

Delivery of aerosolized medication using continuous positive airway pressure

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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.

INTRODUCTION

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. Since albuterol sulfate is produced in the form of a solid substance, it is either administered through a metered dose inhaler or dissolved in normal saline and aerosolized for patient inspiration. To aerosolize the albuterol solution, a nebulizer is used.

An ultrasonic nebulizer was used for the system described in this article. Ultrasonic nebulizers include a piezoelectric crystal that oscillates when an alternating 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 droplets of albuterol formed with an ultrasonic nebulizer are between 3 and 6 μm in diameter (Hickey, 1996). The main benefit to using an ultrasonic nebulizer instead of a jet nebulizer in the CPAP nebulization device is that it is nearly silent, which is important because patients will be using this device while sleeping. Ultrasonic nebulizers are also more efficient than jet nebulizers. The efficiency of a typical ultrasonic nebulizer at delivering aerosolized

medication to ambient has been clinically shown to be about $86 \pm 5\%$, while the efficiency of a typical jet nebulizer was shown to be only about $39 \pm 3\%$ (Gessler et al., 2001).

MATERIALS AND METHODS

Device Construction

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.

Adaptions 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. 1). 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.

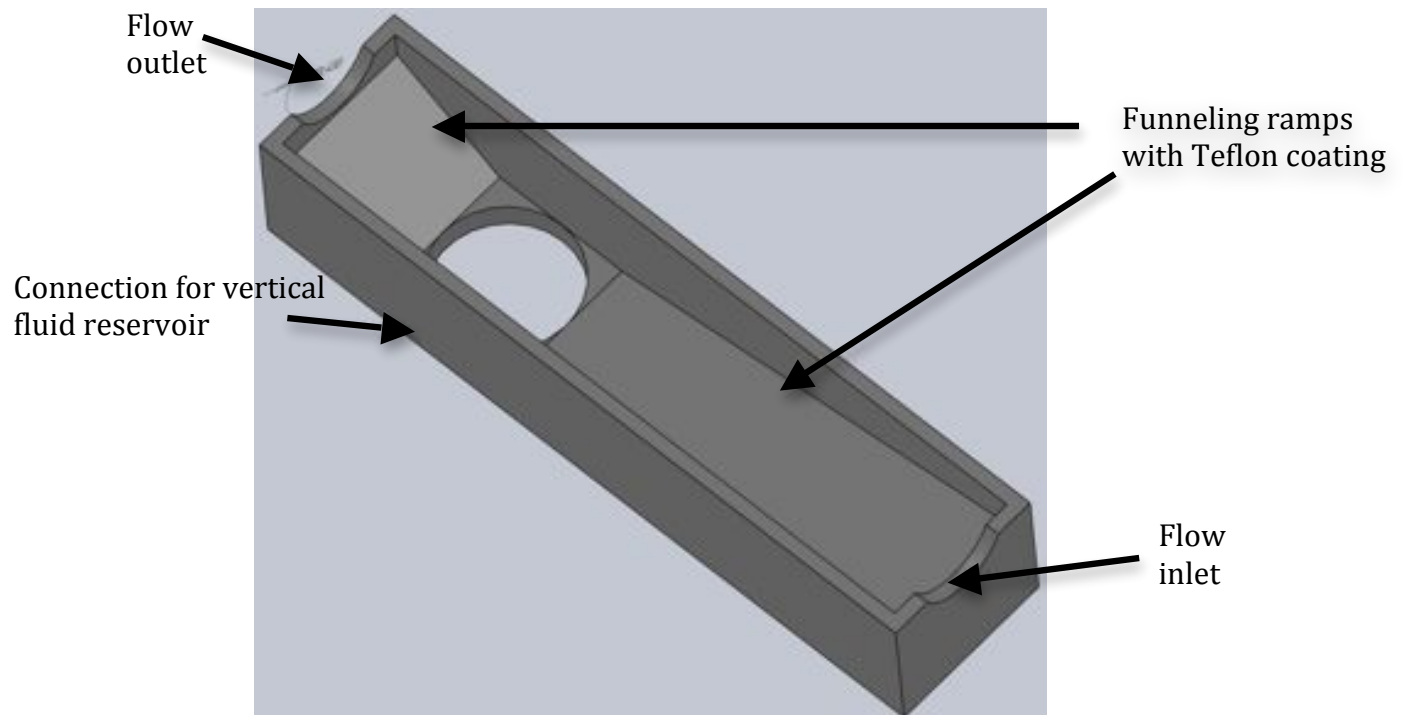


Figure 1 Airflow chamber.

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. 2). 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. 3). 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.

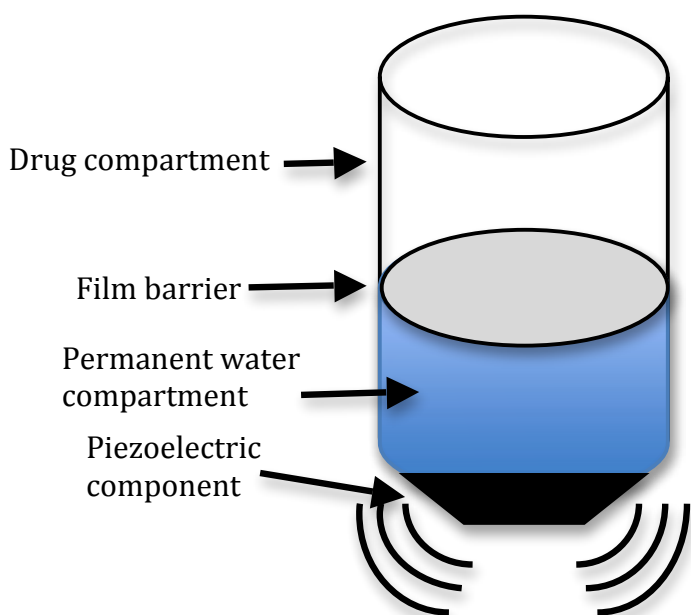


Figure 2 Film barrier method within the fluid reservoir.

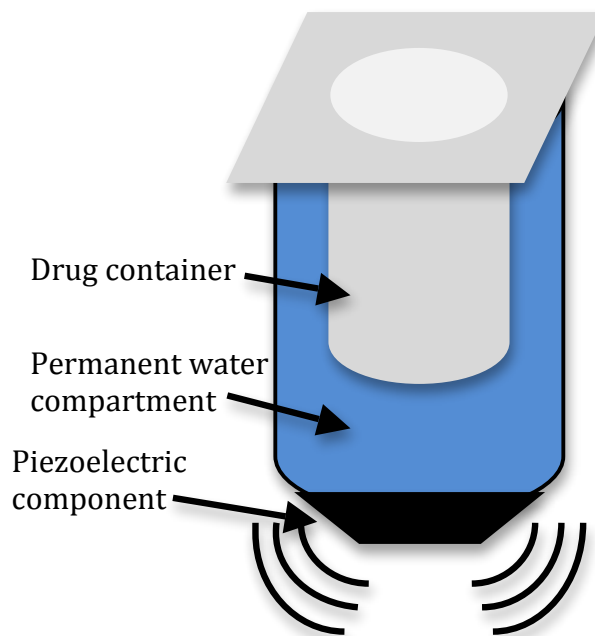


Figure 3 Drug container method within the fluid reservoir.

This fully assembled nebulizer was designed to be compatible with both a CPAP machine for at-home use and a hospital ventilator (Fig. 4). 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.

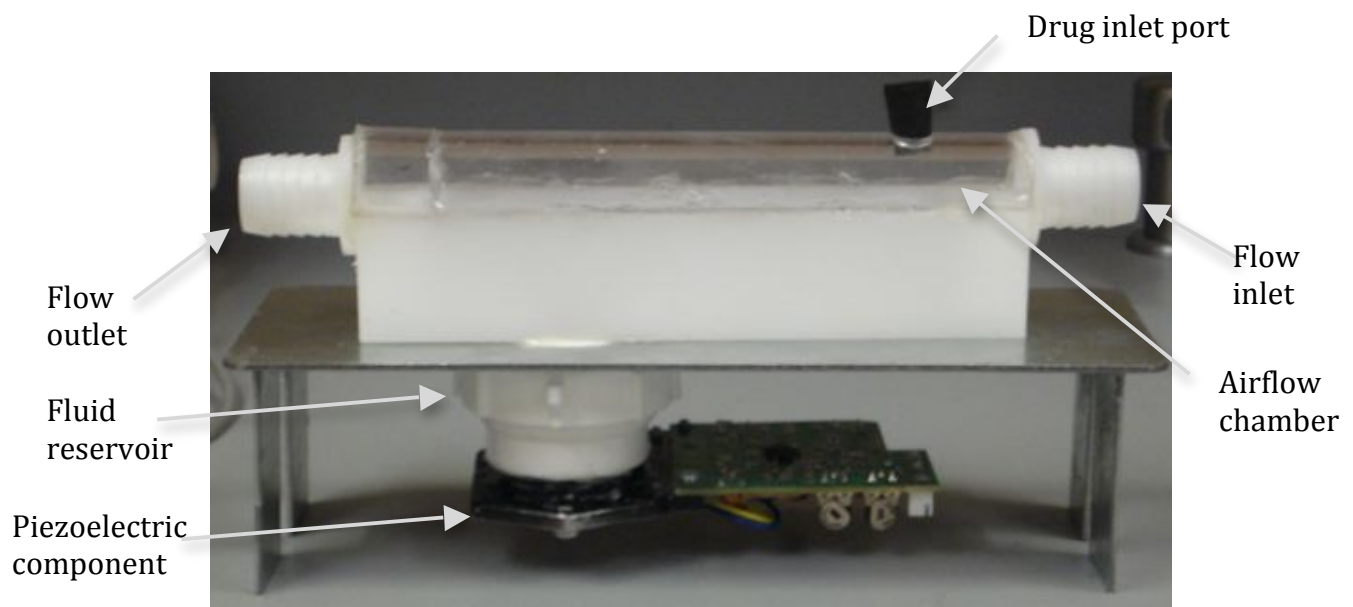


Figure 4 Fully assembled ultrasonic nebulizer.

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. 5). This waveform is transmitted to a data acquisition (DAQ) device where it can be processed by the user interface program.

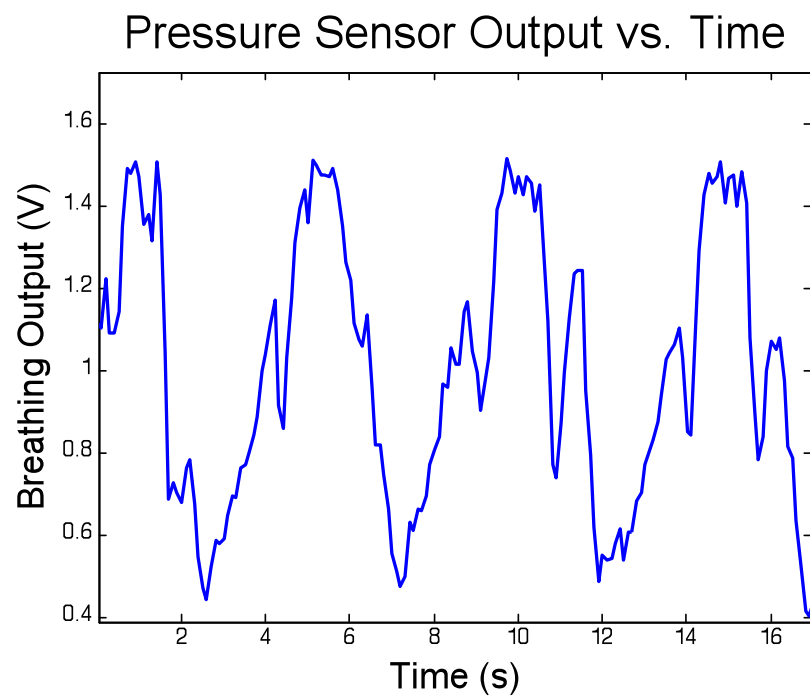


Figure 5 Respiratory Waveform from Pressure Sensor

The user interface program is the control center of the overall design. It processes the respiratory data seen in Figure 5 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. 6). 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. 7).

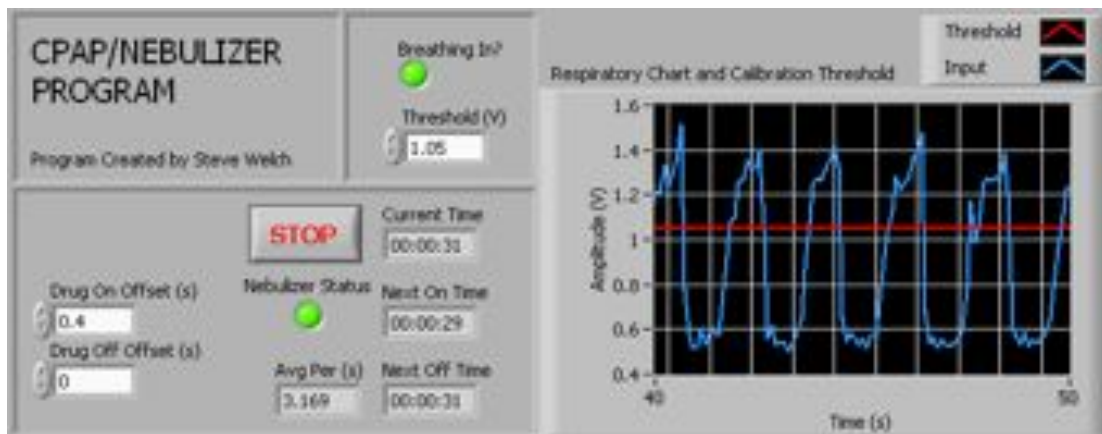


Figure 6 User Interface Program Front Panel.

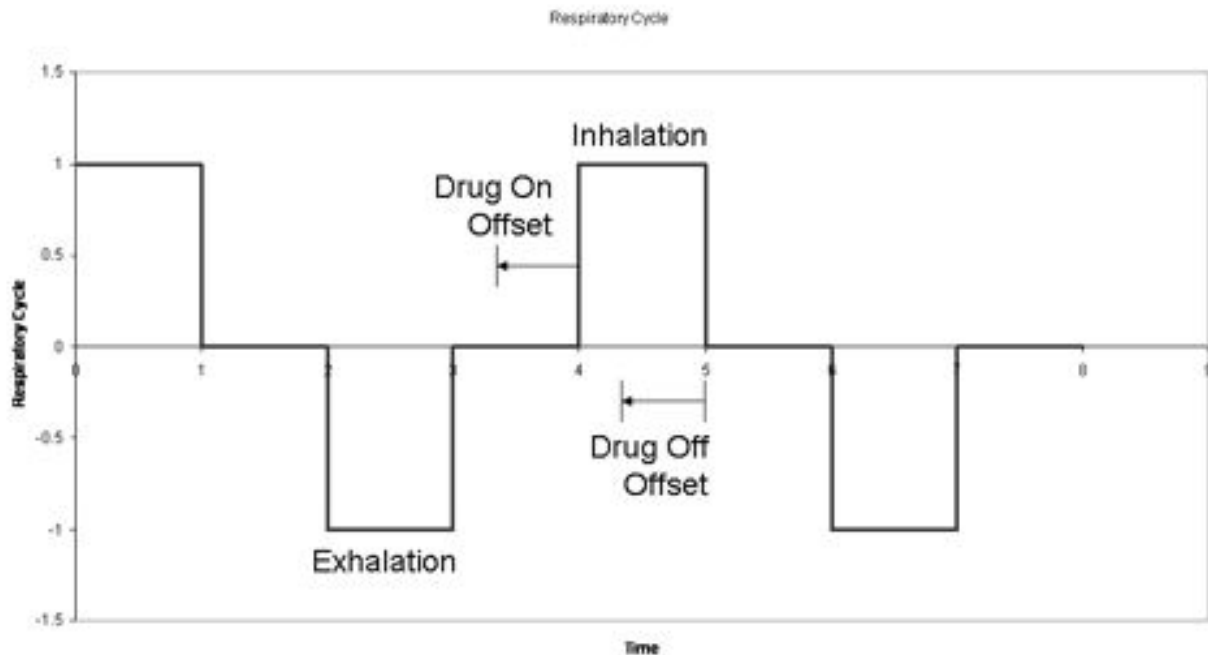


Figure 7 Program Timing.

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 Methods

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.

Part I – 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 nebulization rate of the ultrasonic nebulizer was calculated using the results obtained for each set of three trials.

Part II – 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 Cary 300 Conc Visible-UV spectrophotometer at 296 nm. Absorbances were adjusted using a baseline reading for normal saline. The data was combined to create a standard albuterol absorbance curve (Fig. 8).

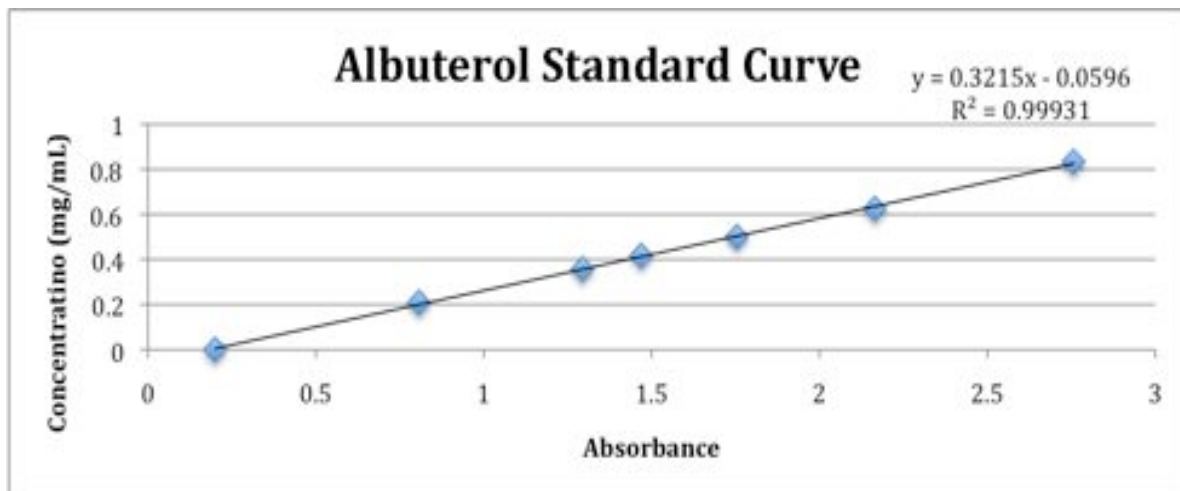


Figure 8 Standard curve for absorbance at 269 nm correlated with albuterol concentration. Resulting equation and R^2 values are included.

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. 9). The distal end of the tubing was connected to a collection flask, where the flask included an outlet for airflow (Fig. 10).



Figure 9 Orientation of CPAP nebulization device during testing of the delivery of aerosol to the CPAP mask.



Figure 10 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

The following data was collected using the methods described for Testing I and Testing II.

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 11, 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 $p=0.05$).

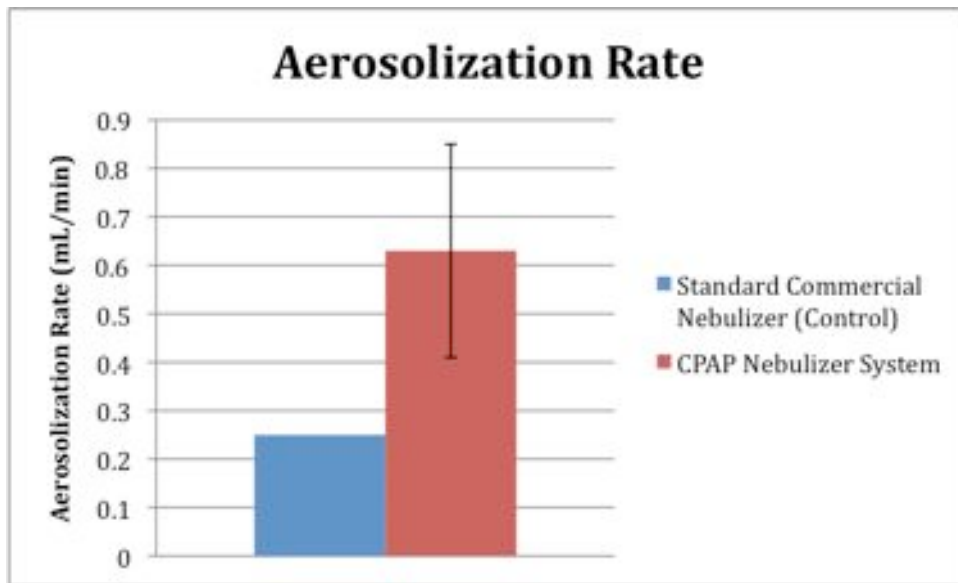


Figure 11 Aerosolization rate of CPAP nebulizer system compared to control. The two values are statistically significant ($P = .05$).

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. 12).

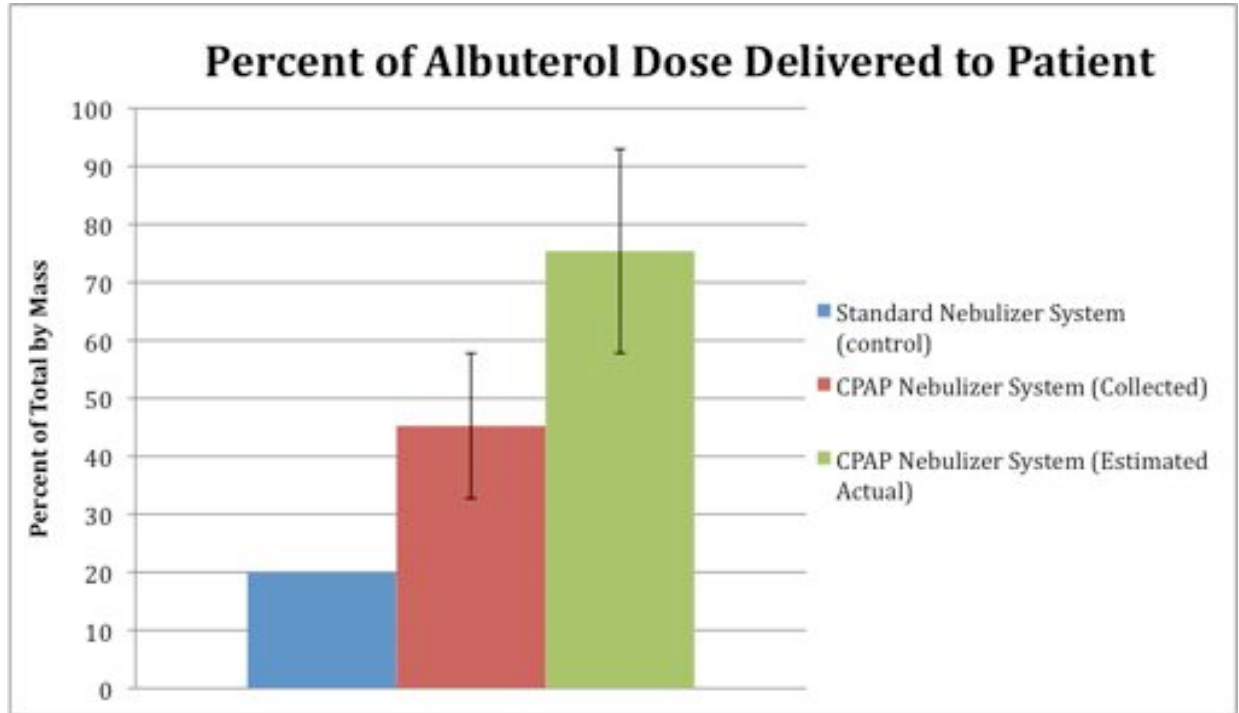


Figure 12 Efficiency comparison between a standard nebulizer system and the CPAP nebulizer system. The differences between the measured and control value is statistically significant ($P=0.05$). Estimated value represents a predicted value based on losses in the collection apparatus.

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.

ACKNOWLEDGMENTS

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APPENDIX A: PREVIOUS 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 A1.

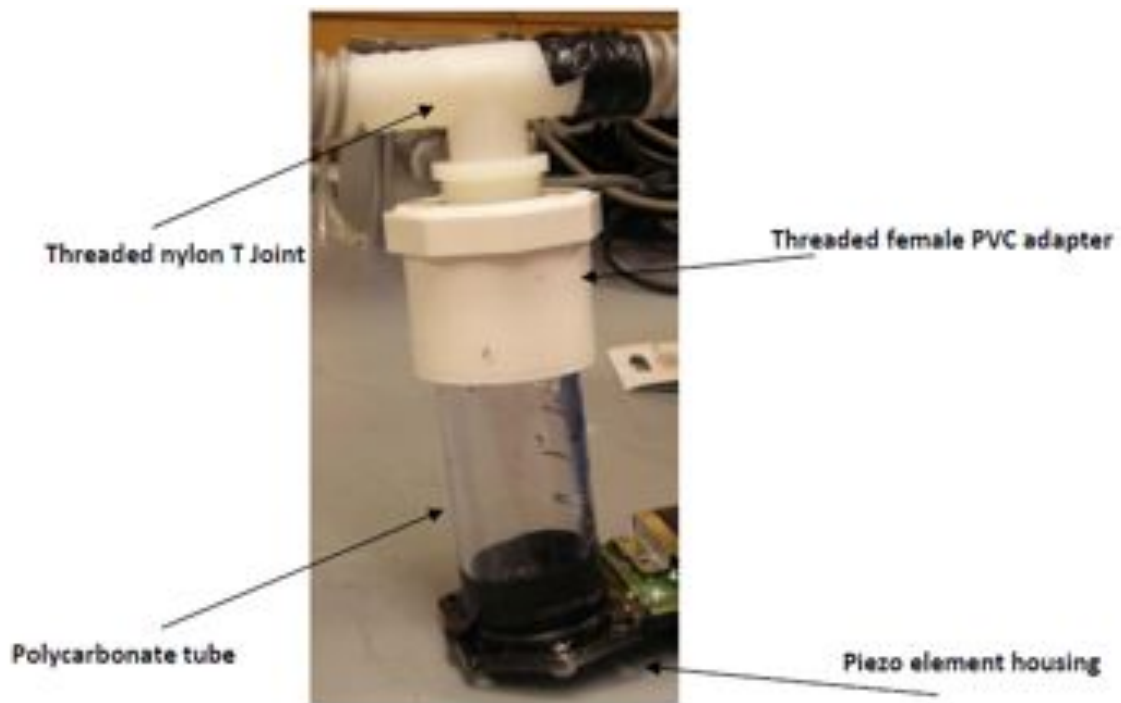


Figure A1: Previous semester reservoir design.

The design in Figure A1 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.

APPENDIX B: FUTURE WORK

The device created is nearing completion. More testing is necessary to determine the appropriate threshold levels for the program, as well as the level of filtering necessary to provide a smooth waveform. The reservoir can also be updated. A hinged top would make the device easier to use for the patient as well as speed up maintenance and allow the reservoir to be easily sterilized. Currently, we are working on submitting an invention disclosure form to WARF, as well as looking into submitting a protocol for IRB approval in order to begin clinical testing in Dr. Teodorescu's lab.

APPENDIX C: CIRCUIT SCHEMATICS

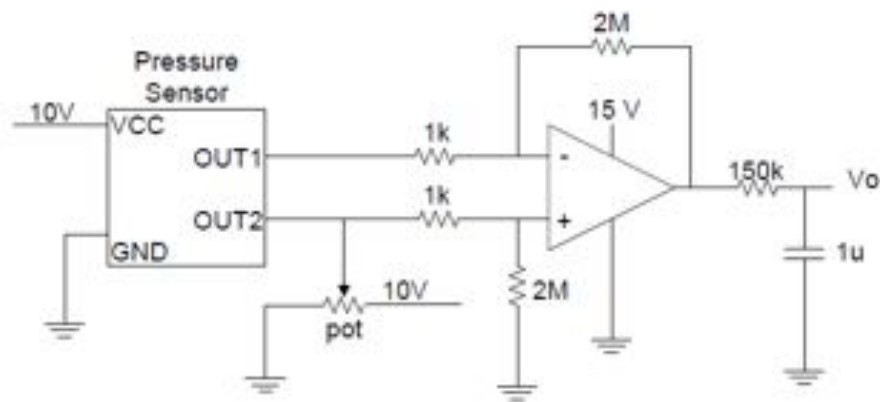


Figure C1 Pressure sensor amplifier and filter circuit. V_o leads to LabJack U3 analog input.

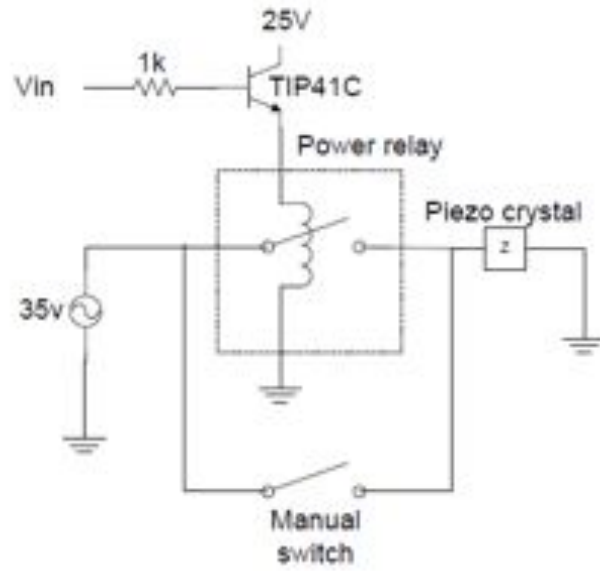


Figure C2 Power relay switching circuit. V_{in} leads from LabJack U3 digital output.