Delivery of Aerosolized Medication through Continuous Positive Airway Pressure Device

BME 400

BIOMEDICAL ENGINEERING DESIGN

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Abstract

A device has been developed for automated delivery of aerosolized medication, such as the bronchodilator albuterol, within the main airflow of a continuous positive airway pressure (CPAP) device, wherein the system is programmable for various dosages, start times, and durations of medication administration. The final design utilizes an ultrasonic nebulizer that has been programmed to switch on and off for set time intervals. In the future, this program will be combined with electronic circuitry to determine when the patient inhales and exhales in order to sync the atomization interval with the patient's inspiration phase to minimize medication loss when the patient exhales. Tests of the ultrasonic nebulizer indicated that when the nebulizer containing 40 mL of albuterol solution (.125 mg/mL) is run for 30 min, 3.12 mg of albuterol are aerosolized. In the future, further testing should be completed to determine the percentage of albuterol delivered to the patient with respect to the amount aerosolized. Based on the results of this test, a program will be created to automatically control the time and duration that the nebulizer is running based on dosage, timing, and duration input from the user.

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.

Background

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 caused by tracheal muscle relaxation, causing the narrowing and closing of the patient's airway. The narrowing of the trachea results in the sleeper repeatedly waking short of breath throughout the night, leading to chronic sleep deprivation. Obstructive sleep apnea is potentially dangerous because the cessation of breathing lowers the patient's blood-oxygen level. In most people, the brain senses

the oxygen deprivation and awakens the sleeper so that he or she resumes a normal breathing cycle; however, in patients with pre-existing health conditions, such as cardiovascular disease, a measured drop in blood-oxygen content could trigger other life-threatening episodes that could potentially result in death. Depending on the patient's symptoms and health history, treatment options for sleep apnea include lifestyle changes or, in serious cases, surgery. The most widely used treatment is to employ a continuous positive airway pressure (CPAP) device during sleep to open the airways.

CPAP devices provide therapy to a sleep apnea patient by delivering positive pressure to the airway, keeping it open when the tracheal muscles relax. Most CPAP designs include a pressure source, electronic 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. A functional block diagram of a CPAP device is shown in Figure 1. The blower (or other pressure source) creates a positive pressure in the airway of the patient. This positive pressure helps to open the patient's airway, preventing airway collapse during inspiration. When the patient exhales, the CPAP can relieve pressure within the circuit using a number of methods. The CPAP device in Figure 1 includes a dump valve, labeled as "Exhausted Valve," which opens when the pressure within the CPAP circuit has reached a threshold. Alternative CPAP designs, such as the Respironics REMstarPro M Series (Model #400M), use control circuitry to turn the motor-driven blower off rather than use an exhaust valve to respond to pressure changes (Estes et al., 2005 and Sanders et al., 1992).

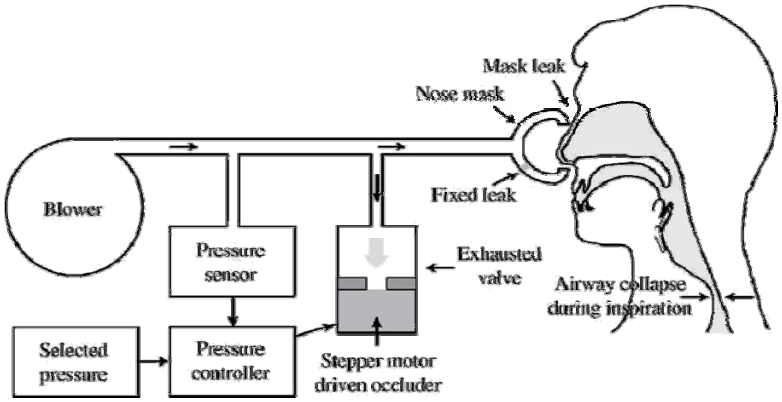

Figure 1. Block Diagram of CPAP Device (Webster, 2009).

Typically, the positive pressure within the CPAP circuit is within the range of 4 to 20 cm H_20 (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 and optimize treatment.

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 (SO_4) 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 to 5) in addition to the active ingredient, albuterol sulfate (the chemical structure of which is shown in Figure 2). 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.

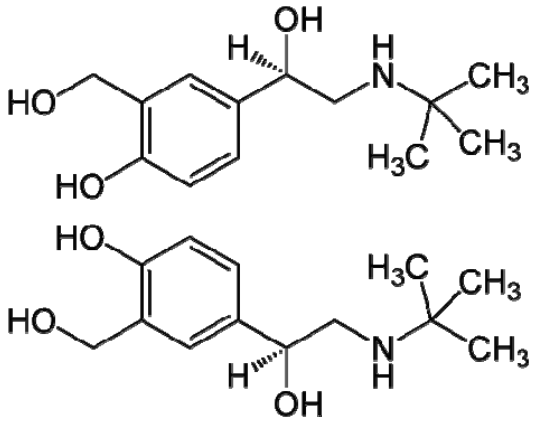

Figure 2. Chemical Structure of Albuterol. The racemic form of albuterol is used in the inhalation solution produced by DEY, Inc. The molecular weight of albuterol is 576.71 g/mol.

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 $beta_2$-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 $beta_2$-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 3. The average droplet size formed by jet nebulizers is between 5 and 600 μm, depending on the nozzle (Hickey,1996).

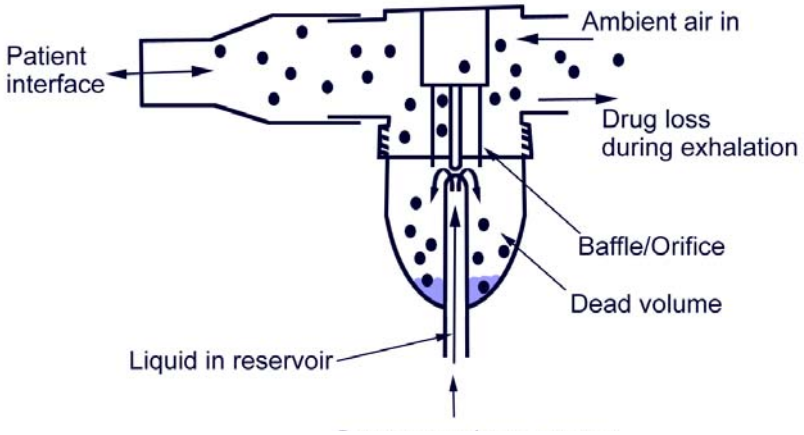

Figure 3. Block Diagram of CPAP Device (img.medscape.com).

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 the patient's lungs has been clinically proven to be only about 39 ± 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 4, 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 to 4.0 MHz.

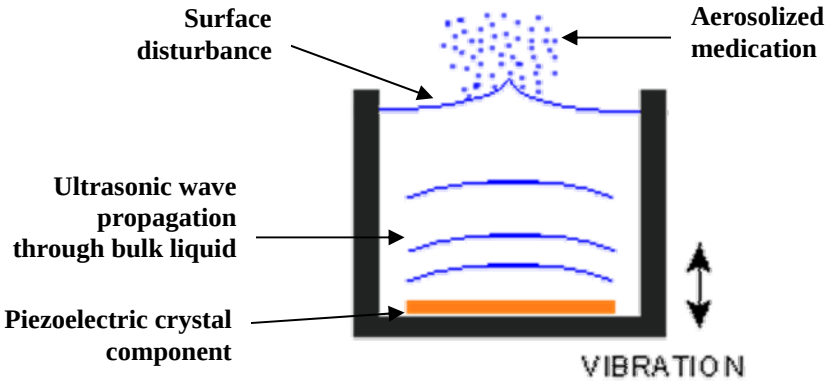

Figure 4. Diagram of Ultrasonic Nebulizer (www.sonozap.com)

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 ± 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 doses of 3 mL of medication each 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 Respironics REMstarPro M Series (Model #400M) pictured in Figure 5.

Figure 5. 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 6) and ultrasonic nebulizers (such as the Duro-Mist Ultrasonic Nebulizer shown in Figure 7). However, these are stand-alone units and cannot be used in-line with a CPAP device.

Figure 6. Lumineb II Model 5710 Nebulizer Device. A currently available jet nebulizer. (www.semedicalsupply.com)

Figure 7. 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 8, is an in-line nebulizer designed to be used within the circuit of mechanical ventilator.

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Figure 8. 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.

Design Options

Three design options have been developed to incorporate all of the desired features for aerosol drug delivery via CPAP, including programmability, automaticity, multiple dosage delivery, and coordination with the patient's breathing cycles. The design options were Design 1 - Jet nebulizer in-line with the CPAP, Design 2 - Ultrasonic nebulizer with one-way valve, and Design 3 - Ultrasonic nebulizer with flow sensor, each of which will be described in detail in the following sections. The advantages and disadvantages of each design option are discussed, with particular emphasis on the efficacy, safety, and feasibility of the design, as well as cost, ease of use, patient comfort, and compatibility of the device at being adapted to different current CPAP devices in different settings. Each of these categories was given a relative weight depending on

the importance of the criteria and each of the three designs was ranked in each category. The rankings for each device are documented in Appendix B. Based on its score for relevant criteria, the design that was chosen for prototyping was Design 3 for an ultrasonic nebulizer with a flow sensor. Designs 1 and 2 will still be discussed as alternative design options.

Alternative Design 1: Jet Nebulizer In-Line with CPAP

The first alternative design utilized a jet nebulizer added directly to the main CPAP flow. As previously mentioned, the jet nebulizer uses an air compressor as a pressure source, and the medication is expelled from the nebulizer reservoir via a nozzle driven by the pressure source. As seen by Figure 9, the jet nebulizer flow is directly injected into the CPAP flow, where the liquid droplets from the nebulizer can be picked up and carried to the patient.

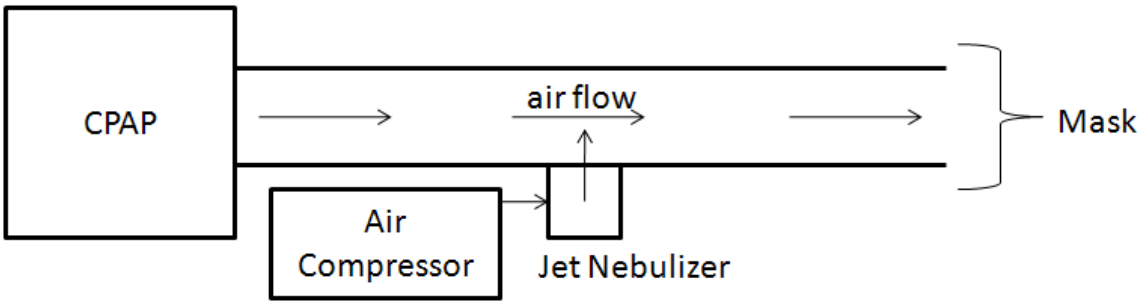

Figure 9. Jet Nebulizer in-line with CPAP.

The jet nebulizer design is simple and inexpensive. The nebulizer nozzle can be easily fitted into the main CPAP line. Jet nebulizers are the most common form of aerosolized drug delivery systems, so they are readily available. The abundance of jet nebulizers also affords them to be disposable if necessary. However, despite its advantages, the jet nebulizer design has a number of flaws.

Adding a jet nebulizer in-line to CPAP flow has been known to cause problems. The CPAP machine relies on a pressure sensor to determine when to increase or decrease its pressure supply to the patient. When the flow from the nebulizer is added to the flow from the CPAP machine, the additional pressure disrupts the sensor's readings. Also, air compressors are very noisy. This design will be put to use on a sleeping subject, and the noise from the air compressor

would likely prevent sleep or cause intermittent interruptions. The flaws of this design outweighed the advantages, so the jet nebulizer design was not pursued.

Alternative Design 2: Ultrasonic Nebulizer with One-Way Valve

The second alternative design uses an ultrasonic nebulizer instead of a jet nebulizer, as shown in Figure 10. Unlike the jet nebulizer, the ultrasonic nebulizer needs no external pressure source. The aerosolized drug is simply emitted into a side chamber, where the CPAP flow picks it up and brings it to the patient. The one-way valve prevents backflow from carrying the drug backwards into the CPAP machine during exhalation. A data acquisition (DAQ) device can be used to operate the nebulizer via a program. The program would be run on a PC with a graphical user interface for convenience.

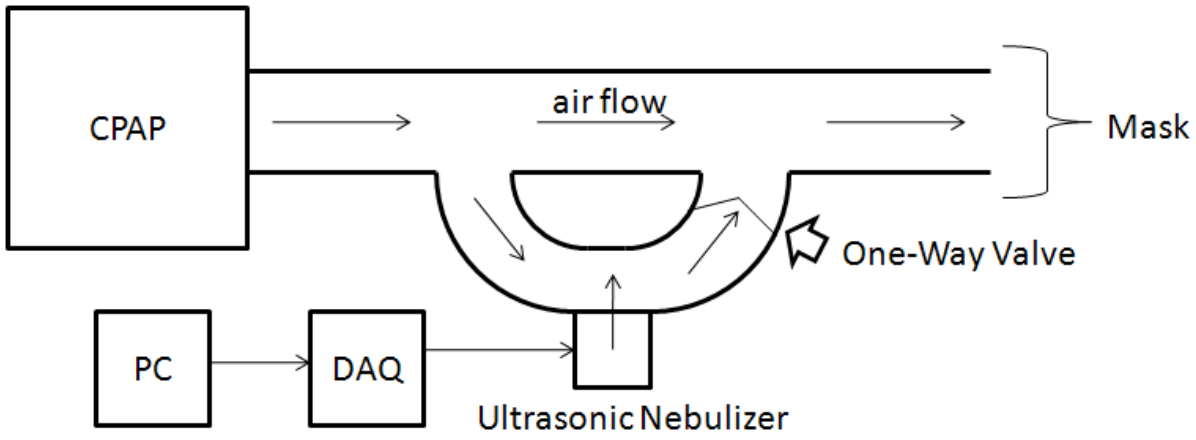

Figure 10. Ultrasonic Nebulizer with One-Way Valve Design.

A strong advantage to this system is the presence of a one-way valve as a safeguard. With the valve in place, the nebulizer can run constantly during drug administration without wasting drug during exhalation. Dosages can be customized by turning the nebulizer on intermittently as controlled by the program. Another advantage to this system is that ultrasonic nebulizers are virtually silent, which is ideal for a system intended for sleep use.

One disadvantage is the uncertainty of effectiveness for this system. A previously mentioned advantage was the fact that the nebulizer can be constantly running without drug being driven back into the CPAP machine during exhalation. However, the drug will hover

suspended above the nebulizer for some time while the patient is exhaling. If the drug is suspended long enough, it might simply re-condense and fall back into the nebulizer before being inhaled by the patient. The one-way valve system was not chosen for this reason, but the problem of a constantly running nebulizer was taken into consideration for the final design.

Final Design

Figure 11 shows a block diagram of the final design for the aerosolized drug delivery system. The individual components of the system, as well as how they work together, are explained in the following subsections.

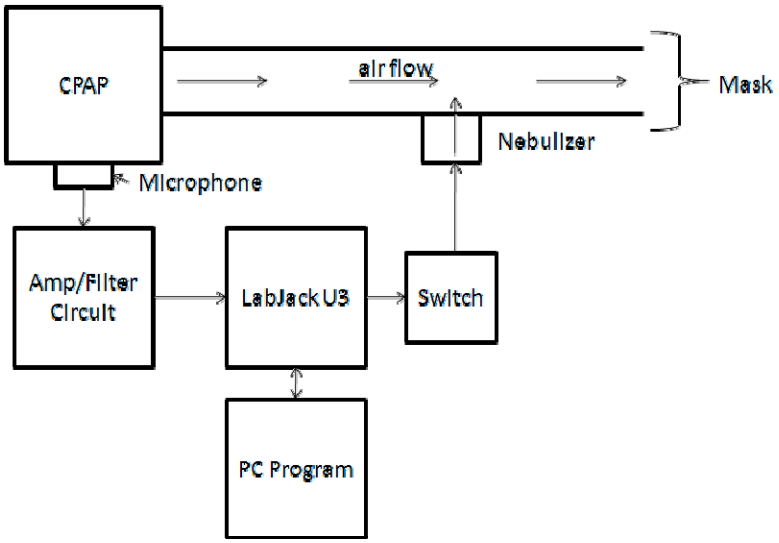

Figure 11. Block diagram of final design.

Mechanical Design

Continuous Positive Airway Pressure Device (CPAP)

The drug delivery system has been designed to work with any commercially available CPAP device. The CPAP used to test our system is a REMstarPro M Series (Model #400M) from Respironics. This CPAP was set to output a pressure of 5 cmH_2O (490 Pa) with a volumetric flow rate of 8.5 L/min.

As requested by the client, the drug delivery system has been designed for use with conditioned air. The most comfortable and successful CPAP devices incorporate a humidifier into their design, thus preventing a patient's mucosa from drying out during sleep. The REMstar Pro has a variable humidifier with five adjustable settings for added clinician control. The humidifier operates as a simple heater, heating a water tank and humidifying the CPAP's output to nearly 100% RH. This presents a challenge when delivering aerosolized drugs. Most aerosols are delivered via powder metered dose inhalers. However, this powder is not compatible with the level of humidity seen in a humidified CPAP circuit. It is therefore desirable to have the drug in liquid form, and to form the aerosol via a nebulizer.

Ultrasonic Nebulizer

An ultrasonic nebulizer was selected for the aerosolized drug delivery system. This is because of the advantages in efficiency and compatibility with sleep experiments afforded by the ultrasonic nebulizer, since the ultrasonic method of atomization creates more uniform droplets and is silent so as not to interfere with the sleep cycle. The piezoelectric component and piezoelectric control board were taken from a Honeywell HUT-102M Cool Moisture Humidifier. While the workings of an ultrasonic humidifier and an ultrasonic nebulizer are not identical, the principle is the same; both use ultrasonic waves to break the surface tension of the liquid and both are capable of creating therapeutically sized droplets. The nebulizer used for this project vibrates at 1.7 MHz, generating an aerosol with droplets of approximately 5 μm in diameter (Hickey 1996).

The Honeywell HUT-102M Cool Moisture Humidifier has several extraneous features that are necessary to incorporate into our design in order to ensure proper function. First is an adjustable piezoelectric component. In the operation of a humidifier, the consumer often desires the option to control the rate of humidification and the degree to which the air is humidified. As such, the Honeywell HUT-102M Cool Moisture Humidifier incorporates a dial that controls the amplitude of the piezoelectric element's vibration, the idea being that the larger the amplitude of vibration, the more aerosol created. The control of amplitude is accomplished through controlling the voltage used to stimulate the piezoelectric element, as the more voltage applied to a piezoelectric material will yield more deformation (Callister, 2006). This affects the final

design by giving the operator of the aerosolized drug delivery system more control over the rate of drug delivery.

The Honeywell HUT-102M Cool Moisture Humidifier also incorporates a magnetic switch to control the water level within the system. A circular magnet floats on a shaft in the bulk fluid; when the fluid level gets too low, the switch closes and the nebulizer shuts off. This is a necessary component to the humidifier, as the circuit for the piezoelectric element relies on the added resistance of the water to operate. Without any liquid, the piezoelectric element will overheat and no longer work properly. In the prototype of the system, the bulk fluid volume is too low to incorporate this element as a protective measure. Bypassing the switch has proven difficult. It has therefore been locked in the on position, with the hope of incorporating it into a later design.

The piezoelectric element of the Honeywell HUT-102M Cool Moisture Humidifier, along with creating a therapeutic aerosol, creates large droplets (2 to 3 mm in diameter) that are above the therapeutic size . This is a common characteristic of any nebulizer system, and must be dealt with to avoid losing a large volume of solution. The current design incorporates a sloped roof on the drug reservoir to account for splashing, allowing oversized droplets to return to the bulk solution as well as insuring retention of aerosol that has recombined due to contact with the splashed fluid.

Drug Reservoir

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 12.

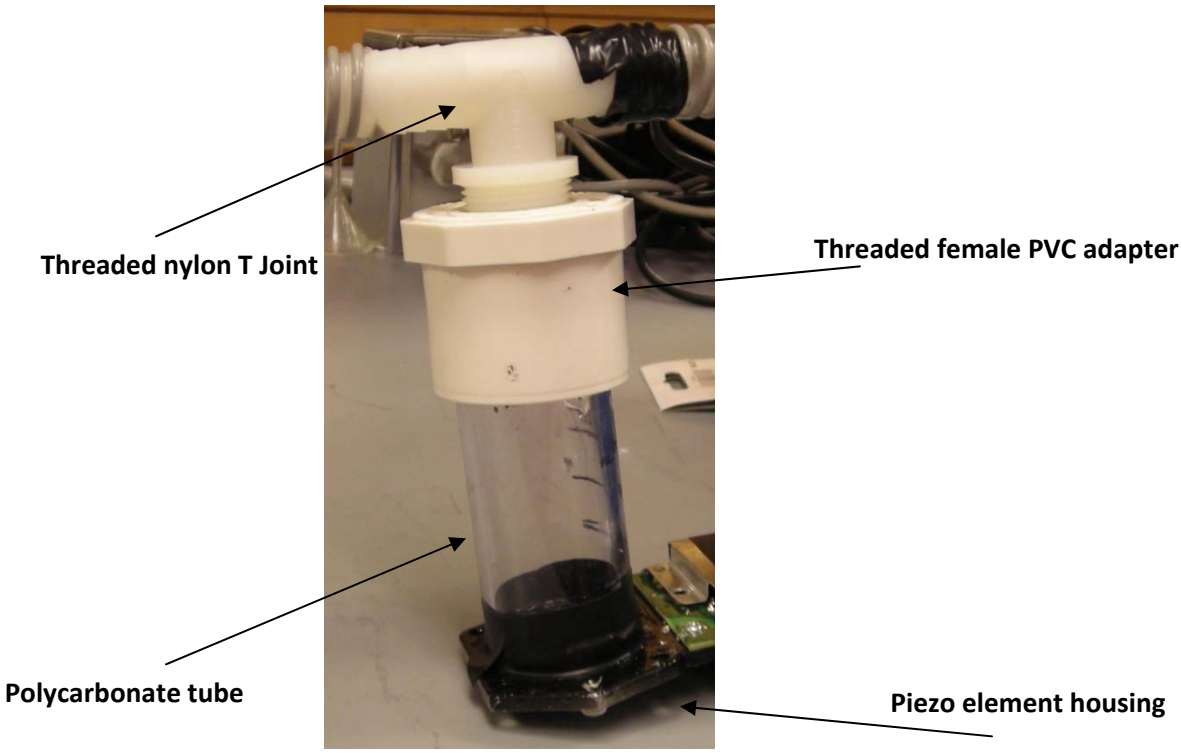

Figure 12. Nebulizer with drug reservoir. Full nebulizer control board not shown

Currently, the system is designed to have a maximum of 40 mL of liquid solution, or at most 6 doses of 3 mL of albuterol diluted with water at a 1:1 ratio. Polycarbonate was chosen because it is cost effective, bio-inert (contains no chlorides or other species that will leach into solution and illicit an adverse reaction in a biological system), and allows for accurate measurements of liquid drug in the system. The epoxy was used because it can generate a leak-proof seal and produce a strong bond between the materials in question. The epoxy, however, is not biocompatible; in fact, this particular epoxy is inflammatory to the respiratory system. The current prototype is being used for testing purposes only, and any final design that may go to clinical trials will have seals that are clinically safe and biocompatible.

CPAP Airflow

The nebulizer unit and reservoir is designed to interface with the standard CPAP tubing for the REMstar Pro. This tubing is flexible with a slight corrugation and inner diameter of 14.35 mm. When combined with the CPAP at the default settings, the air in the system has a Reynolds number of 453, indicating laminar flow in the system (Appendix C). The corrugations

in tubing will add turbulence to the system; however, the correlation observed in the figure in Appendix C shows that the tube radius must decrease dramatically in order to have turbulent flow at the current CPAP output, and the turbulence introduced by the corrugation is small. In order to eliminate this turbulence, a future design may incorporate a smooth, flexible tube of an inner diameter above 6.2 mm.

The biggest obstacle in designing an aerosol delivery system is transport of the mist from the point of generation (the nebulizer) into the patient's lungs. Any system designed to transport an aerosol will have losses within the system. Losses in our system will occur in three areas: the tubing between the CPAP and the patient mask, within the patient mask, and in the patient's airway before reaching the lungs. Losses in the mask can be considered negligible if the aerosol is delivered during inhalation, and deposition models exist for aerosol entering an airway, allowing us to predict the amount of drug that will be available to the body based on how much is delivered to the mask (Hickey 1996, Franca et al. 2006). The task becomes more difficult when transporting the aerosol from the nebulizer to the mask. Peak efficiency is achieved in a mechanically ventilated system when the ultrasonic nebulizer is placed in a Y joint with the mask (Dhand 2004). However, the mechanically ventilated model does not allow for patient movement, as mechanically ventilated patients are generally unable to rotate. This is not compatible with a sleep study; the ultrasonic nebulizer must be fixed in an upright position to maintain function and the patient is allowed to turn and twist during sleep. If a device *were* designed to maintain a vertical nebulizer close to the CPAP mask, such a system would likely be bulky and uncomfortable for the patient, and would interfere with the individual's sleep. Thus, the nebulizer must be placed in the proximal portion of the circuit, near the CPAP and far from the patient as seen in Figure 13.

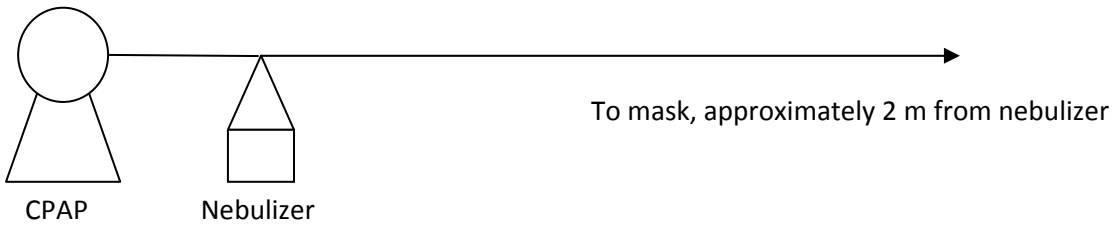

Figure 13. CPAP flow schematic. CPAP and nebulizer are approximately 0.1 m apart.

The proximal location of the CPAP creates an aerosol loss problem for the drug delivery system, primarily through deposition on the walls. Spontaneous recombination of aerosol droplets has not been observed, and is likely not thermodynamically favorable. The existence of theoretical laminar flow in the system enables accurate modeling of the flow within the system to obtain an estimate of the amount of aerosol that reaches the mask (in terms of adjustable parameters). A relevant model can be found in Ingham (1975). Currently, the medication delivery system is not optimized beyond establishing laminar flow (turbulent flow would result in random aerosol motion within a given plane and increase the likelihood of contact with the walls, creating a less efficient system). Future designs will optimize the flow system to allow for the maximum amount of aerosol to reach the patient.

Electronics and Program

The electronics and programming parts of the design operate on the principle of control. The overall goal of the project is the ability to control drug dosage delivery and timing in conjunction with a CPAP machine. When completed, the program should have an interface that specifies the amount of drug being delivered, the pattern of drug delivery, and the times at which the drug will be delivered. Steps have been made to reach this goal, but more progress is needed.

To control drug delivery, the breathing cycle should first be monitored. Then, the nebulizer can be programmed to turn on or off based on the estimated breathing cycle of the subject. This will ensure the maximum amount of drug will be delivered to the patient and the minimum amount will be wasted. For the final design, a simple microphone was used to determine the breathing rate of the subject. The microphone was attached externally near the fan of the CPAP machine. When the subject inhaled, the fan turned on and produced an audible output. When the subject exhaled, the fan turned off, but some of the exhaled air from the subject escaped through the fan port, creating another audible output. After being amplified and filtered, this yielded a waveform that indicated when the subject breathed in and out (Figure 14). The first large spike for every cycle indicated inhalation; the second large spike indicated exhalation. This waveform can then be sent to the DAQ device to be processed by a computer program.

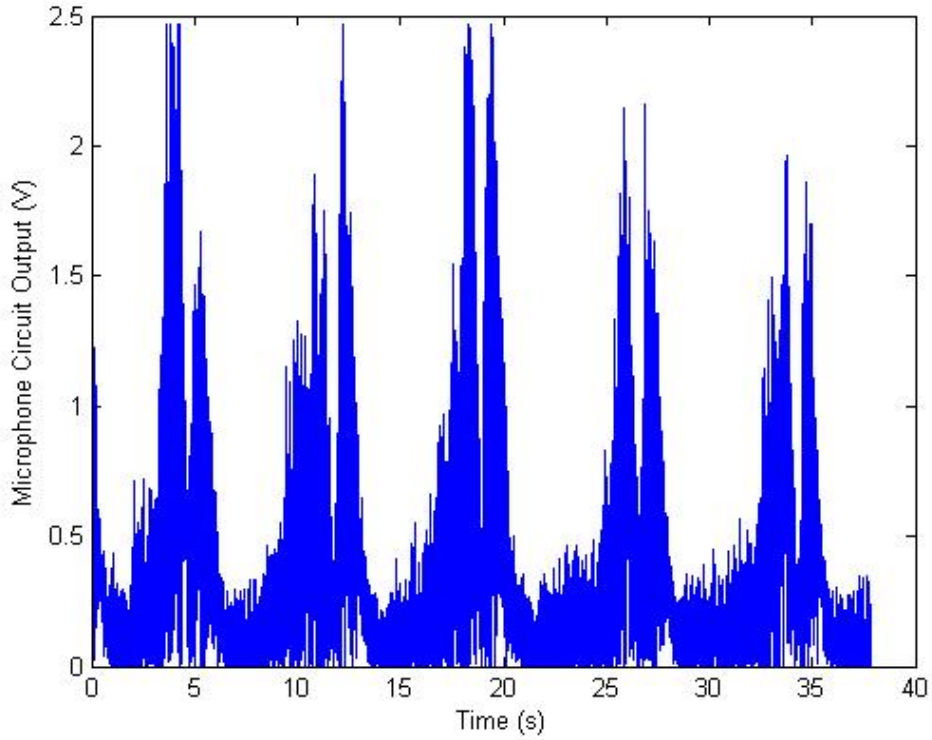

Figure 14. Breathing Cycle Waveform from Microphone.

Once the program has decided to activate the nebulizer, it instructs the DAQ device to turn the nebulizer on. This surprisingly complex process uses many components, starting with the DAQ device itself.

The DAQ device used for this project was the LabJack U3, made by the LabJack Corporation. Priced at $108, it is a cheap and effective solution for signal acquisition and manipulation. It operates completely through a USB port and can be programmed using several languages. For this project, LabVIEW from National Instruments was used to operate the LabJack U3. Its analog input ports can accurately read signals from 0 to 2.5 V. It has eight digital I/O ports with a high rail at 3.3 V (LabJack Corp). One of these ports was used as a digital output. When the program decided to turn the nebulizer on, the digital output port was set to 3.3 V. Unfortunately, because the device is completely powered through USB, it has very limited power. To combat this disadvantage, a switch network was developed.

The switch network responds to a digital input from the LabJack U3 with the sole purpose of activating the ultrasonic nebulizer. It consists of an external power supply, a transistor circuit, and a power relay acting as a voltage-controlled switch. The switch network is shown in Figure 15. Since the LabJack U3 cannot supply enough power to activate the power relay, a TIP 41 bipolar junction transistor (BJT) was used as a switch for the power relay. LabJack supplies 3.3 V through its digital output (D01), which activates the BJT and turns on the power relay. The power relay was connected so that it activates the ultrasonic nebulizer when turned on.

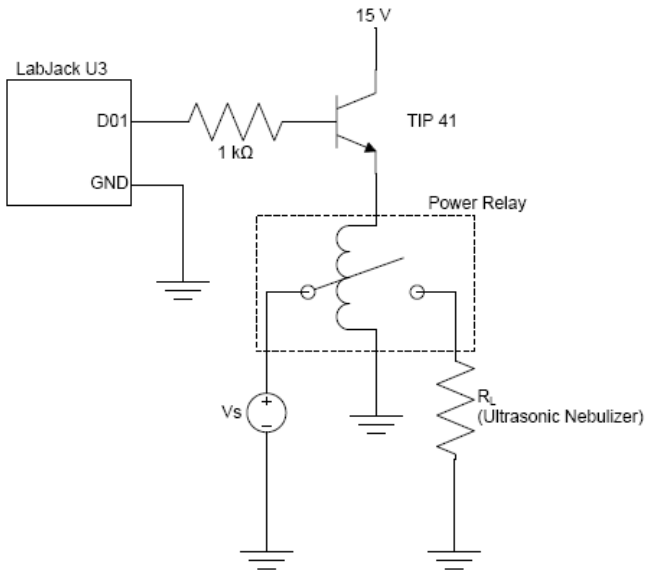

Figure 15. Switch Network.

Testing

The goal of the first set of device testing experiments was to establish the existence of albuterol in the aerosol created by the nebulizer to verify the ability of the nebulizer to aerosolize albuterol. This 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 tested for absorbance in a Carly 300 Conc Visible-UV spectrophotometer at 296 nm. Absorbances were adjusted for a baseline reading of 0.334 for

normal saline. The data was combined to create a standard albuterol absorbance curve, seen in Figure 16.

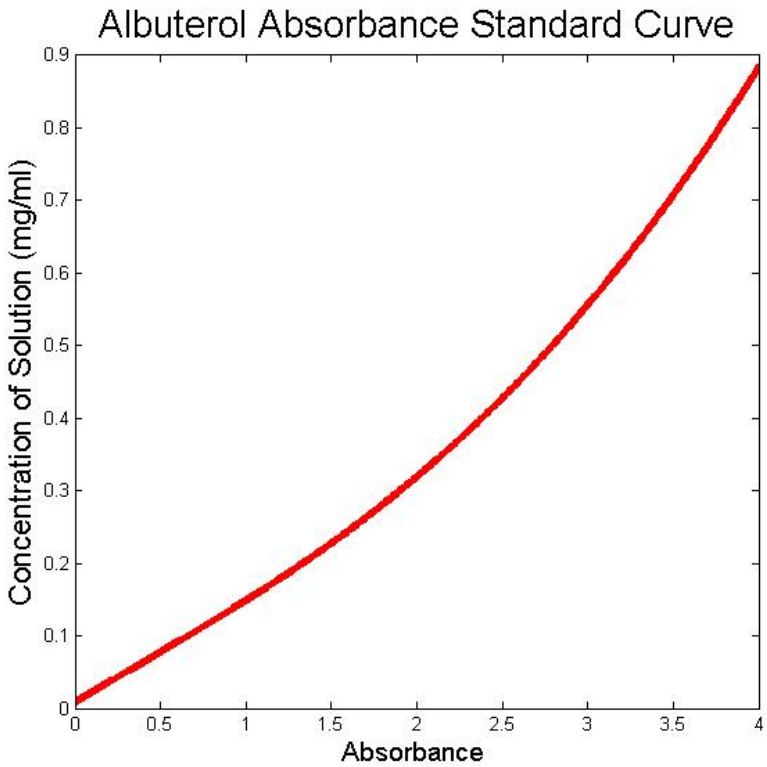

Figure 16: Standard absorbance curve for albuterol. Curve adjusted for baseline absorbance from solvent.

Next, a solution of 5 mg/40 mL albuterol was prepared. This drug solution was aerosolized, with samples measured every 5 min for 30 min. The concentration of albuterol in the system was calculated using the standard curve in Figure 16 and compared to the theoretical concentration of albuterol if no drug had been atomized; this comparison can be seen in Figure 17.

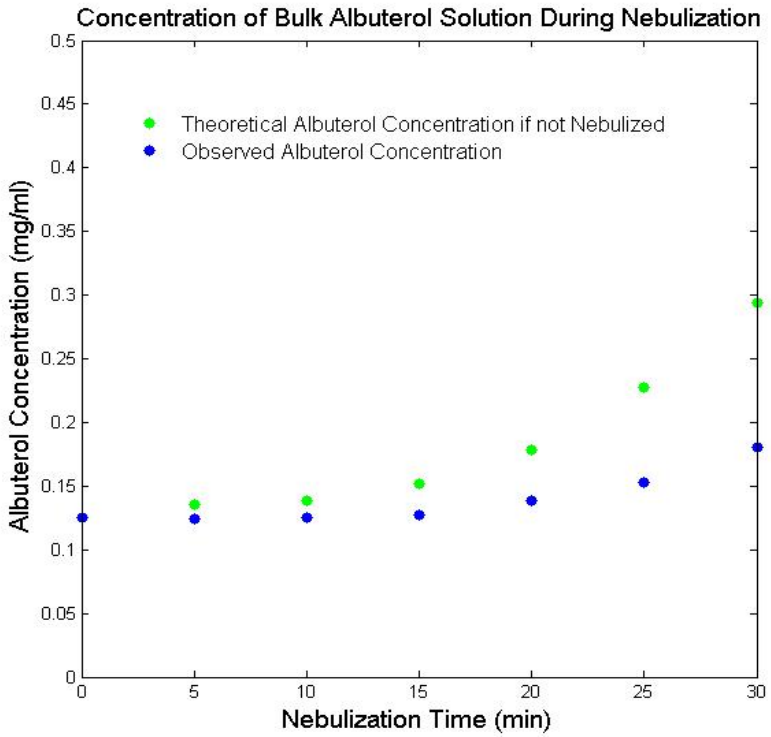

Figure 17: Concentration of bulk albuterol solution during nebulization. Green dots are the theoretical concentration if no albuterol leaves the solution, and blue dots are the observed concentration

Figure 17 shows a difference between the measured and theoretical concentrations of albuterol, indicating that our system is capable of aerosolizing albuterol. However, due to a shortage of supplies, a statistical difference between the two has yet to be proven.

Ethical Considerations

One of the most essential tests that must be run with any drug delivery system involves measuring the efficacy of the drug that is delivered in the system. In order to test the effect of the delivered albuterol of our system, lung function for a person using our system should be tested before, during, and after use. This involves getting consent from the individual and taking every possible precaution to insure the person is not harmed by our device. Currently, we cannot ethically test our device on people, due to the chance of respiratory inflammation from the adhesives used in the drug reservoir. Testing will be possible after this issue is fixed and we receive approval to test the device on humans. Until that time, we can assume the drug remains

clinically active in our system due to results obtained by others using similar nebulizers and delivery systems (Hickey, 1996).

Future Work

While significant progress has been accomplished toward the design of the aerosolized medication delivery system using the CPAP, further work remains to achieve optimization of all of the desired features and functionality of the final device.

The nebulizer system must be redesigned to eliminate losses due to splashing. This will be accomplished by redesigning the drug reservoir to create a reservoir cover that stretches its volume horizontally, rather than the vertical volume placement currently employed, returning splashed liquid back into the bulk fluid. This design will hold two major benefits. First, it will eliminate losses due to splashing, as bulk fluid kicked up by the nebulizer will not travel far enough to leave the reservoir. Secondly, the nebulizer will now create aerosol directly into the airstream, rather than relying on mixing as the current system does. This will help improve efficiency by increasing the amount of aerosol in the system at a given time as well as eliminate turbulence created by the T joint.

The medication delivery system must be optimized in order to ensure we deliver the proper volume of aerosol at a given time. This will involve using literature and generated models to predict the amount of aerosol reaching the mask and lungs, verifying these models, and redesigning the system to obtain optimal drug delivery. It must be kept in mind that the model in Ingham (1975) is not perfect and will likely need to be altered to fit our system.

Finally, the microphone control system must be implemented and tested. Currently, only the waveform and circuitry for the microphone control have been successfully implemented. LabVIEW code must be written to interpret this waveform and provide control to the circuit. The control will take into account both the airflow and the breathing pattern, so this step cannot be fully completed until the new reservoir is built and the system is optimized.

Ideally, this future work will be completed during the course of the following semester, during BME 402 in Spring 2010.

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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
- Compatible with albuterol
- 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

Cost – Additional components beyond to be integrated with CPAP should not exceed $500.

Drug Types – Albuterol, with compatibility with other inhalation aerosols

Drug Delivery – Appropriate dose of aerosolized drug should be deliverable either in intervals or continuously. Amount of drug used will have to be compensated for depending on how efficiently the aerosolized drug can make it from the nebulizer to the patient's lungs.

Durability – Modified component should, with proper maintenance, should be usable for six months without need for replacement.

Ergonomics – Must be comfortable, quiet, and not interfere with the patient's sleep.

Performance Requirements – Must not compromise the normal function of the CPAP or efficacy of drug. Normal functioning of aerosolized drug should take place during use of CPAP. Atomization should be timed to correspond with the patient's inhalation, so that minimal drug is wasted.

Safety – The device must deliver a safe, measurable dose of drug with no contaminants introduced by the delivery system

Size/ Weight – Modification to CPAP device should not weigh more than 1 kg and should not protrude from original device more than 10 cm.

Targeted Users - Adults (18+) with sleep apnea or other respiratory disorder

Usage Time/ Frequency – Device should be made to work for nightly 8 h intervals.

Maintenance – A marketable design should require less than 10 min of maintenance by the patient on a daily basis. Maintenance by a specialist should be necessary no more than twice a month.

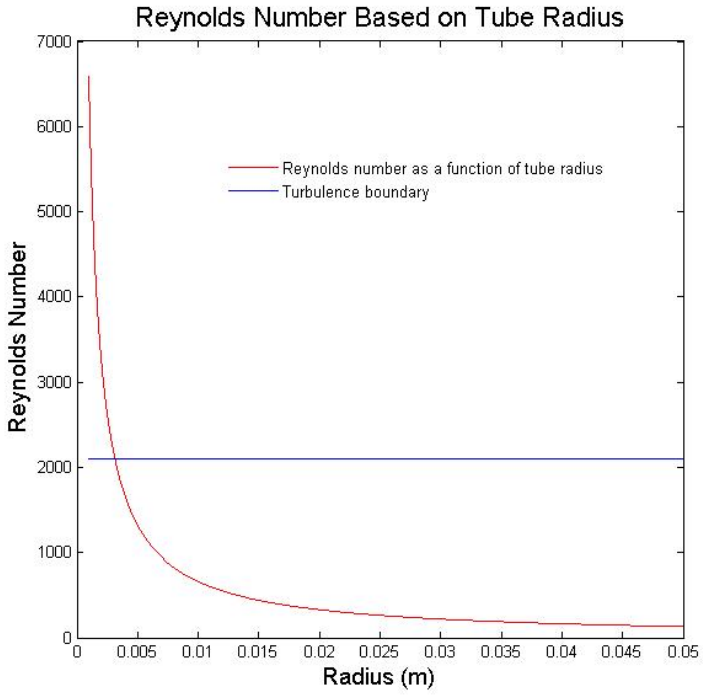
Usage Environment – Used by patient in patient's home or at a hospital.

Appendix B – Design Matrix

	Efficacy (25)	Safety (20)	Compatibility/Feasibility (20)	Patient Comfort (20)	Ease of Use (10)	Cost (5)	Total (100)
Jet Nebulizer	15	20	15	0	5	5	70
Ultrasonic One-Way Valve	20	15	20	20	10	4	89
Ultrasonic Flow Sensor	25	15	18	20	10	3	91

The design matrix for this project shows an emphasis on product efficacy, safety, compatibility and comfort for the patient. The ultrasonic flow sensor was the design we chose to pursue. This design was determined to be the most efficient, as it provided the most control over the nebulizer in terms of synchronization. It lost some points in safety due to heat issues with the nebulizer. These are eliminated in the final design by placing the nebulizer far from the patient. The design was determined to be feasible after we were able to show a breathing waveform using a simple microphone circuit (Figure 15).

Appendix C – Reynolds Number Plot



The graph shows Reynolds number as a function of tube radius. The red line is Reynolds number, and the blue line is 2100, the accepted boundary between turbulent and laminar flow (Bird et al. 2007). The Reynolds number calculation described in Bird et al. (2007) was modified for this specific CPAP device to generate the Reynolds number function.

Appendix D – Budget

Dr. Teodorescu did not specify a limit for the cost of prototype construction, so an arbitrary limit was set of $500 total. This value seemed reasonable since the cost of a new CPAP machine can be upwards of $649.00 (Respironics, 2009) and a Respironics REMstarPro M Series (Model #400M) CPAP device was donated to the project at no cost. At the end of one semester's work, a total of $224.68 has been spent on the CPAP drug delivery device, as documented in Table 1. While work still needs to be done to fulfill the requirements in the PDS it can be estimated that the total cost of the future work to the final prototype will not exceed the $500 total limit. The cost of the prototype will likely be significantly greater than the cost of

manufacturing the final device due to experimentation with the prototype device and discounts on bulk components when manufacturing more than one final device.

Table 1: Cost of Prototype Construction

Item	Vendor	Purpose	Cost
Ultrasonic Humidifier	Wal-Mart	For ultrasonic piezoelectric component	$30.56
Ultrasonic Humidifier	Home Depot	To replace broken piezoelectric component from first ultrasonic humidifier	$31.64
PVC pipe fittings/ piping	ACE Hardware	For connection of piezoelectric component to the CPAP circuit	$6.50
DAQ Board	LabJack	For processing of signals to and from microphone and piezoelectric component.	$111.99
Microphone	Radio Shack	Detection of CPAP flow and subject's breathing for more efficient use of Albuterol.	$4.00
DC Voltage Adapter	Prime Electronic components	To provide the required power to the DAQ board / microphone	$11.83
PC tubing 1.25" I.D.	McMaster-Carr	To serve as a clear reservoir to hold liquid to be aerosolized	$9.87
Pipe Fittings	McMaster-Carr	To replace PVC pipe fittings purchased earlier with something less bulky.	$14.14
120 V Switch	DigiKey	Will switch power to piezoelectric component on and off to control nebulization amount	$4.15
CPAP unit	UW-Hospital	Used to test feasibility of prototype ideas	Donated
Albuterol Nebulizer Doses	UW-Hospital	Used to test feasibility of prototype ideas	Donated
Total			$224.68