Delivery of Inhaled Drugs through Continuous Positive Airway Pressure

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abstract

Treatment of concurrent diseases often involves the integration of multiple therapies. Our client treats individuals suffering from both obstructive sleep apnea and asthma with continuous positive airway pressure (CPAP) to prevent apneic episodes during sleep. To treat asthma symptoms that occur in the early morning hours, Dr. Teodorescu has proposed the design of a device capable of automated delivery of inhaled asthma medication in-line with the CPAP ventilation circuit. This semester began with background research on disease states, aerosolized medication delivery, and relevant technologies. Subsequent work included the design and production of a mechanical prototype capable of vibrating and actuating an asthma inhaler based on work accomplished by a previous design group. Finally, circuitry capable of detecting the onset of inhalation and initiating the sequence of events responsible for vibration and actuation was developed. The ultimate goal of this project will be a self-contained, automated device capable of fulfilling the client's requirements. Future development of the mechanical and electrical components of the design, including miniaturization and hardware-software integration, are planned for future semesters.

background + motivation

Obstructive Sleep Apnea

- Chronic airway blockage during sleep (Figure 1)
- **Primary cause**: airway muscle relaxation
- Cessation of breathing → brain attempts to increase airflow into the lungs, breathing effort increases
  > CO_2 levels increase, condition worsens exponentially until brain causes arousal from sleep

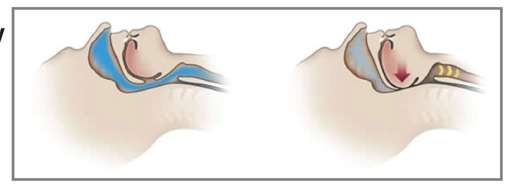


Figure 1. Illustrated effect of OSA on airway conformation: unobstructed breathing passage (left) becomes fully obstructed (right) due to the relaxation of muscles controlling anatomy in the nasal/oral cavities (fusionsleep.com).

CPAP= Continuous Positive Airway Pressure

- Treats sleep apnea using air as a stent to sustain open airway
- Constant pressure prescribed according to patient's needs
- Air compressed in CPAP machine flows through tubing, forced into airway + lungs of patient

Metered-dose inhalers

- Deliver fixed volume of active ingredients to alveoli w/ assistance of propellant
- Specialized mouthpiece facilitates actuation + direction of drug distribution (Figure 2)

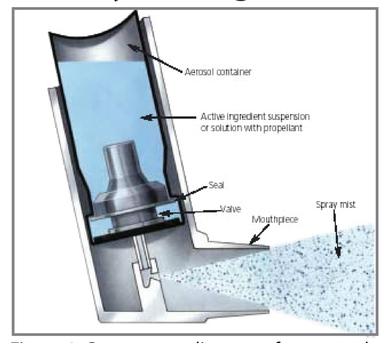


Figure 2. Component diagram of a metered dose inhaler (MDI) indicating location of seal, valve, mouthpiece, and solution of active ingredients within canister (solvay-fluor.com).

Aerosolized medication

- Long-acting beta 2-adrenergic agonist (LABA) coupled with corticosteroid
  > **LABA**: Bronchodilation (relaxation of smooth muscle lining airways)
  > **Corticosteroid**: Down-regulation of proinflammatory molecules, up-regulation of proteins that inhibit inflammatory responses

Drug delivery (aerosol)

- **Physiological factors**:
  > Breathing cycle, mechanism and severity of airway obstruction
- **Particle factors**:
  > Size, target site, formulation/composition
- **Equipment factors**:
  > Humidity, use of holding chamber/spacer (Figure 3), proximity to mask
- **CPAP factors**:
  > Current research is contradictory

Figure 3. Photograph of an example holding chamber for use with an MDI (aafa.org).

design criteria

- Agitate MDI to mix drug and propellant at specified time
- Detect breathing pattern to coordinate drug delivery with onset of inhalation
  > Incorporate sensor with full face mask (Figure 4) rather than common nasal mask (maximize oral delivery of drug)
- Deliver aerosolized drug through existing tubing
  > Utilize flow generated by machine (bidirectional in-line MDI adapter)
- Depress inhaler to deliver one or more doses during sleep
- Size, weight, and noise levels appropriate for in-home use
- Accessibility: minimal dexterity required during patient interaction (replacement of inhaler canisters)

Figure 4. Full face CPAP mask w/ mouth (black arrow) + nose (red arrow) ports (cpapplus.com).

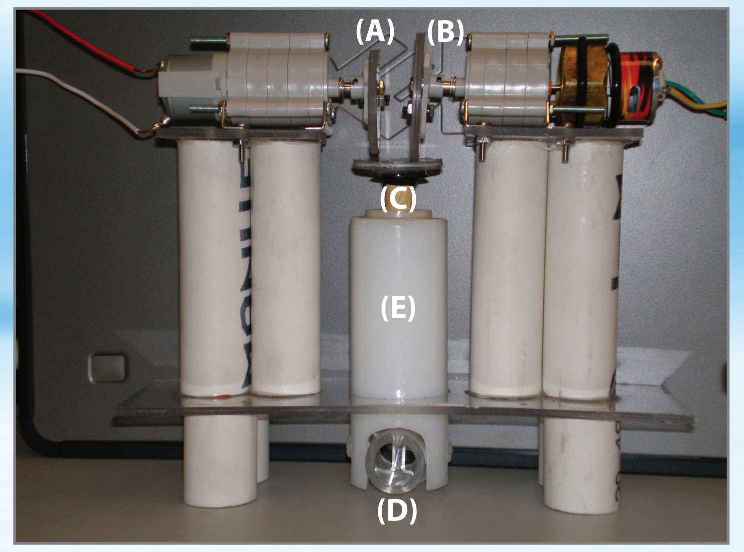


Figure 5. Photograph of current mechanical prototype: vibration cam (A), actuation cam (B), plunger (C), in-line MDI actuator (D), tube (E).

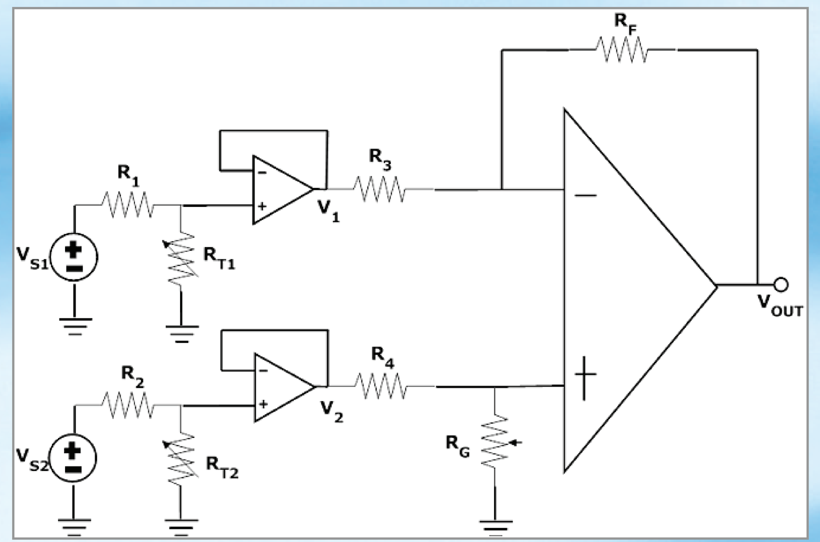


Figure 6. Diagram of differential amplifier circuit: R_{T1}, R_{T2} correspond to thermistors (R_{T2}: room temperature, R_{T1}: exhalation); R_3, R_4 ~4 kΩ; R_F, R_G ~ 80 kΩ. V_{S1} and V_{S2} ~ 5 V, all op amps powered by +/- 12 V.

final design

Mechanical Device

- *Used Spring 2004 group project concept of rotating cams (Quinn et al. 2004)*
  > Smaller diameter **agitation cam** shakes canister
  > Larger diameter **actuation cam** depresses canister for drug release
- Design modified to reduce size and allow for replacement of inhaler canister by patient (Figure 5)
- Energy calculations performed to define displacement + speed of shaking required

- **2 separate motors** drive individual cams
  > Agitation cam: 10,500 rpm w/ gear ratio of 64:1 powered by (2) AA batteries
  > Actuation cam: 20,000 rpm w/ gear ratio of 125:1 powered by (1) 9V battery

- **Spring constant** of 4.75 lb/in used to counteract cam force
  > Permits agitation + returns canister to original position

- **Tube** w/ 0.90 in. ID ensures vertical canister movement
  > Custom milled at one end to allow for in-line actuator removal + canister replacement

Circuitry

Purpose:

- Power on shaker motor @ 4:00 am for 10 seconds
- Detect inhalation + exhalation by sensing fluctuation in temperature of air leaving mouth port of mask
- Power on actuation motor to deliver drug at onset of inhalation

Thermistor Circuit: (Figure 6)

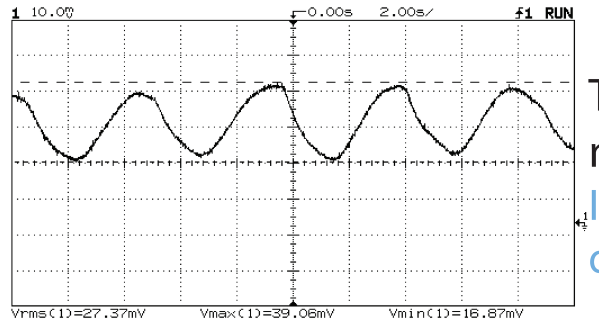
- Uses difference amplifier to minimize effect of room temperature variation and introduce gain of ~20 (V_{in} in mV, V_{out} in V)

LabVIEW program:

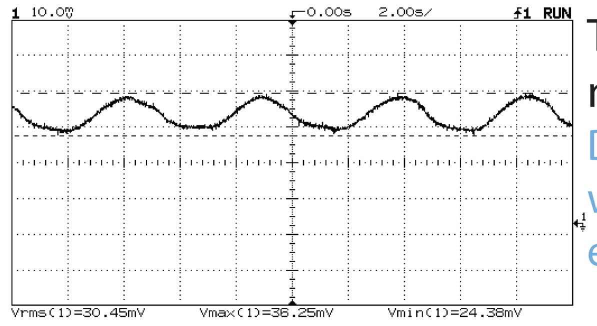
Software solution/signal processing necessary (see Testing)

- Turns on shaker motor at 4:00 am for 10 seconds
  > Calculates period of voltage signal
- Powers on actuation motor after time delay
  > Delay (equals period minus lag time) follows detection of a voltage maximum
  > Lag time = delay b/t powering of motor + actuation

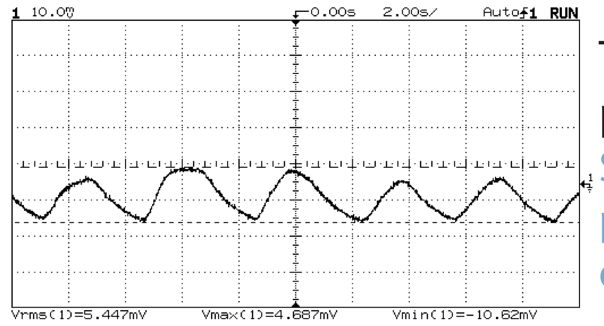
testing



Trace 1: No CPAP, sensor at mouth port
Increased amplitude, well-defined peaks



Trace 2: No CPAP, sensor at nasal leak ports
Decreased amplitude, peaks less well-defined, possible delay b/t exhalation and sensing



Trace 3: CPAP, sensor at mouth port
Slightly decreased amplitude, peaks less well-defined, downward shift of waveform

- Local maxima on output voltage of thermistor correspond to transition from exhalation to inhalation
- Sensor located at mouth port produces larger, more well-defined signal w/ negligible delay b/t exhalation + thermistor response
- Variation in peak voltage from breath to breath and between individuals necessitates signal processing

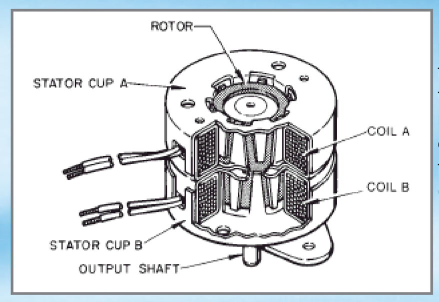


Figure 7. Diagram of stepper motor proposed for future mechanical prototype development to reduce error resulting from drift of cam location following each use (engineersedge.com).

future work

- Test drug delivery at varying time intervals after shaking to determine if user can shake inhaler before going to bed
- Incorporate stepper motor (Figure 7) to ensure each use involves one complete rotation of cam
- Miniaturize mechanical cam device for placement on "helmet"
- Develop bite plate through which drug travels directly from inhaler to user's mouth (Figure 8)
- Further develop and test current LabVIEW program; program microcontroller to execute program
- Utilize relay or transformer to power on each motor when signaled by program

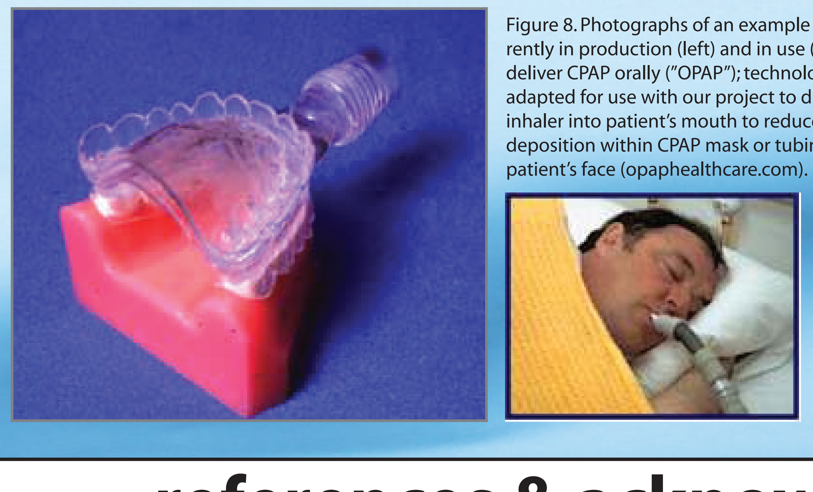


Figure 8. Photographs of an example bite plate currently in production (left) and in use (below) to deliver CPAP orally ("OPAP"); technology could be adapted for use with our project to direct spray of inhaler into patient's mouth to reduce risk of drug deposition within CPAP mask or tubing and on patient's face (opaphealthcare.com).

references & acknowledgments

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