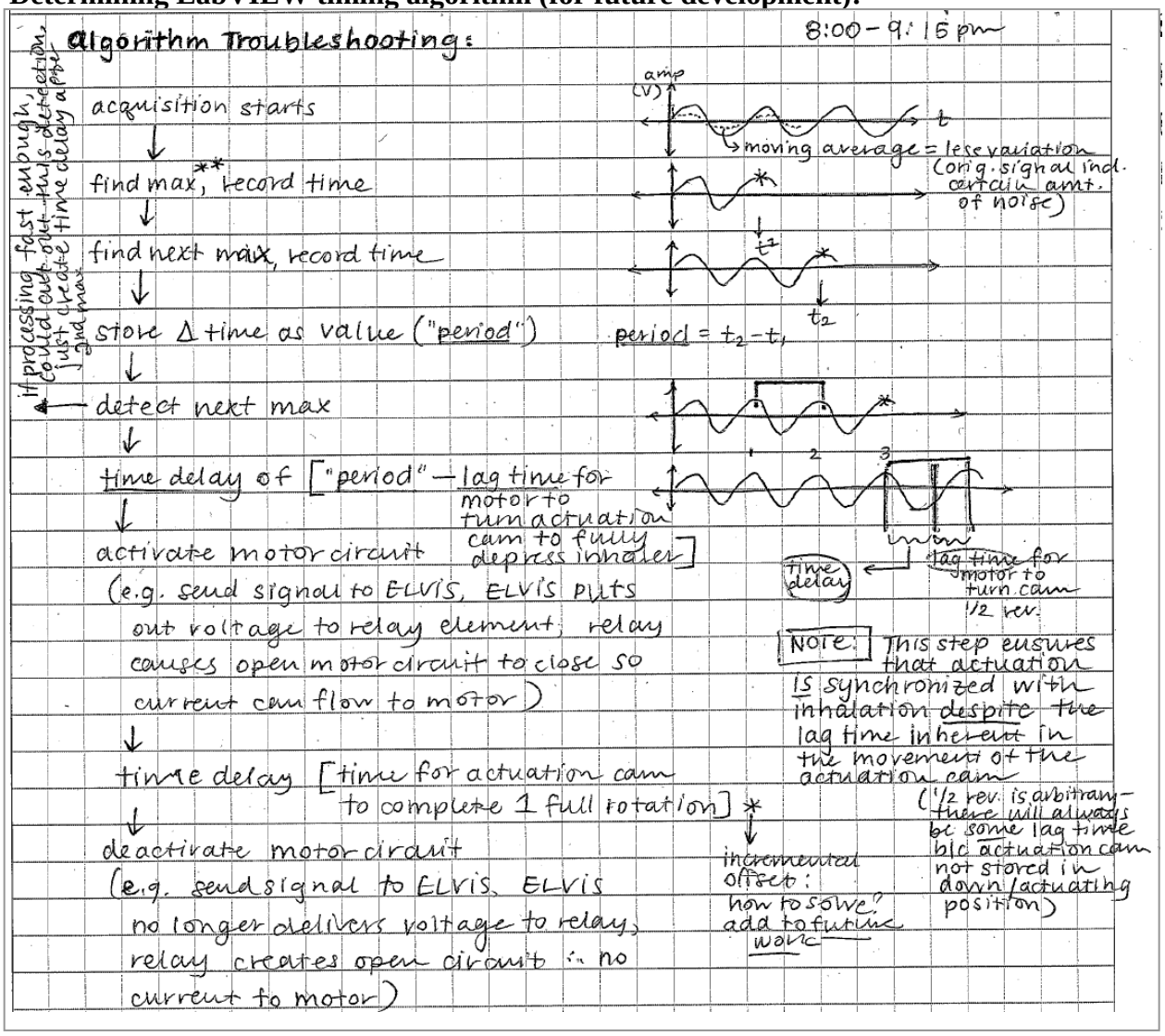
R_{therm} @ 308.9 K = $2000e^{3500(\frac{1}{308.9}-\frac{1}{296.15})} = 1228\Omega$

Calculating minimum R_B (secondary resistor) values for 1st stage:



Source: BME Design notebook, p. 43 (Lorenz 2007)

Determining LabVIEW timing algorithm (for future development):



Source: BME Design notebook, p. 50 (Lorenz 2007)

DELIVERY OF INHALED DRUGS THROUGH CPAP

Product Design Specifications

Team Members:
Sara Karle – Team Leader
Michele Lorenz - BSAC
Emily Maslonkowski – BWIG
Ashley Matsick - Communicator

Advisor: *Professor Mitch Tyler*
Department of Biomedical Engineering, UW-Madison
Orthopedics and Rehabilitation, UW-Madison

Client: *Dr. Mihai Teodorescu*
Assistant Professor, Department of Medicine - Geriatrics and Sleep Medicine
University of Wisconsin School of Medicine & Public Health

December 10, 2007

FUNCTION:
The purpose of this project is to create a device for in-home use to provide pulsed delivery of inhaled aerosol medication, achieved by automated shaking and timed actuation, in line with commercial CPAP machines using the circuit (tubing) and flow generated by the CPAP.

CLIENT REQUIREMENTS:
- The device will only be used on adults
- Due to the possible complications of inhaling oral steroids through the nose, a full face mask will be integrated into the design to allow for oral inhalation of the medication

DESIGN REQUIREMENTS:

1) Physical and Operational Characteristics

a) *Performance requirements*:
- Used by one patient every night during sleep
- Each use will be administered at approximately 4 am and will deliver one pulse of the drug, unless otherwise specified by the patient's physician
- Delivery of medication should be coordinated with inhalation to provide maximal delivery to lungs
- The inhaler must sit in an upright position when actuated unless testing suggests that other conditions may be acceptable
- A countdown mechanism should indicate doses remaining or alert user when replacement of drug canister is needed
- Current drugs that will be delivered are orally inhaled aerosols intended for use as long-acting medications
- Device should allow for use of various aerosolized drugs and respective canisters
- Patients with limited dexterity should easily be able to disassemble any parts involved in replacement of drug canisters and be able to interact with the feedback

(counting) mechanism of the device once a stand-alone unit is designed and produced

b) *Safety*:
- Must meet FDA requirements relating to drug administration, drug/material interactions, dosage accuracy, and mechanical ventilation
- Drug should be delivered through mouth to avoid damage to and discomfort in nasal mucosal membranes
- Cannot compromise enclosed nature of ventilation circuit - connections must pass pull test with protocol to be determined after further prototype development
- Controls for setting dosage and time of delivery must be programmable by physician but unalterable by patient
- Edges/corners must be rounded to prevent patient injury during movement in sleep
- Changes in dosing through integration with CPAP to be determined in order to prevent over- or under dosing of a patient
- If device is placed in close proximity to face of patient, miniaturization of product required to reduce claustrophobic sensations experienced by user

c) *Accuracy and Reliability*:
- Drug delivery must occur during inspiration only
- Deviation from set internal pressure of CPAP machine caused by activation of device cannot be greater than ±1 cm H_20
- Power sources used to run device must ensure proper working conditions each night
- Indicator stating doses remaining will allow user to consistently receive required medication
- Circuitry developed must be flexible enough to account for variations among patient expiration temperatures and thus signal amplitudes
- Actuation of drug canister must be completed by mechanism that consistently returns to proper starting position
- Medication must be agitated with an energy input equal to that of a manual shake for 5 seconds in order to achieve suspension level of mixture equal to that of what is produced by following manufacturers' instructions
- Incorporate in-line actuator to produce same results as depressing inhaler in mouthpiece device provided with the original inhaler canister

d) *Life in Service*:
- One year minimum

e) *Operating Environment*:
- Will be used in the home; not exposed to external environment
- Used by one patient for life of device
- Dosing may change during lifetime, e.g. 2 actuations vs. 1 actuation
- CPAP masks involved will allow for mouth delivery of aerosolized drug
- Sleeping environment (uncontrolled movement of patient, passive interaction of patient with integrated system while asleep)

f) *Ergonomics*:
- Drug cartridge replacement should be easily accomplished by patients with minimal hand dexterity.

- Total device should not interfere with patient's sleeping conditions and comfort should not be reduced further than what is comparable to use of CPAP

g) *Size*:
   - Tubing and any connections must be compatible with patient circuit
   - Portion of device that actuates drug release should add no more than 3 cm to each dimension of canister (goal of future development)
   - Holding chamber, if used, should not add excessive bulk to ventilator circuit.
   - Device must be placed in area near patient's face to allow for optimal placement of drug canister; this cannot, however, interfere with patient comfort, especially in terms of sleeping and claustrophobic sensations
   - Circuitry must be incorporated into a microprocessor and printed circuit to further reduce added dimension to current system

h) *Weight*:
   - Must be lightweight to avoid deformation of original CPAP tubing leading to disruptions in ventilation
   - If system is incorporated near the head region of the patient, it cannot be bulky or add excessive weight that may compromise the efficacy of CPAP or drug delivery, and also not interfere with user comfort

i) *Materials*:
   - Cannot have negative interactions with drugs used, may have to be disposable or easily cleaned by individual patients, hypoallergenic

j) *Aesthetics, Appearance, and Finish*:
   - Finish should be simple and mimic commercial CPAP machine
   - System must be self-contained

2) Production Characteristics

a) *Quantity*:
   - Ultimately one device per patient will be needed
   - One prototype for developmental purposes; more devices may be needed if human studies are performed

b) *Target Product Cost*:
   - $1000 maximum for initial prototype

3) Miscellaneous

a) *Standards and Specifications*:
   - Bioengineering unit at University of Wisconsin must test and approve device prior to use in client's research
   - Final device must meet FDA regulations for medical devices
   - Any testing involving human subjects to determine proper dosing, efficacy, etc. must have protocol approved by IRB

b) *Customer*:
   - Use of humidifier in ventilation circuit preferred by half of client's patients to prevent drying of mucosal membranes, although will not necessarily be taken into account during initial design of integrated device
   - Full face mask must be used to ensure inhalation through the mouth
   - OPAP mask could be option for this system which would also direct flow of air and drug directly to mouth

c) *Patient-related Concerns*:
   - Minimal bulk near face will prevent patient claustrophobia and discomfort.
   - Portion of device in line with ventilation circuit should be easily cleaned to remove drug residue.
   - Size, weight, and noise of device should not disrupt patient sleep

d) *Competition*:
   - Research currently performed on pediatric patients to develop similar system
   - Current research regarding integration of aerosol delivery with CPAP or other ventilation systems focuses on nebulizer deliver system rather than the use of MDIs, and most studies are concerned with invasive ventilation (intubation)
   - No commercial or research product has been found that is applicable for adults
   - Stand-alone CPAP being researched to determine affects on sleep apnea patients with concurrent asthma, but currently no published studies found on effects of CPAP with integrated inhalers

APPENDIX C: **Experimental Protocol #1**
Effect of tubing length between CPAP and patient mask on amount of aerosolized medication delivered from metered-dose inhalers (MDIs) shaken manually for 5 seconds

Rationale
Metered-dose inhalers allow for the administration of aerosol medication by pressurizing the active ingredient(s) and a propellant. Manufacturers of MDIs offer several preparatory steps to follow before actuating the product for use as a medical treatment, which include approximately 5 seconds of manual shaking as well as priming (actuating the inhaler several times before use), especially after periods of latency (GlaxoSmithKline 2007). The active ingredients used in the Advair® MDIs prescribed by the client of this project are salmeterol xinafoate and fluticasone propionate. The inhalation aerosol solutions also contain HFA-134a (1,1,1,2-tetrafluoroethane), a hydrofluoroalkane used to help propel the drug upon actuation. Proper mixing of the aforementioned substances prior to actuating the MDI appears to be crucial to the delivery of active ingredient doses that match the dosage claimed by the manufacturer.

Following sufficient mixing of the canister contents, delivery of the drug will be contained within the CPAP tubing in the integrated system as it travels from the site of actuation to the mask used by the patient. An important consideration in this integration with portable CPAP machines is the effect of tubing length on drug delivery to the mask. CPAP tubing is sold in lengths ranging from 1-10" in 1" increments to accommodate different usage conditions. Previous studies involving nebulizer integration with mechanical ventilation strategies have demonstrated that increasing the distance between the patient and the nebulizer improves delivery as aerosol particles decrease in size due to evaporation of the suspension over time. However, applications involving positive pressure therapy show that drug delivery increases if the aerosol generator is closer to the patient (Dhand 2004).

In order to clarify how a CPAP system will affect aerosolized drug delivery to the mask, quantification of the amount of drug reaching the end of a length of tubing as a percentage of the initial dose delivered from the MDI (tubing length of zero) was attempted. Actuation of an Advair® HFA (45/21) MDI following 5 seconds of manual shaking was performed and the relative mass of drug expelled was analyzed by UV spectrophotometry. An average "native" dose delivered directly from the MDI valve was compared to doses delivered 1-6" from the collection point at 1" increments.

Methods and Materials
Equipment
- One (1) Advair® MDI (45 μg fluticasone propionate/21 μg salmeterol xinafoate)
- Modified CPAP tubing (mfg. by Taga Medical Technologies)
- REMStar® Pro 2 CPAP (mfg. by Respironics)
- 10 mL glass beaker
- Plastic funnel
- UV spectrophotometer (Spectronic 610) & cuvettes
- Solvent (methanol)
- Kimwipes

Experimental conditions & controls
One Advair® HFA (45 μg fluticasone propionate/21 μg salmeterol) MDI was used (provided by Dr. Mihaela Teodorescu) and underwent no actuation or unnecessary movement prior to testing.

Methods and Materials continued

Three actuations were performed for each experimental condition (1-6" in 1" increments) to obtain an average absorbance value representing the drug delivered per condition.

Collection of aerosol spray

To prepare the MDI for testing, the canister underwent 5 seconds of manual shaking and two priming actuations. Before each experimental actuation, the MDI was manually shaken for 5 seconds, with a delay of no more than 20 seconds between shaking and actuation. Between actuations, the MDI was stored on a surface free of unnecessary vibration.

Holes approximately 1" apart were cut in a 6" length of CPAP Tubing (mfg. by Taga Medical Technologies) large enough to accommodate the mouthpiece of the Advair® MDI. In order to evaluate spray collection at each tubing length, all holes were covered with Parafilm except for the hole at the length being tested to prevent substantial spray loss or escape of air (Figure 1).

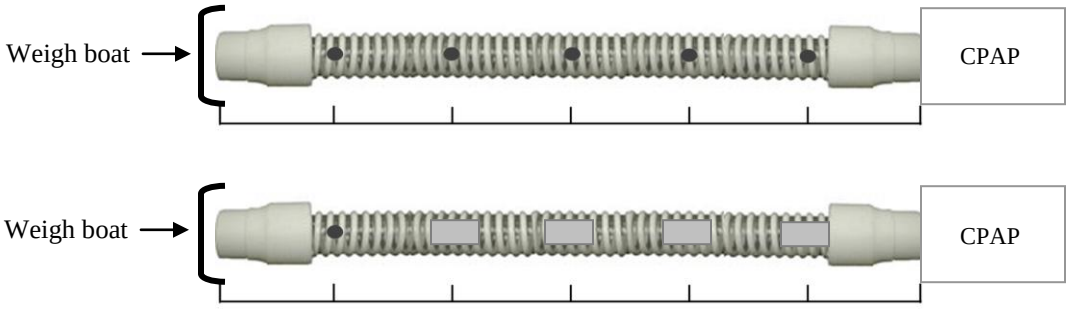


Figure 1. Illustration depicting experimental set-up of 6" CPAP tubing with holes cut at 1" intervals with CPAP at one end and collecting container at the other (top). Diagram of set-up when testing is being performed at a "tubing length" of 1" in which all other holes are covered to prevent airflow through them (bottom).

Actuation occurred after: 1) the mouthpiece of the MDI was fully inserted into the hole cut at the length being tested and 2) the CPAP air flow had been allowed to stabilize for at least 5 seconds at a rate of 8.65 cm H_2O. The collection of drug particles that traveled through the CPAP tubing was accomplished by using a small 1" x 1" weigh boat placed at the open end of the tubing. A series of methanol washes was used to clean the surface of the weigh boat, and the resulting solution was collected by a funnel into a 10 mL beaker (<10 mL of methanol used). The solution was then transferred to the glass cuvette for spectrophotometric analysis.

Analysis using UV spectrophotometry

Using a Spectronic 610 set to 228 nm (Murnane *et al.* 2006) a "blank" setting was established first by filling a cuvette with ~ 3 mL of methanol and activating the "100%T / zero A" button on the spectrophotometer. This step was performed to attempt to eliminate any effect on absorbance readings that could have been caused by impurities in the methanol.

For each sample produced by the actuation of the MDI and subsequent collection into a glass beaker, ~ 3 mL of the 10 mL solution was added to a clean cuvette. The cuvette was placed into the holding chamber and the absorbance value recorded. Every three readings, the absorbance value obtained using the "blank" cuvette filled with methanol was verified as zero. If inconsistencies occurred with this reading, the machine was re-zeroed before continuing.

Results & Discussion

No substantial difference was observed in the average absorbance values between different experimental conditions (Figure 2). Within each condition (tubing length), there was a large amount of variation between absorbance values collected, which may be attributed to several possible sources of error. Factors that may have affected the data but which were undetectable include the presence/absence of included impurities in the methanol, previous contamination of vessels/equipment used (e.g. cuvettes), and inconsistent shape of the CPAP tubing (bent/straight sections, amount/degree of bending, etc.).

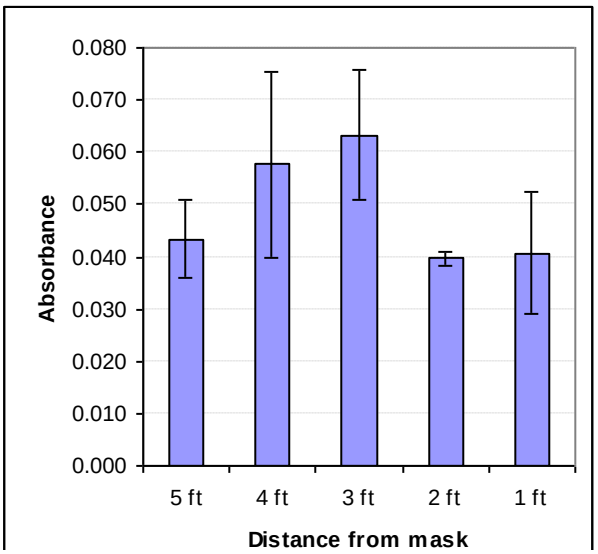


Figure 2. Average absorbance values ± 1 SE (no units) obtained by UV spectrophotometric analysis at 228 nm of solutions consisting of <5 mL of methanol and trace amounts of both salmeterol xinafoate and fluticasone propionate. SX/FP were collected in a weigh boat after actuation of an Advair® HFA 45/21 MDI at different points (1-5 ft from the weigh boat) along a CPAP tube when a REMStar Pro 2® CPAP was producing a pressure of 8.65 cm H_2O through the tubing.

When the absorbance values obtained at "0 ft" (the MDI was directly actuated into the weigh boat) were compared to those for the experimental conditions (MDI actuated along the CPAP tubing), it was clear that a substantial amount of the drug initially expelled from the inhaler was lost within the tubing (Table 1). The deposition of the drugs was observed on the inner surface of the CPAP tubing directly across from the access holes, which would explain the small absorbance values obtained when the inhaler was actuated through one of the holes in the tubing.

It is questionable whether the absorbance values measured actually correspond to the amount of drug delivered to the end of the tubing due to the tremendous variability in the absorbance values obtained and the high probability that impurities from various sources were the true source of the absorbance readings. To clarify, it can not be stated confidently that the absorbance values were due to the presence of the drug rather than random impurities from the solvent or environment. Therefore, it is suggested that the protocol should be repeated with a higher-grade solvent (spectrophotometric-grade methanol), that the tubing should be maintained in a straight conformation during testing, and that the inhaler should be integrated into the ventilation circuit using a Y-connector to minimize drug deposition on the wall of the CPAP tubing.

Table 1. Absorbance values (no units) obtained by UV spectrophotometric analysis at 228 nm of solutions consisting of <5 mL of methanol and trace amounts of both salmeterol xinafoate and fluticasone propionate. SX/FP were collected in a weigh boat after actuation of an Advair® HFA 45/21 MDI at different points (1-5 ft from the weigh boat) along a CPAP tube when a REMStar Pro 2® CPAP was producing a pressure of 8.65 cm H_2O through the tubing. Three trials were performed for each experimental condition.

	Absorbance					
Distance from open end ("mask" end)	Trial 1	Trial 2	Trial 3	Average	SD	SE
5 ft	0.033	0.039	0.058	0.043	0.013	0.008
4 ft	0.093	0.042	0.038	0.058	0.031	0.018
3 ft	0.081	0.039	0.07	0.063	0.022	0.013
2 ft	0.042	0.038	0.039	0.040	0.002	0.001
1 ft	0.019	0.059	0.044	0.041	0.020	0.012
0 ft	0.995	0.68	0.733	0.803	0.169	0.097

Appendix C References

Dhand R (MD), "Basic Techniques for Aerosol Delivery During Mechanical Ventilation." Respiratory Care, 49.6 (2004): 611-622.

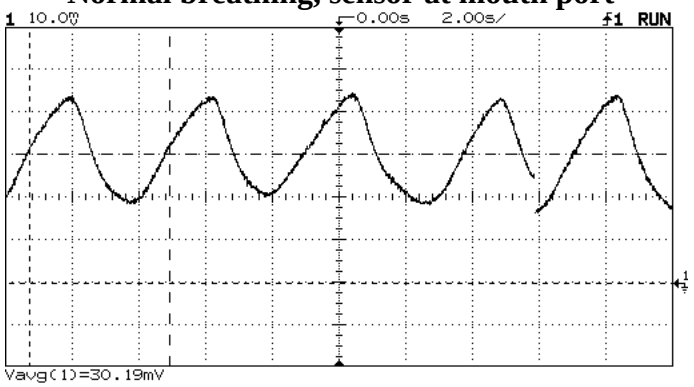
Murnane D, Martin GP, Marriott C. "Validation of a reverse-phase high performance liquid chromatographic method for concurrent assay of a weak base (salmeterol xinafoate) and a pharmacologically active steroid (fluticasone propionate)." Journal of Pharmaceutical and Biomedical Analysis, 40.5 (2006): 1149-1154.

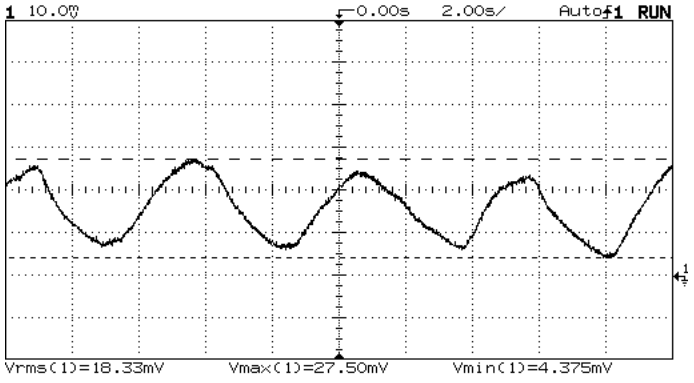
"Prescribing Information: Advair® HFA." GlaxoSmithKline. 03 Oct 2007. <http://us.gsk.com/products/assets/us_advair_hfa.pdf>

Quinn K, Lam Y, Vanderpool R. "Metered Dose Inhaler Vibrational Device." Madison, WI: University of Wisconsin – Madison, 2004.

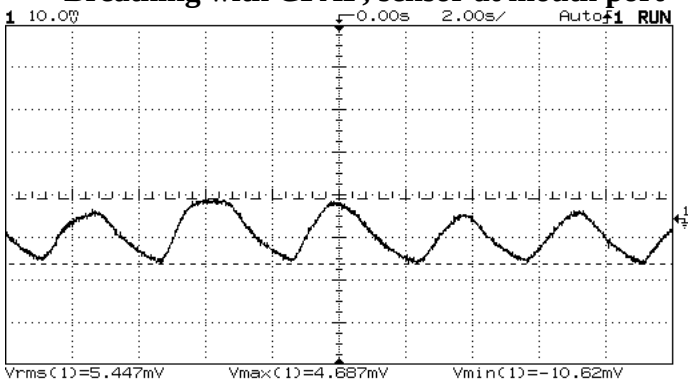
APPENDIX D: CIRCUIT OUTPUT GRAPHICS

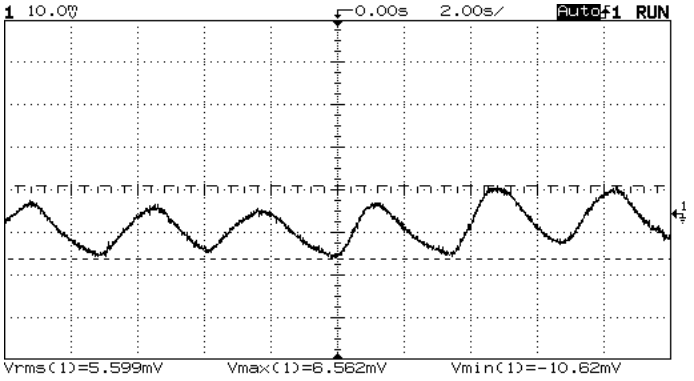
Normal breathing, sensor at mouth port



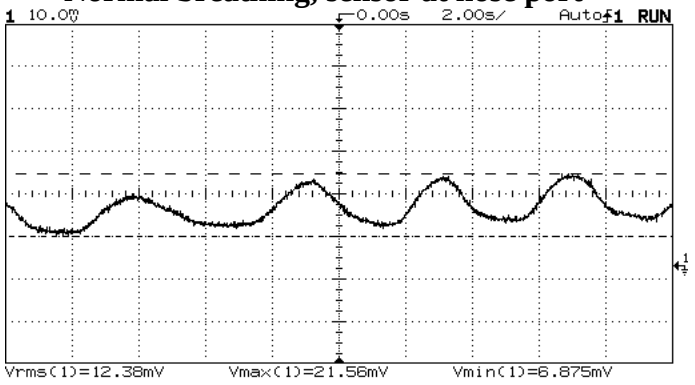


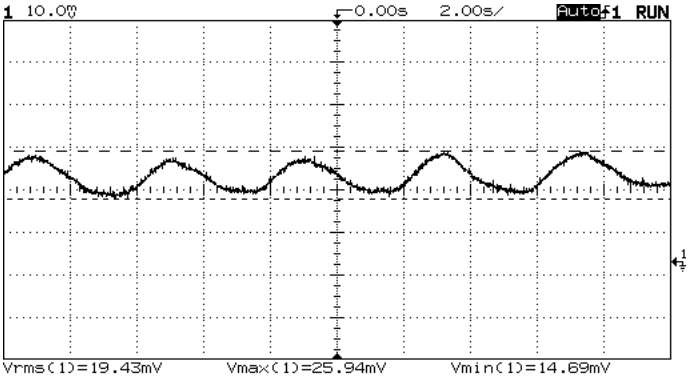
Breathing with CPAP, sensor at mouth port



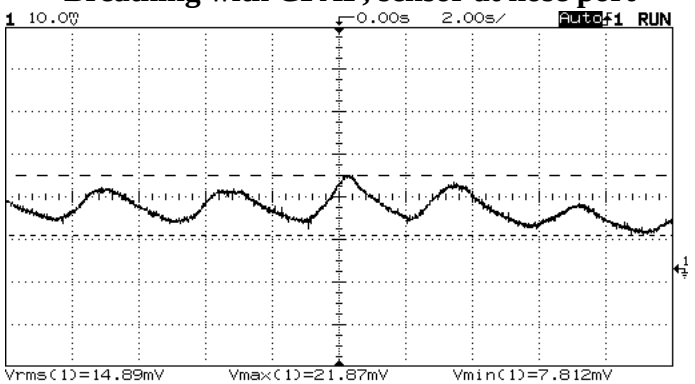


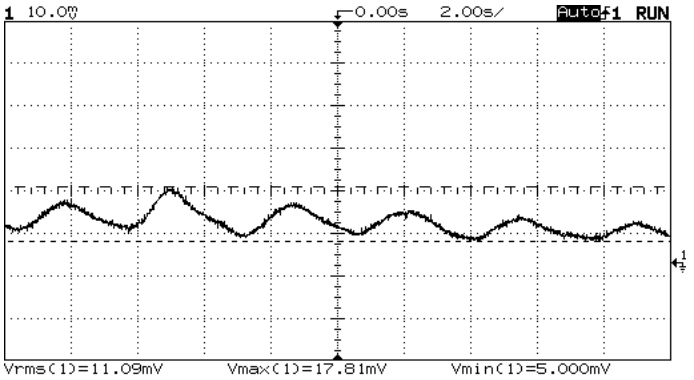
Normal breathing, sensor at nose port





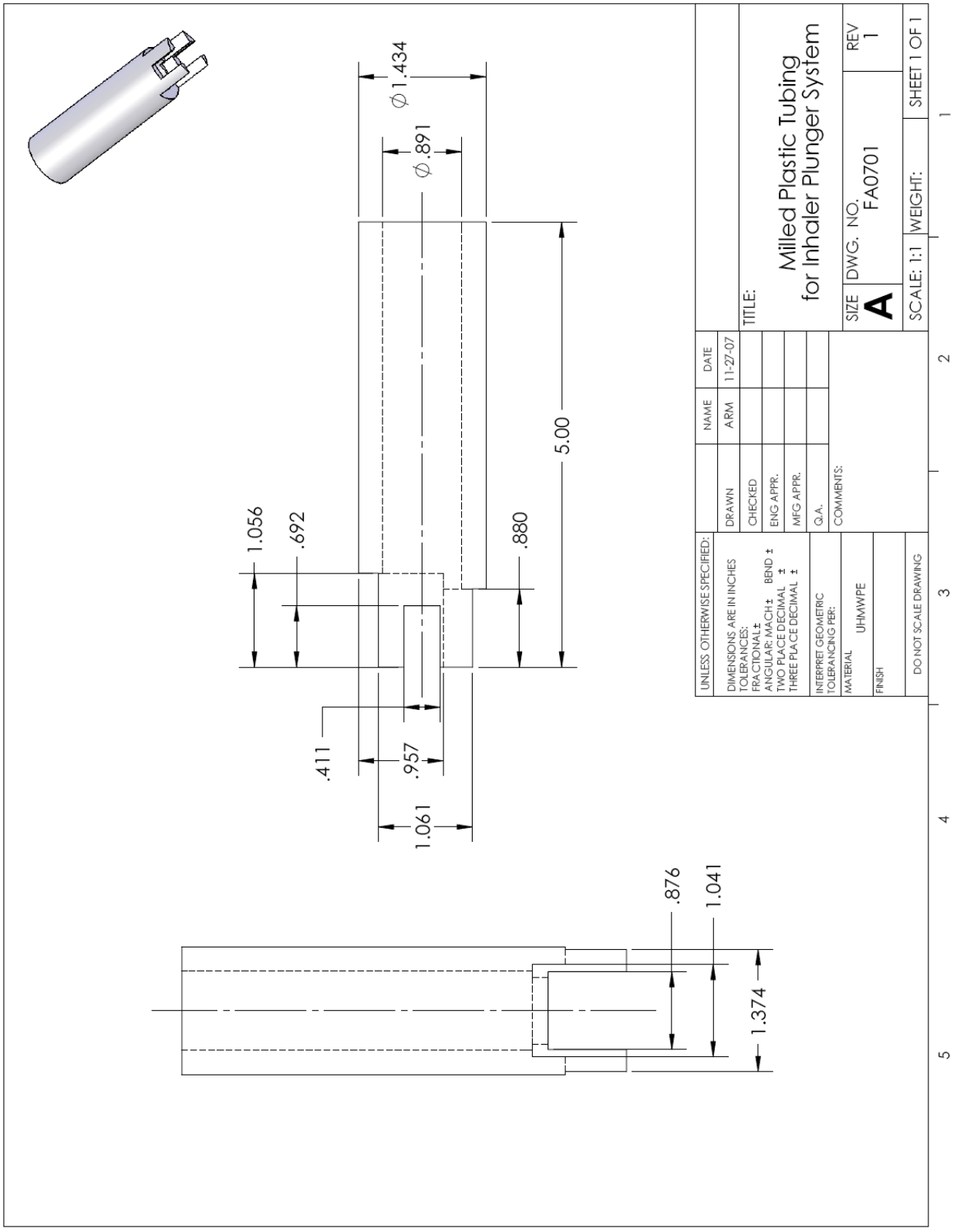
Breathing with CPAP, sensor at nose port





Note: All traces illustrate breathing of a single subject during a testing session of approximately 1 hour. Each trace shows ~20 seconds of data, with 10 mV per vertical division.

APPENDIX E: PROTOTYPE DRAWING (MILLED TUBING)



APPENDIX F: TOTAL PROJECT COST

The money spent on the project for the semester can be broken into two categories:

1) Materials needed to test and construct the prototype of the design, and
2) The anticipated cost of future construction of device units.

Total Expenditures:

Company/Store, Date of Purchase, Amount	**Item**
Tina's Homecare 10/30/07= $36.75	Tubing for drug delivery testing
Hobby Horse 11/1/07= $14.54	Original test motor and gears
McMaster-Carr 11/7/07= $37.22	1/8th thick polycarbonate sheet
Hobby Horse 11/9/07= $39.04	Motors and gear boxes
Home Depot 11/9/07= $7.41	PVC tubing and 9V batteries
Ace Hardware 11/9/07 = $18.62	Epoxy, putty knife, AA batteries, dowel and springs
McMaster-Carr 11/12/07= $15.29	UHMW polyethylene tube, polycarbonate round tube
Radioshack 11/13/07= $4.07	AA battery packs (to hold 2 AA batteries)
Ace Hardware 11/13/07= $16.07	Nuts/bolts, springs, wire and hinges
McMaster-Carr 11/15/07= $22.35	Compression springs
Hobby Horse 11/30/07= $16.84	"Viper" motor
Radioshack 12/5/07= $14.34	Backup batteries and battery packs (9V and AA)
TOTAL= $242.54	

Anticipate amount to build single unit

-$15 for polycarbonate sheet
-$40 for motors and gear boxes
-$15 for batteries
-$4 for PVC
-$3 for Epoxy
-$6 for agitation tube
-$1 for nuts/bolts

Total= $84*

*This price may decrease when buying components in bulk