

Delivery of Aerosolized Medication through Continuous Positive Airway Pressure Device

BME 402

BIOMEDICAL ENGINEERING DESIGN

Team Leader: Patrick Kurkiewicz

Team Leader: Annie Loevinger

BSAC: Joe Decker

BWIG: Ryan Kimmel

Communicator: Steve Welch

Client: Dr. Mihai Teodorescu

Advisor: Professor John Webster

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ABSTRACT

A device has been constructed for the purpose of aerosolizing albuterol with an ultrasonic piezoelectric crystal and delivering it through corrugated tubing using a continuous positive airway pressure (CPAP) machine. It has been proven that the device delivers albuterol through standard CPAP tubing (6 ft (1.8 m) length, 0.75 in (1.9 cm) inner diameter) to a CPAP mask at an efficiency of $42.5\% \pm 11\%$. A program was also constructed to control the functioning of the ultrasonic crystal and shown to be effective at responding to a patient's breathing cycle.

PROBLEM STATEMENT

The goal of this project is to develop a device and accompanying method for automated delivery of aerosolized medication, such as the bronchodilator, albuterol, within the main airflow circuit of a continuous positive airway pressure (CPAP) device, wherein the system is programmable for various dosages, start times, and durations of medication administration.

MOTIVATION

More than 12 million people in the United States are currently affected by sleep apnea (ASAA, 2008). Several forms of the disease exist. The most common form, obstructive sleep apnea, is characterized by the periodic cessation of breathing during sleep due to tracheal muscle relaxation, which causes narrowing and closing of the patient's airway. The most widely used treatment is to employ a continuous positive airway pressure (CPAP) device during sleep to open the airways.

The main goal of developing a CPAP drug delivery device is to automatically deliver aerosolized albuterol to a sleeping patient. It is hoped that the developed device will better alleviate the symptoms of sleep apnea than either the CPAP or bronchodilators alone. The drug delivery system developed in this paper uses ultrasonic nebulization to generate a medicated

aerosol which enters the CPAP airflow through an elongated reservoir designed to maximize drug uptake efficiency while still allowing the CPAP to function properly. The system is controlled via an adaptive computer interface which reads pressure data from the CPAP system and uses a predictive algorithm to optimally synchronize aerosol generation and patient breathing. Proof of concept testing was performed to verify drug delivery efficiency and justify moving to clinical trials.

BACKGROUND

CPAP devices provide therapy to a sleep apnea patient by delivering positive pressure to the patient's airway to keep it open as the tracheal muscles relax. Most CPAP designs include a pressure source, circuitry to control the pressure source, and tubing connected to a mask worn by a patient. The CPAP pressure source, connective tubing, and mask create a selectively closed circuit for airflow between the patient's airways and the CPAP device. The blower (or other pressure source) creates a positive pressure within the airway of the system. This positive pressure helps to open the patient's airway, preventing airway collapse during inhalation. When the patient begins to exhale, CPAP devices, such as the CPAP used for this study (Respironics REMstarPro M Series Model #400M), sense an increase in pressure and shut off the positive pressure source. This allows the patient to exhale effortlessly (Estes et al., 2005 and Sanders et al., 1992).

Typically, the positive pressure within the CPAP circuit is within the range of 4 to 20 cmH₂O (392 to 1960 Pa). The pressure settings of the CPAP are adjusted depending on the level of breathing assistance necessary to counteract the airway closure and constriction of the trachea in patients with sleep apnea or asthma.

Albuterol is a bronchodilator that is commonly used to treat respiratory maladies such as asthma and chronic obstructive pulmonary disease. It is produced in bulk and ionically bonded with a sulfate (SO₄) molecule. Since albuterol sulfate is a solid substance, it is either administered through a metered dose inhaler or dissolved in water and aerosolized, so that a

patient can easily inhale the aerosolized medication. Albuterol intended for atomization is manufactured by DEY, Inc. as Albuterol Sulfate Inhalation Solution (NDC 49502-697-24) (U.S. F.D.A., 2009). The albuterol sulfate solution is typically packaged in sterile, single unit-dosage vials, each containing 2.5 mg of albuterol in 3 mL of solution. The inhalation solution is colorless and includes the inactive ingredients sodium chloride, edentate disodium, sodium citrate, and hypochloric acid (to adjust the pH of the solution to the range of 3-5) in addition to the active ingredient, albuterol sulfate (the chemical structure of which is shown in Figure 1). The albuterol solution has a 0.083% potency expressed with respect to albuterol, so each milliliter of solution contains 0.83 mg of albuterol, which exists as a white powder, freely soluble in water.

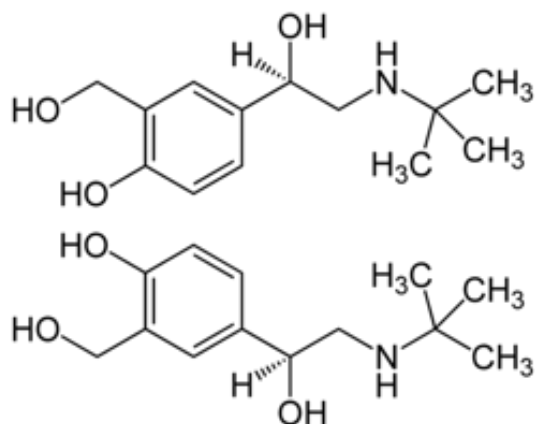


Figure 1. Chemical Structure of Albuterol. The racemic form of albuterol is used in the inhalation solution produced by DEY, Inc. The molecular weight of albuterol is 576.71 g/mol.

Since albuterol sulfate is a solid material that is dissolved within a liquid solution, a simple and effective medication delivery method is to aerosolize the liquid. Medication delivery through direct inhalation is a widely accepted administration technique. Due to the large surface area of the alveoli of the lungs and the density of the pulmonary capillaries, the lungs represent a relatively large surface area for medication to be absorbed and rapidly taken up by the bloodstream. Additionally, since bronchodilators target the beta₂-adrenergic receptors of the respiratory tract, direct medication inhalation delivers the medication directly to targeted receptors, which maximizes absorption and mitigates side effects due to unwanted medication delivery to other areas of the body (such as the beta₂-adrenergic receptors of the cardiovascular

tract). Nebulizers are commonly used for delivery of inhaled medications since they transform a liquid medication into a mist that can be comfortably and easily inhaled by a patient. The mist consists of a suspension of many miniscule liquid droplets in air and is created by the nebulizer rapidly, forcibly, and repeatedly disrupting the surface tension of the water and throwing droplets from the bulk liquid surface into the air. The two different types of nebulizers commonly used for inhalation therapy are the jet nebulizer and the ultrasonic nebulizer, each of which have different advantages and disadvantages.

Jet nebulizers use a narrow stream of pressurized air to disrupt the surface tension of the bulk liquid in order to aerosolize the liquid medication, as shown in Figure 2. The average droplet size formed by jet nebulizers is between 5 and 600 μm , depending on the nozzle (Hickey, 1996).

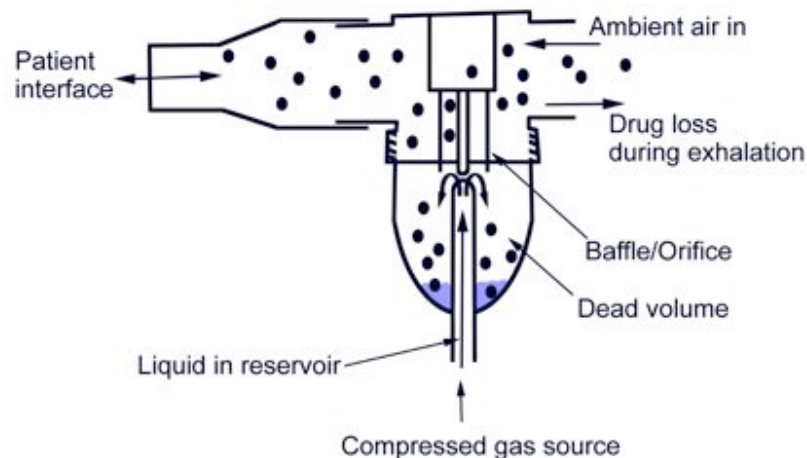


Figure 2. Diagram of a jet nebulizer (img.medscape.com).

The jet nebulizer creates a thick mist allowing the flow of the air to carry the aerosolized medication to the patient. However, the efficiency of jet nebulizers at delivering aerosolized medication to ambient has been clinically proven to be only about 39 \pm 3% (Gessler et al., 2001). Additionally, the pressured air source for the jet nebulizer produces a relatively loud noise. Another disadvantage with regard to usage with a programmable device is that the rate that the medication is aerosolized is difficult to control. Overall, the jet nebulizer is inefficient at medication delivery and is most suitable when a fast and low-cost nebulizer option is needed.

Ultrasonic nebulizers achieve a higher efficiency of drug delivery to the patient than the jet nebulizers typically achieve. As shown in Figure 3, ultrasonic nebulizers include a piezoelectric crystal component that oscillates when an electric current is applied to the material. These oscillations generate ultrasonic waves that propagate through the bulk liquid before disrupting the surface tension of the liquid and causing the liquid medication to aerosolize into droplets. The oscillation of the piezoelectric component occurs at a frequency within the range of 1.0 - 4.0 MHz.

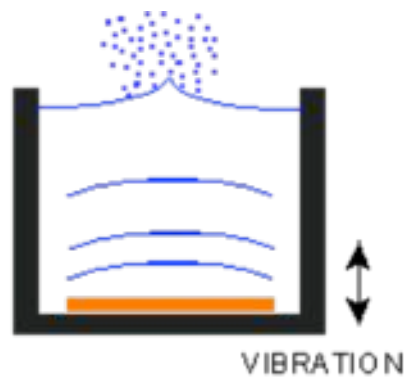


Image from www.sonozap.com/nebulizer.htm

Figure 3. Diagram of Ultrasonic Nebulizer (www.sonozap.com)

The typical droplet size formed from ultrasonic nebulizers is between 3 and 6 μm ; this size has been shown to be the more clinically effective than the larger droplets sometimes seen in jet nebulizers (Hickey, 1996). Further, the efficiency of ultrasonic nebulizers at delivering aerosolized medication to the patient's lungs has been clinically shown to be about 86 \pm 5% (Gessler et al., 2001). In addition to a significantly higher efficiency of drug delivery than a jet nebulizer, ultrasonic humidifiers are nearly silent. However, ultrasonic nebulizers are on average more expensive than jet nebulizers (ultrasonic nebulizers can be purchased starting at about \$75 and averaging around \$300, whereas jet nebulizers start at about \$40). Some models of ultrasonic nebulizers generate heat when run for an extended period of time, which could potentially alter the structure, and therefore efficacy, of the medication. Overall, the ultrasonic

nebulizer has an advantage over the jet nebulizer in that it is more efficient at delivering medication, generates smaller droplets of aerosolized medication, and is quieter during use.

DESIGN SPECIFICATIONS

The nebulizer for drug delivery with the CPAP device should be useable for the treatment of relevant diseases including sleep apnea, asthma, and chronic obstructive pulmonary disease. The new device should deliver the aerosolized medication directly within the CPAP circuit and should be compatible with any CPAP device currently on the market. Since the device is intended to be used during normal sleep, it must operate for 8 continuous hours and allow the user to sleep comfortably and safely during use. The device should be able to deliver up to 3 – 3 mL doses of medication during a single usage duration without input from the user or a health care provider. Therefore, the device must incorporate a location to store liquid medication. Since the device should be able to function without any user input for its duration of use, the device should also include a user-friendly programmable that specifies the dosage, delivery timing, and duration information. Additional information can be found regarding the desired features and functionalities of the device and be found in the Product Design Specifications document in Appendix A.

COMMERCIALLY AVAILABLE PRODUCTS

There are currently a large number of commercially available products that provide breathing assistance or inhalation therapy. CPAP machines, purchased online or from medical supply companies, include an array of competitive models, such as Respiroics REMstarPro M Series (Model #400M) pictured in Figure 4.



Figure 4. Respironics REMstarPro M Series (Model #400M) CPAP Device. (www.respironics.com)

Currently available nebulizers include a variety of jet nebulizers (such as the Lumineb II Model 5710 shown in Figure 5) and ultrasonic nebulizers (such as the Duro-Mist Ultrasonic Nebulizer shown in Figure 6). However, these are stand-alone units and cannot be used in-line with a CPAP device.



Figure 5. Lumineb II Model 5710 Nebulizer Device. A currently available jet nebulizer. (www.semedicalsupply.com)



Figure 6. Duro-Mist Ultrasonic Nebulizer Device. (ucanhealth.com)

Few devices exist that provide aerosolized medication via mechanically generated flow. The Aeroneb[®] Pro from Aerogen[™], Inc., covered by U.S. Patent No. 7,290,541 (Ivri et al., 2007), is one such device. The Aeroneb[®], pictured in Figure 7, is an in-line nebulizer designed to be used within the circuit of mechanical ventilator.



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Figure 7. Aeroneb[®] Nebulizer Device from Aerogen[™]. (aeroneb.respironics.eu)

However, the Aeroneb[®] is only intended for use with a mechanical ventilator, is not programmable or automatic, cannot accommodate multiple doses of medication, and cannot react to a patient's natural breathing. No commercially available device could be found that fulfills all of the design requirements for aerosol delivery via a CPAP device.

PREVIOUS SEMESTER DESIGN

The drug reservoir was fashioned directly onto the nebulizer board. It consists of a clear polycarbonate tube, 3.175 cm (1.25 in) in diameter and 12.7 cm (5 in) long, adhered to the nebulizer board with quick setting epoxy. To integrate this design with the main flow of the CPAP, a female threaded PVC adapter was adhered to the top of the tube with quick setting epoxy. A threaded nylon T joint (14.35 mm in diameter) was then used to connect the two systems. The nebulizer and drug reservoir can be seen in Figure 8.

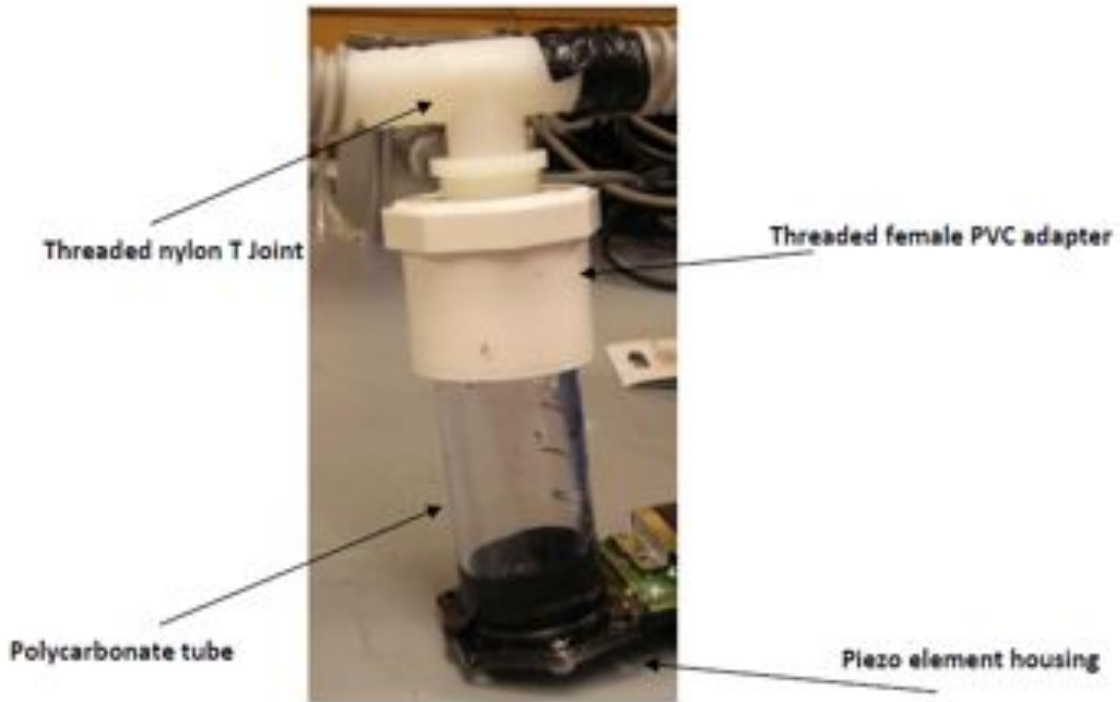


Figure 8: Previous semester reservoir design.

The design in Figure 8 was abandoned because it did not deliver aerosol effectively into the CPAP airstream. It helped demonstrate the need to have an airflow chamber within the reservoir housing, which led to the current design.

CURRENT DESIGN

A schematic of the final design can be seen in Figure 9:

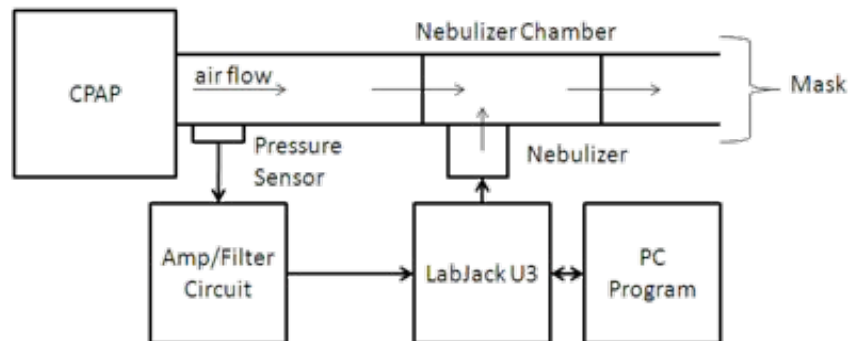


Figure 9: Final design schematic

Mechanical Design

The initial step of the design process was to select the optimal nebulization technique for the albuterol sulfate inhalation solution. The ultrasonic nebulizer was chosen over a jet nebulizer for its lower noise level and superior particle size constancy. This design incorporates the piezoelectric component of a standard home humidifier that can run at three different intensities. The next step was to design and fabricate a reservoir to accommodate both the liquid drug and aerosolized particulate airflow without hindering the proper functions of the CPAP machine.

Adaptations were made to a cylindrical home plumbing tube with a screw connection to form the bulk fluid reservoir. The cylindrical tube conforms to the piezoelectric housing and can hold relatively small and controlled fluid volumes. The fluid reservoir was then aligned vertically and attached to a custom-built airflow chamber made from high-density polyethylene (Fig. 10). This chamber has several distinguishing features. During use, air flows horizontally from the CPAP into the device. As the piezoelectric component aerosolizes the liquid, the airflow chamber fills with mist. The inflow of air mixes with the mist and carries it to the chamber outlet. A splashguard over the fluid reservoir ensures that no bulk liquid flows to the outlet. Two sloped funneling ramps coated with Teflon film ensure that any aerosol that condenses within the airflow chamber flows back into the bulk solution within the fluid reservoir.

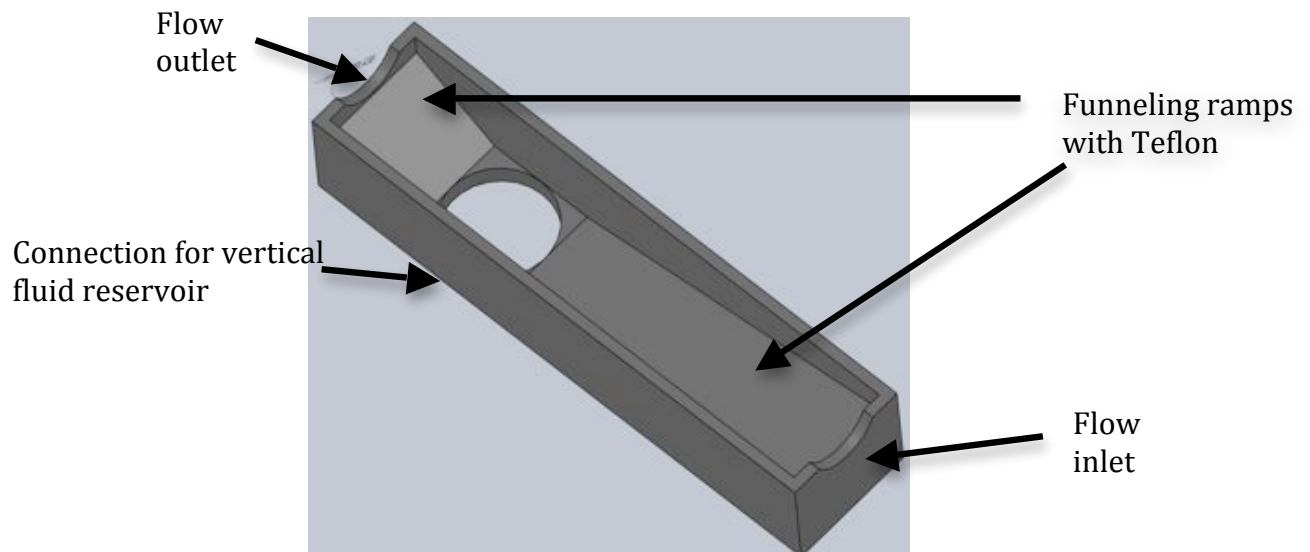
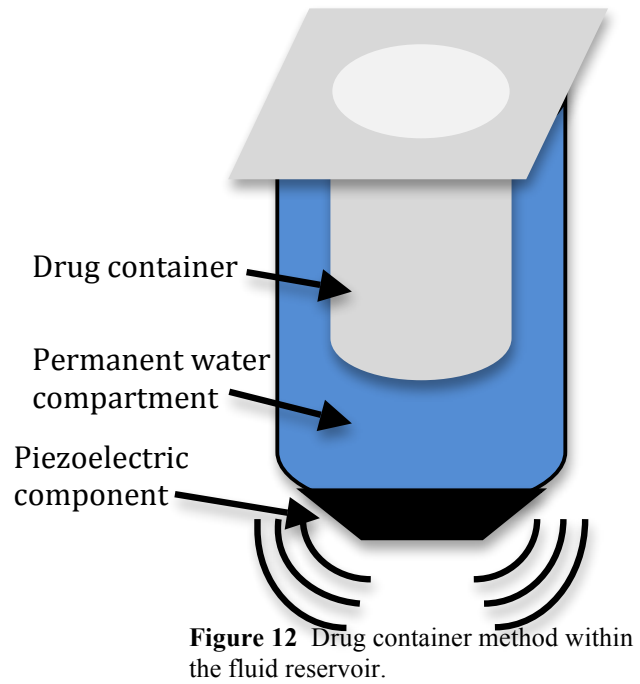
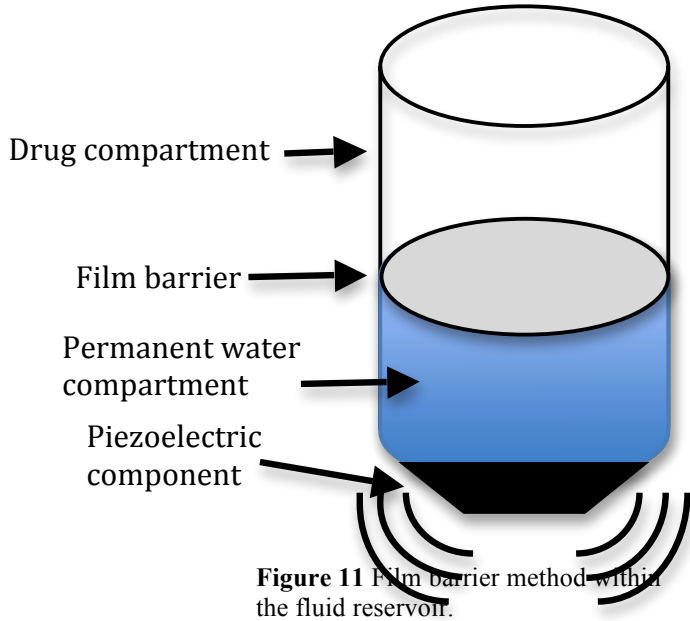


Figure 10. Airflow chamber.

Next, a method was developed for drug containment within the fluid reservoir. The piezoelectric crystal malfunctions if it runs without any liquid, so the crystal must always be submerged in a liquid coolant. Since medication intended for delivery to a patient should not be used as a coolant, it is necessary to have two separate volumes of liquid. The coolant can act as a coupler for the drug, allowing the energy from the crystal to aerosolize liquid albuterol solution while not directly contacting it. Two methods were proposed to keep this liquid coolant compartment separate from the medication.

The first design was to position a plastic film within the screw connection (Fig. 11). This method worked very well, but it provided a few complications. The film can be difficult to put into place, and it would need to be replaced after a few uses. Furthermore, it does not allow the user to aerosolize small volumes of medication efficiently due to its large cross sectional area. The second design was to fabricate a custom medication container that would fit inside of vertical plumbing while the bottom section would be filled with water (Fig. 12). This allows for a precise control of the medication volume with a smaller inner diameter; it is easy to use, and it would not need to be replaced. After testing, it was determined that the fluid container was not the optimal solution for drug delivery. The design itself worked very well; however, the ultrasonic waves penetrated the high-density polyethylene and caused the bottom wall to melt. This melting was enough to impede proper aerosolization and delivery of the drug. Therefore, the best solution was to position a plastic film barrier within the vertical plumbing tube to separate the drug from the water compartment.



This fully assembled nebulizer was designed to be compatible with both a CPAP machine for at-home use and a hospital ventilator (Fig. 13). The reservoir has a port on the topside for easy drug entry into the fluid container. Also, the airflow chamber is connected to the fluid reservoir by a screw mechanism for easy cleaning. Finally a custom-built table was constructed to keep both the airflow chamber horizontal and the fluid container vertical while keeping the piezoelectric components and electronics protected.

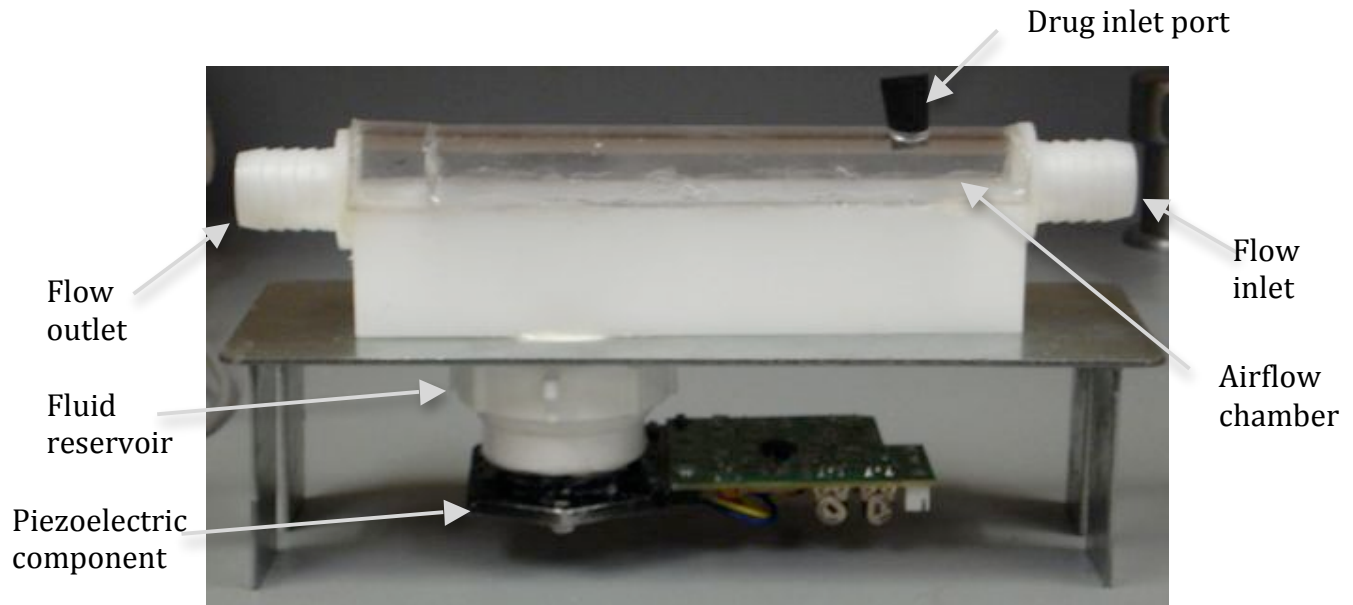


Figure 13. Fully assembled ultrasonic nebulizer.

Electronics and Program

The electronics and program part of the design operate on the principle of control. Ultimately, the program will have an interface where the user will specify the amount of drug to be delivered, the start time of delivery, and the duration of time over which the drug is to be delivered. This goal is nearly completed, but more testing is needed to provide the information needed for the program's logic.

To control drug delivery, the designed system monitors the subject's respiratory rate and uses the information to determine when the nebulizer should be activated or deactivated. This ensures the maximum possible amount of drug is delivered to the subject, and the minimum possible amount is wasted. For the final design, a pressure sensor with an amplifier circuit was used to determine the respiratory rate of the subject. The sensor output then displays a breathing output waveform (Fig. 14). This waveform is transmitted to a data acquisition (DAQ) device where it can be processed by the user interface program.

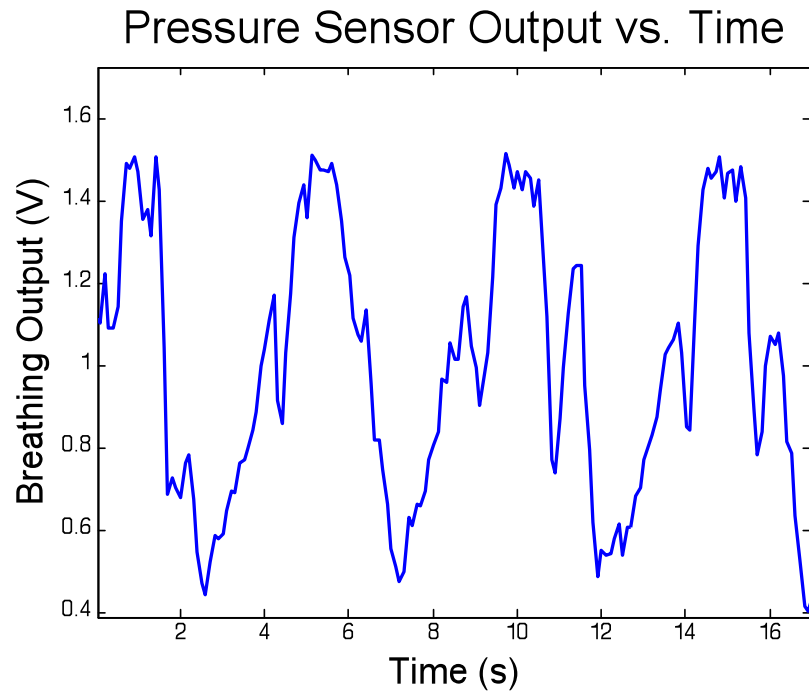


Figure 14. Respiratory Waveform from Pressure Sensor

The user interface program is the control center of the overall design. It processes the respiratory data seen in Figure 14 to control the nebulizer based on user specifications (from user inputs). Currently, the program operates on the principle of timing alone, but the final stage will allow adjustability of drug dosage delivery.

The program's front panel includes a real-time chart of the pressure sensor output and two timing control inputs (Fig. 15). The purpose of the chart and the two timing control inputs is to adjust the amount of time the nebulizer is activated for each respiratory cycle. The user can instruct the program to activate and deactivate the nebulizer at a set time with respect to the anticipated start of inspiration and expiration, respectively. If more drug is to be delivered, the nebulizer can be activated for a longer time and vice versa (Fig. 16).

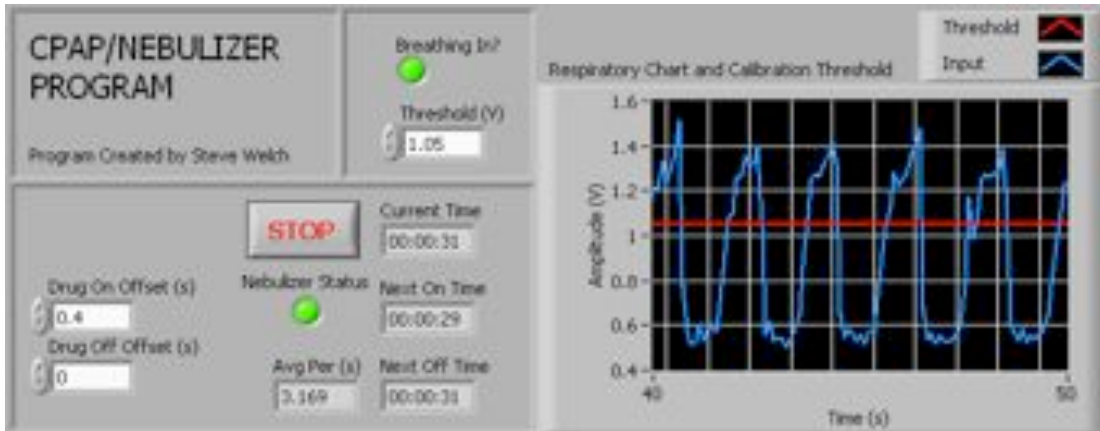


Figure 15 User Interface Program Front Panel.

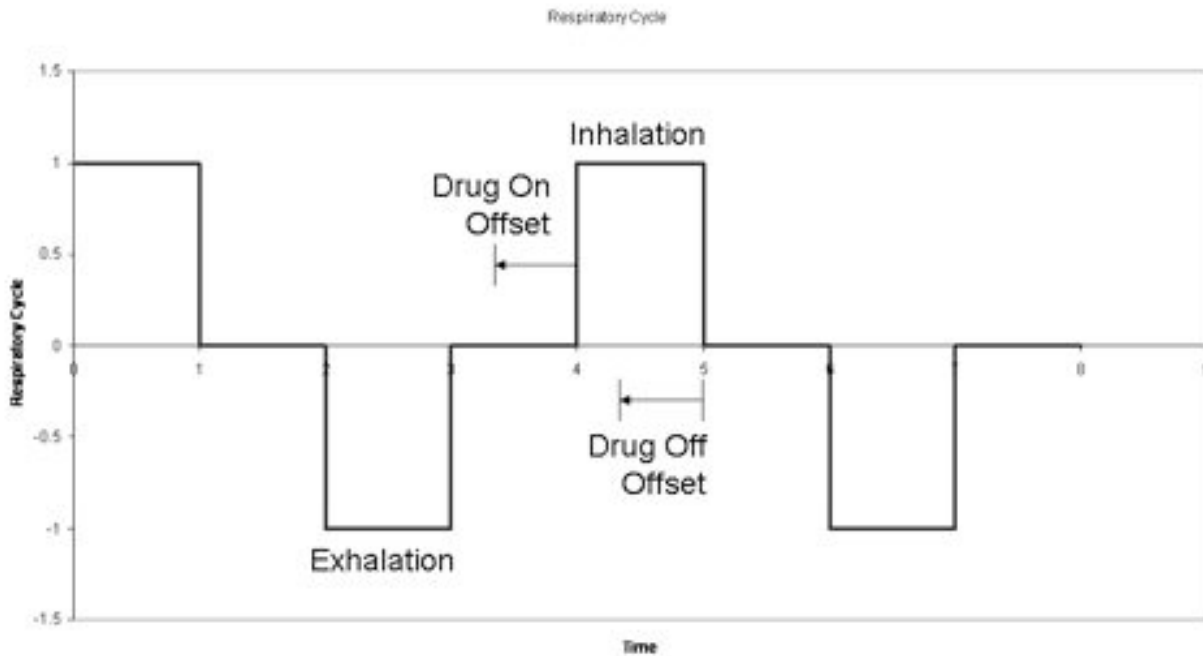


Figure 16 Program Timing.

When the program decides to activate the nebulizer, it instructs the DAQ (Data Acquisition) device to turn the nebulizer on. This complex process uses many components, starting with the DAQ device itself.

The DAQ device used for this project is the LabJack U3, made by the LabJack Corporation and priced at \$108 (Labjack 2009). It allows for cheap and effective signal acquisition and manipulation, since it can interface with a laptop via a USB port. LabVIEW, from National Instruments, is used to operate the device, which has eight digital I/O (input-output) ports with a high rail at 3.3 V. For this project, one of these ports is used as a digital output. When the program decides to turn the nebulizer on, the digital output port is set to 3.3 V. Unfortunately, because the device is completely powered through USB, it has very limited power.

To accommodate for the LabJack U3's low power supply, a switch network is used to activate the nebulizer. The switch network consists of an external power supply, a transistor circuit, and a power relay acting as a voltage-controlled switch.

The current user interface is set up for testing purposes. Eventually, the program will use information about drug delivery acquired from further testing to supply a more convenient user interface. Instead of entering the activation time for a respiratory cycle, the user will simply need to enter the amount of drug he or she wishes to deliver, the start time of delivery, and the duration of time over which the drug is to be delivered. Based on this input, the program will determine the most effective way to run the nebulizer.

TESTING

Testing of the CPAP-nebulizer system was completed to determine the rate of aerosol formation by the ultrasonic nebulizer and the amount of aerosolized medication delivered to CPAP mask in a given time interval. While this testing was done without the program mentioned above, it will be used to create a simpler user interface so that the system can be run with the program in the future.

Nebulization Rate Testing

A first set of experiments was conducted to determine the rate of albuterol sulfate aerosol formation. The nebulizer reservoir's inlet port was first connected to a Respironics REMstar Pro M-Series CPAP and the outlet port was connected to 6 ft (1.8 m) of corrugated, 0.75 in (1.9 cm) inner diameter tubing. Next, 6 mL of solution was added to the medication reservoir of the nebulizer. The ultrasonic crystal was turned on to begin aerosolizing the solution and the CPAP was simultaneously turned on to provide a constant positive pressure of 5 mmH₂O (49 Pa). As soon as the ultrasonic nebulizer began aerosolizing the solution (following an approximately 1 second delay from initiation), timing began. The CPAP and the nebulizer were both run continuously for 3.0 min. The volume of solution remaining in the medication reservoir after the 3.0 min trial was measured and recorded.

Nine trials were conducted during the first set of experiments. During the first three trials, the solution was 6 mL of deionized water. The following three trials were conducted using a solution of 3 mL of deionized water mixed with 3 mL of standard albuterol sulfate solution. The final three trials of this set of experiments were conducted using 6 mL of standard albuterol sulfate solution. The albuterol solution used in this experiment was manufactured by DEY, Inc. under the name: "Albuterol Sulfate Inhalation Solution" (NDC 49502-697-24) (U.S.F.D.A., 2009). The colorless solution is packaged in sterile, single unit-dosage vials, each containing 2.5 mg of albuterol in 3 mL of solution. This is equivalent to a 0.083% albuterol by mass. Therefore, one single-dose vial was used for trials requiring 3 mL of albuterol solution, while two single-dose vials were used for trials requiring 6 mL of albuterol solution.

Finally, the aerosolization rate of the ultrasonic nebulizer was calculated using the results obtained for each set of three trials.

Delivery of aerosol to CPAP mask

A second set of experiments was carried out to quantify the amount of aerosolized medication delivered to the CPAP mask. This aim was accomplished through the use of UV spectrophotometry by the method described by Wright, et al. (2009) and Hess, et al. (1996).

Samples of albuterol solution of known concentration were first tested for absorbance in a Carly 300 Conc Visible-UV spectrophotometer at 296 nm. The data was combined to create a standard albuterol absorbance curve (Fig. 17).

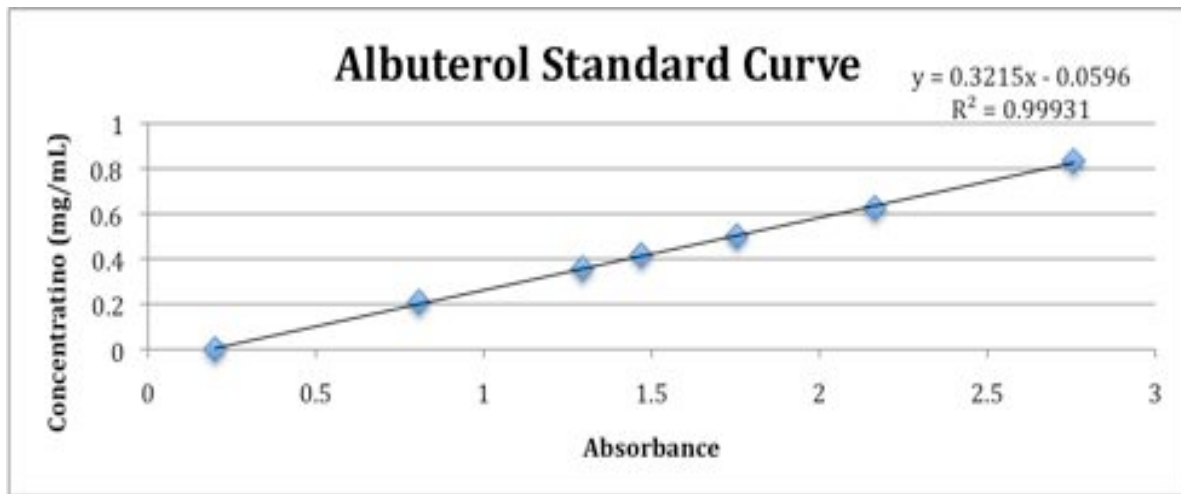


Figure 17. Standard curve for absorbance at 269 nm correlated with albuterol concentration. Resulting equation and R^2 values are included.

To conduct the second set of experiments, the nebulizer reservoir inlet port was first connected to a Respironics REMstar Pro M-Series CPAP and the outlet port was connected to 6 in of corrugated, 0.75 inch in diameter tubing (Fig. 18). The distal end of the tubing was connected to a collection flask, where the flask included an outlet for airflow (Fig. 19).



Figure 18 Orientation of CPAP nebulization device during testing of the delivery of aerosol to the CPAP mask.



Figure 19 An Erlenmeyer flask with an outlet port was used to collect rainout of the albuterol mist into a graduated cylinder.

Next, 9 mL of standard albuterol sulfate solution was added to the nebulizer medication reservoir. The ultrasonic nebulizer was turned on to begin aerosolizing the solution and the CPAP was simultaneously turned on to provide a constant positive pressure of 5 mmH₂O. As soon as the ultrasonic nebulizer began aerosolizing the solution (following an approximately 1 second delay from initiation), timing began. The CPAP and the nebulizer were both run continuously until all for 9.0 min. The volume of solution remaining in the medication reservoir after the 9.0 min trial was measured and recorded. The volume of solution in the distal collection flask was also measured and recorded, and the sample was analyzed using the UV spectrophotometer. The concentration of the collected sample solution was calculated using the measured absorbance with a correction factor established by the standard absorbance curve. Lastly, the amount of albuterol collected was calculated using the measured volume and concentration.

RESULTS

Aerosolization Rate

The results obtained from Part I of testing methods suggest that the aerosolization rate of the CPAP nebulizer system is significantly greater than that of commercially available nebulizers (such as those described by Wright (2009)). As illustrated in Figure 20, the developed CPAP-nebulizer system was found to aerosolize liquid solution at an average rate of 0.62 ± 0.22 mL/min, while the standard nebulizer systems are only capable of aerosolization at an average rate of about 0.24 mL/min (this difference is statistically significant, with $p=0.05$).

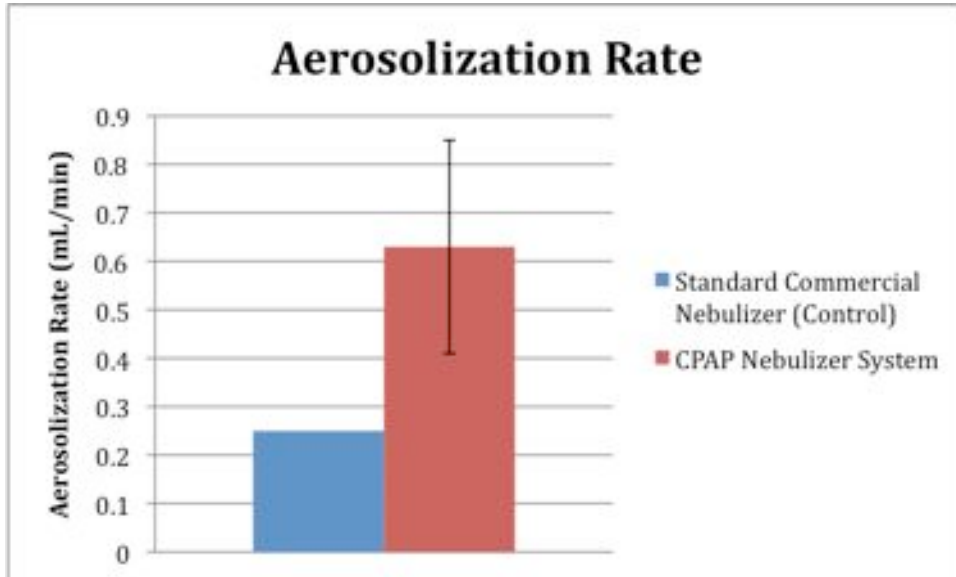


Figure 20. Aerosolization rate of CPAP nebulizer system compared to control. The two values are statistically significant ($p = .05$).

Amount of Albuterol Delivered

The results obtained from Part II of testing methods are shown in Table 1. The albuterol concentration data show that the albuterol concentration varied from 0.741 – 1.139 mg/mL over the course of the three trials, showing increasing concentrations by nearly 0.5 mg/mL from the beginning of the study to the end (Table 1). This may be explained by the fact that the nebulizer had been in use for 30 minutes by the end of the third trial. Wright, et al. also observed that the concentration of albuterol in the drug reservoir increased as the nebulization time increased. While this comparison is not a direct analog to the testing system here (new doses were added, and the piezo element was shut off between trials) it is possible that a similar phenomenon is occurring in this system. Potential causes could originate from inefficient dispersion of heat generated by the piezoelectric crystal, resulting in accumulation of heat within the heat sink and residual liquid volume that propagated to the medication reservoir causing heating of the albuterol sulfate solution and facilitating evaporation of the aqueous medium. Other influences are likely contributing to the increase in concentration throughout the course of the experiment, as well.

Table 1 Amount and concentration of albuterol delivered to mask

Trial	Albuterol Concentration (mg/mL)	Amount of Albuterol Delivered (mg)
1	0.714	1.607
2	1.098	1.572
3	1.139	1.708

Despite the variance in albuterol concentration throughout the experiment, the amount of albuterol delivered to the mask remained fairly consistent over the three trials. The average amount of albuterol collected in 9 min was 1.629 ± 0.071 mg. This consistency implies that the effects of heating and other factors contributing to the increase in concentration observed do not significantly affect the amount of albuterol delivered to the patient.

Delivery Efficiency

Drug delivery efficiency, calculated as the percent of albuterol that makes it to the mask compared to the amount nebulized, was shown to be greater than what is expected by the drug manufacturer (DEY, Inc.). The efficiency of the CPAP-nebulizer system was compared to that of commercially available nebulizers (Fig. 21).

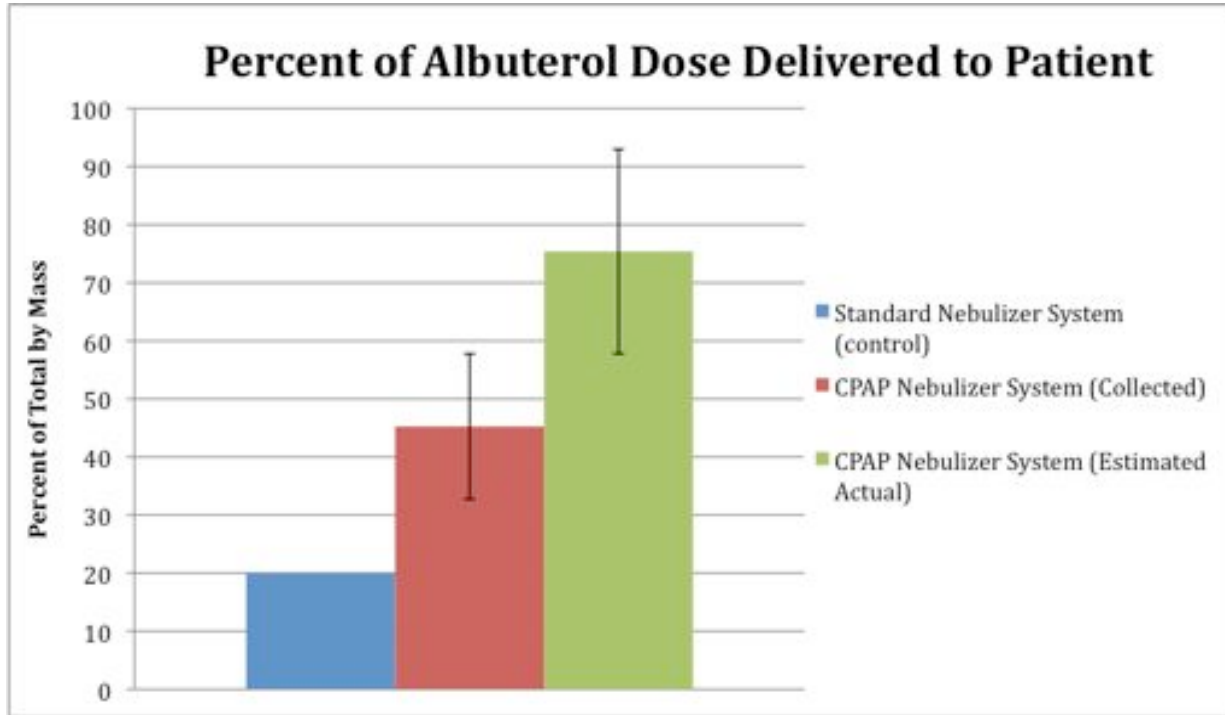


Figure 21 Efficiency comparison between a standard nebulizer system and the CPAP nebulizer system. The differences between the measured and control value is statistically significant ($p < .05$). Estimated value represents a predicted maximum value based on observed losses at collection.

The measured albuterol delivery efficiency was shown to be significantly higher than that of the control (commercially available nebulizer systems). This is consistent with other systems that employ control over aerosol generation. Note that the estimated value accounts for the observed inefficiencies in the aerosol collection apparatus, such as air leakage and uncollected aerosol deposition on the interior of the flask.

DISCUSSION

The higher aerosolization rate obtainable by the CPAP-nebulizer system compared to commercially available systems means that a set dose of medication can be delivered to a patient in less time. This ability could prove critical when used during emergency situations as well as convenient when used for a sleeping patient. Further, the relative invariance in the amount of albuterol delivered to the mask within a set amount of time, regardless of concentrations, shows that the CPAP-nebulizer system may be an effective medication delivery system to use for

patients requiring a CPAP or ventilator during aerosolized medication therapy. Combined with the functionality of the program, the efficiency of the system will likely increase (since the program will time the nebulization with the patient's breathing), providing a highly efficient method of aerosolized medication delivery. However, further testing is necessary to determine the true value of efficiency of this delivery system.

FUTURE WORK

Significant progress has been accomplished on the CPAP-nebulizer system during the Spring 2010 semester. The device is in working condition and testing has been performed to validate the efficacy of the system. Based on the results of the testing, the CPAP-nebulizer system was shown to be more efficient at delivering aerosolized albuterol sulfate solution to the patient. After completion of device construction and testing, an Invention Disclosure Statement was submitted to WARF as a pre-application for patent protection of the device described within this report.

Slight modifications to the device could be implemented to improve the ease of use of the device. Modifications include the addition of a hinged top to the nebulizer reservoir to allow for easier addition of medication into the medication reservoir and to improve the ease of sterilization of the nebulizer device. Additionally, improvements could be made to the user interface to increase ease of parameter input (dosage, timing, etc.) by the physicians to facilitate more intuitive use and minimize the training involved for device utilization.

In the future, the system should be validated to be effective for use on live subjects in the UW-Sleep Research Laboratory, following the approval of the IRB.

REFERENCES

- American Sleep Apnea Association (ASAA). 2008. [Online]. www.sleepapnea.org
- Estes, M. C., J. Fiore, D. M. Mechlenburg, H. Ressler, and J. Kepler. 2005. *Method and Apparatus for Providing Positive Airway Pressure to a Patient*. US Patent, 6,932,084.
- Gessler, T., T. Schmehl, M. M. Hoeper, F. Rose, H. A. Ghofrani, H. Olschewski, F. Grimminger, and W. Seeger. 2001. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. *Euro Resp*, **17**(1):14-9.
- Ivri, E. and J. Fink. 2007. *Aerosol Delivery Apparatus and Method for Pressure-Assisted Breathing Systems*. US Patent, 7,290,541.
- Hess, D., Fisher, D., Williams, P., Pooler, S., and Kacmarek, R. M. 1996. Medication nebulizer performance effects of diluent volume, nebulizer flow, and nebulizer brand. *Chest*, **110**(2): 498-505.
- Hickey, A. J. 1996. Inhalation Aerosols: Physical and Biological Basis for Therapy. New York, NY: Marcel Dekker, Inc.
- LabJack U3. 2009. *U3 Specs*. [Online] www.labjack.com
- Sanders, M. H. and R. J. Zdrojowski. 1992. *Method and Apparatus for Maintaining Airway Patency to Treat Sleep Apnea and Other Disorders*. US Patent, 5,148,802.
- United States Food and Drug Administration. 2009. *National Drug Code Directory*. United States Department of Health and Human Services. [Online] www.fda.gov
- Wright, J., Bouma, C., and Latman, L. July 2009 Drug Delivery Characteristics of Six Nebulizer Systems. *ASTM Internat*, **5**(7).

Appendix A - Product Design Specifications

Function

To automatically deliver aerosolized drugs during use of CPAP device without compromising the function of the CPAP. This added function will improve the CPAP's effectiveness in alleviating the symptoms of sleep apnea.

Client Requirements

- Automatic
- Must not interfere with function of CPAP
- Compatible with albuterol
- Must incorporate humidifier
- Adjustable amount of drug delivery
- User interface to adjust the start time and duration of administration of up to three doses of albuterol during the patient's sleep cycle

Design Requirements

- Must be able to be used nightly for eight hours
- Must incorporate nebulizer to aerosolize drug
- Delivery must be efficient
- Must have computer interface
- Must have dosage control
- Must be sterilizable
- Easy to set up
- Must not disrupt sleep

1. Physical and Operational Characteristics

a. Performance Requirements: The drug delivery system must be capable of running efficiently every day for approximately 8 continuous hours. During this time, the drug must be delivered in accurate doses at times specified by the user. It also must be compatible with a CPAP device and not compromise the positive pressure in the patient's airway.

b. Safety: The drug delivery system must not disrupt CPAP operation. It must also not allow the possibility of a drug overdose.

c. Accuracy and Reliability: The drug delivery system must be at least as efficient as existing nebulizers at delivering aerosolized albuterol. The user must be able to have precise control over the dose of drug delivered, with control to .1 mg drug.

d. Life in Service: Parts should be made replaceable, increasing the service life indefinitely. The CPAP tubing must be replaced periodically; however the use of standardized parts should minimize this cost.

e. Shelf Life: The drug delivery system should last in storage as long as the shelf life of the commercially available parts used (the CPAP, piezo buzzer, etc.). A ten-year life span is desirable.

f. Operating Environment: The drug delivery system will be used for sleep studies conducted in a controlled environment. It must not interfere with the sleep of the individual using it, not can it interfere with any other instruments used in the study

g. Ergonomics: The computer interface should be easily navigated with minimal training. Any mask or additive to the drug compound that will contact the patient must not be irritating and be compatible with 8 h of continuous use

h. Size: The drug delivery system must be able to contain at least two doses of drug (6 mL fluid)

i. Weight: The drug delivery system must be easily moved by a single person. A weight less than 5 kg is desired.

j. Materials: Materials used must be FDA approved for use in drug delivery systems, must not alter the properties of the drug, must not promote drug adhesion, and must not be an irritant to the patient.

k. Aesthetics, Appearance, and Finish: The drug delivery system should be designed with functionality in mind, and aesthetics are of secondary concern.

2. Product Characteristics

a. Quantity: One unit will be needed.

b. Production Cost:
Estimated budget: \$250.00 - \$400.00

Appendix B– Spring 2010 Semester Budget

Item	Vendor	Purpose	Unit Cost	Cost
Total from Fall 2009 semester	Various	Used to develop effective prototype designs	\$159.61	\$224.68
HDPE Plastic block	McMaster	Machined into nebulizer reservoir base	\$3.00	\$12.00
Polycarbonate tube	McMaster	Cut and epoxy to form nebulizer chamber	\$2.19	\$17.53
Tubing and adaptors	ACE Hardware	Non-corrugated substitute for CPAP tubing and adaptors to connect to nebulizer	\$13.06	\$13.06
Plumbing kit	ACE Hardware	Fix to nebulizer making reservoir removable	\$5.26	\$5.26
PTFE Sheet	McMaster	Promote hydrophobic inner surfaces of nebulizer chamber	\$3.00	\$22.10
CPAP unit	UW-Hospital	Used to test feasibility of prototype ideas	\$0	Donated
Albuterol Nebulizer Doses	UW-Hospital	Used to test feasibility of prototype ideas	\$0	Donated
Total from this semester			\$26.51	\$69.95
Total overall			\$186.12	\$294.63

APPENDIX C: CIRCUIT SCHEMATICS

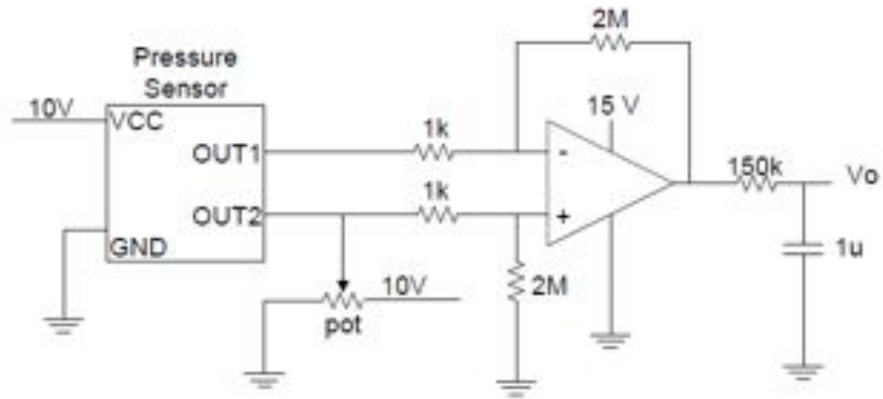


Figure C1 Pressure sensor amplifier and filter circuit. V_o leads to LabJack U3 analog input.

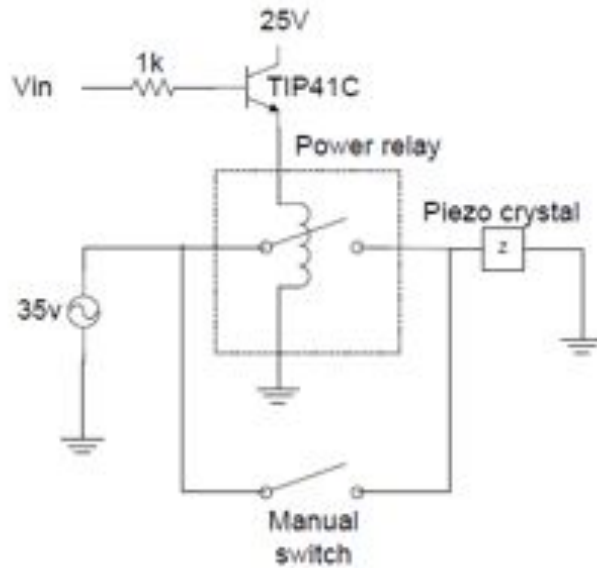


Figure C2 Power relay switching circuit. V_{in} leads from LabJack U3 digital output.