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RESEARCH ARTICLE

Biomedical Engineering

Novel nebulizer design with adaptive flow regulation

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Abstract: Pharmaceutical therapy for certain respiratory diseases involves delivering aerosolized drugs directly to the respiratory tract through inhalation with nebulizers. This research is focused on designing an automated jet nebulizer that possesses the capability of dynamic flow regulation. The proposed nebulizer is composed of two modes, namely, the Compressed Air mode and the Oxygen Therapy mode. The automated triggering from one mode to another will be dependent upon the percentage of oxygen saturation of the patient, monitored from the SpO_2 sensor. The compressed airflow will be delivered to the patient according to his or her volumetric breathing rate, derived with the aid of a temperature sensor-based algorithm. The compressor circuitry is incorporated with a PID control unit, which is a novel feature that acts as feedback as well as a safety mechanism in ensuring that the patient receives compressed air as per the flow rate decided by the system. At the end of the drug delivery, if the liquid level sensor detects the absence of medication within the nebulizer chamber, the nebulization process will be terminated. The results obtained from simulations showed that the PID unit functioned smoothly, with less overshoot and response time. Thus, the dynamic regulation of the motor speed with respect to the volumetric breathing rates was accomplished. A laminar flow was obtained from the outlet of the compressor towards the nebulizer tubing, and a turbulent flow was obtained within the chamber, as expected. No excessive turbulent flows or rotational flow patterns were detected.

Keywords: Inhalation therapy, jet nebulizer, proportional integral derivative controller.

INTRODUCTION

A considerable percentage of people suffer from respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). As per WHO statistics, 235 million people are affected with asthma and 64 million people are affected with COPD, while millions of others suffer from other unidentified chronic respiratory diseases (Hubbard, 2006). Jet nebulizers which atomize medication are widely used in aerosolized inhalation therapy for such respiratory diseases.

The nebulizer is a device which functions by converting drugs which are in liquid form into a wet mist, more specifically, aerosols of a size that can be inhaled by the lower respiratory tract, with the aid of a driven compressed gas flow (Hess, 2000 ; Ari, 2014).

Despite the introduction of lightweight and portable devices like metered-dose inhalers and dry powder inhalers, the popularity of nebulizers has not diminished due to their simplicity and their ability to be frequently used in inhalation therapy for infants, small children, and the elderly (Clay, 1987 ; Rau & Hess, 2009). They are considered advantageous because they have the ability to aerosolize several drug solutions and drug mixtures, and can be useful in treating debilitated or distressed

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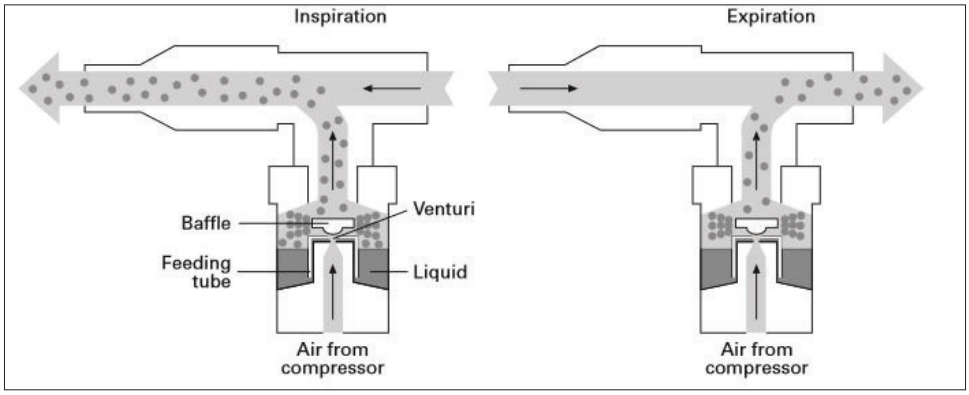

Figure 1: Conventional nebulizer design (O'Callaghan & Barry, 1997)

patients (Rau & Hess, 2009). However, most of the conventional nebulizers (Figure 1) fall short of desired preferences. One of the issues with the current nebulizers is the inadequate amount of aerosolized drugs delivered to the patient. According to several research reports (O'Callaghan & Barry, 1997; Chatburn & McPeck, 2007; Volsko & Chatburn, 2014), conventional nebulizers are considered highly inefficient due to the high wastage of aerosol.

The efficacy and the quality of the aerosol generated by a jet nebulizer are a product of the design of the device and the drug formulation (Bisgaard *et al*., 2014). It was mentioned that the driving gas flow rate, the ratio of liquid to gas flow, and the characteristics of the compressor have an impact on the size of the droplets produced by a nebulizer (Barry, 1997; Hess, 2000; O'Callaghan & Kendrick *et al*., 2014; Mittal *et al*., 2014). In addition to that, controlling the relative humidity within the airflow between the nebulization source and patient can be achieved by simply controlling the flow rates in the system (Haddrell *et al*., 2014). Furthermore, patient factors such as breathing rate also have an effect on drug delivery. In the case of a continuously operating compressor, a high fraction of the aerosol is lost to the atmosphere through the vent, if the patient doesn't inhale fast enough (Le Brun *et al*., 2014). Specifically, 50 % of the volume of aerosol generated is wasted during exhalation (O'Callaghan & Barry, 1997). Some consequences of neglecting the importance of delivering the prescribed dosage of the inhaled medication and, applying proper administration techniques using aerosol generators include adverse reactions, bronchospasm, and exposure to high drug concentrations. (Rau & Hess, 2009).

Yardimci (2014) has developed a micro controller based on a jet nebulizer, in which the compressor is controlled using the fuzzy logic system for domiciliary use. However, the inhalation profile, which is an important factor, hasn't been considered when regulating the compressor. Ivanova and Glazova (2015) have conducted research on enhancing the performance of the ultrasonic nebulizer, through the incorporation of an indicator that registers time, duration of an asthma attack, and dosage. The study has been limited to children who are suffering from bronchial asthma.

One of the reasons behind the inability of conventional devices to deliver the entire dosage, as mentioned in the literature, is the fact that the driving gas flow is unidirectional and constant in contrast to the breathing pattern, which is bidirectional and variable. In order to address these issues, the proposed research is specifically focused on the regulation of the dynamic flow of the compressor in sync with the inhalation profile of the patient. The proposed design employed the use of a digital temperature sensor for monitoring the respiration rate during nebulization. How the temperature sensors could be incorporated in detecting respiration rate was studied with the help of the conceptual model described by Gupta and Qudsi (2013). For the purpose of regulating the compressed air flow, the proposed research takes the approach of employing an Arduino-based proportional integral derivative (PID) control system. PID control is one of the most widely used dynamic control techniques in industrial applications (Paz, 2013). It involves the use of a feedback controller, which changes the output based on the sensed or observed result, as shown in Figure 2.

The process variable of a given setpoint is measured by the sensor, which in turn is compared to the setpoint (desired output), in order to determine the error. The error signal is used to determine the controller output, which is delivered to the actuator. The difference between the process variable and the setpoint is the error (Knospe, 2013). Here the integral time (T_i) and derivative time (T_d) refers to the time constants which are required to acquire the manipulated variable using the integral action and derivative action respectively.

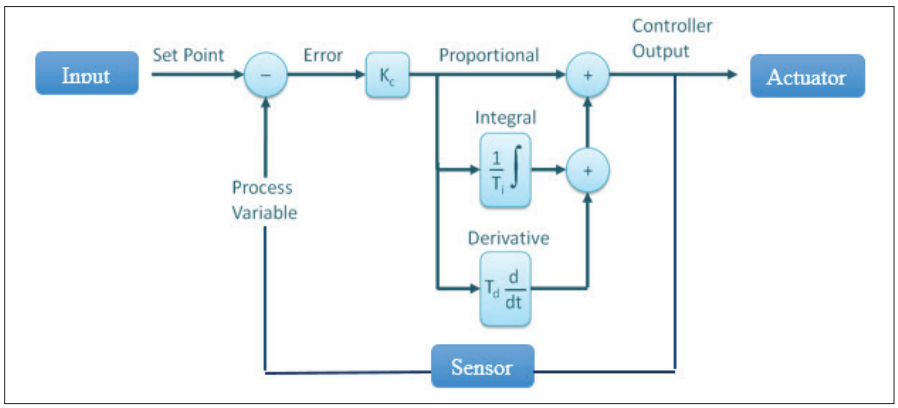

Figure 2: The schematic of a PID controller (Paz, 2013)

The present error is taken into account by the proportional term. The integral response takes all the errors, which are present in the system, from the starting point to a particular point of time in the process. The derivative response is proportional to the rate of change in process variable (Theopaga & Rizal, 2014).

MATERIALS AND METHODS

The approach and information gathering

After conducting market analysis on existing products, and a literature survey, the research problem was identified. Furthermore, information regarding nebulization was gathered during a visit to the National Hospital for Respiratory Diseases, located at Welisara.

The conceptual design and hardware components

The conceptual design (Figure 3) was done in such a way that there are two modes of operation, the compressed air Mode and oxygen therapy mode. The oxygen therapy mode is triggered, depending on the percentage of oxygen saturation of the patient being nebulized (94 % is the threshold). The temperature sensor monitors the temperature difference which occurs during inhalation and exhalation. Hence, the breathing count will be determined, which will be converted to a volumetric breathing rate. The SpO_2 circuit monitors the percentage of oxygen saturation of the arterial blood. An initial set flow rate will be given to the diaphragm pump through the controlling unit of the nebulizer. The airflow sensor monitors whether the diaphragm pump is operating at that given flow rate. The airflow sensor readings will be taken up by the controlling unit. If there is some error present between the desired flow rate and the sensed flow rate, it will be altered by the PID function through the variation of the voltage fed to the motor controller through pulse width modulation. This process continues only if the oxygen saturation percentage is within the required range. If the oxygen saturation percentage of the arterial blood of the patient decreases below the specified limit, the oxygen therapy mode is triggered. Triggering of the oxygen therapy mode will cause oxygen therapy to be delivered via the opening and closing of the specific solenoid valves which will be done through the controlling unit. The non-contact liquid level sensor monitors the level of the medication in liquid form. Once it detects that no liquid is present within the nebulizer chamber, the process of nebulization will be terminated.

The sensing elements used for nebulizer design include one wire DS18B20 temperature sensor for monitoring the temperature of inhaled air and exhaled air. It has the capability of reading temperatures to a resolution of 0.0625. In addition to that, the YF-S201

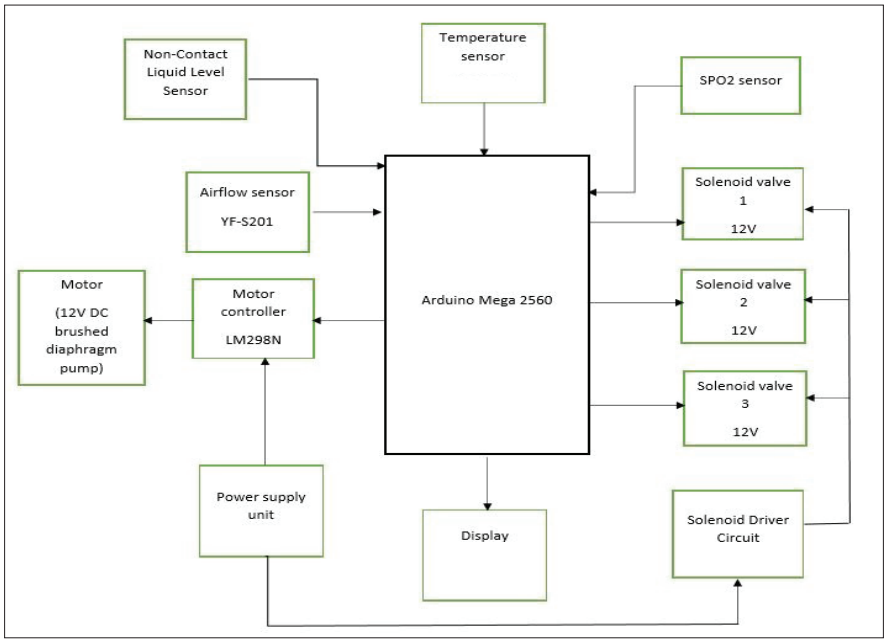

Figure 3: Conceptual design of the proposed nebulizer

airflow sensor was used for monitoring the compressed air flow rate. It consists of an integrated magnetic hall sensor which outputs an electrical pulse with every revolution. A non-contact liquid level sensor was used to achieve non-contact liquid level detection. The actuators used for the proposed nebulizer include a micro diaphragm pump (Figure 4), and an L298N motor controller. The micro diaphragm pump is composed of a DC brushed motor. The rotational movement of the motor is converted into oscillating movement by an eccentric. It is connected through a connecting rod to the diaphragm, which moves up and down its central point. The elastic diaphragm in conjunction with an inlet and outlet valve generates a pumping action. The particular pump can be mounted in any position and can deliver a flow rate of up to 11 L/min.

Figure 4: DC micro diaphragm pump

The Arduino Mega 2560 microcontroller reads the signals obtained from the relevant sensors, makes logical decisions such as comparing the sensed signals with the desired signals, and finally transmits the necessary PWM signals to the actuators.

Designing the 3D model of the nebulizer

The dimensions were determined by referring to the service manuals of conventional nebulizers and altering those dimensions according to the requirements of the proposed equipment. The 3D model of the design was created with the aid of the SOLIDWORKS software, as depicted in Figure 5.

Figure 5: 3D model of the proposed nebulizer

The 3D model of the interior of the nebulizer was designed using SOLIDWORKS software as presented in Figure 6. The dimensions of every single component were studied thoroughly prior to designing it. Medical standards and guidelines were followed while doing so. Here the volume of the pump is equal to 88 mm x 65 mm x 40.5 mm. The inlet and outlet diameters are 3.4 mm and 6.5 mm, respectively. The airflow sensor is connected to the outlet of the pump and the tubing is connected to the outlet of the airflow sensor. The nebulizer tubing is connected to the nebulizer chamber and the mask is attached to the nebulizer chamber. The mask, nebulizer

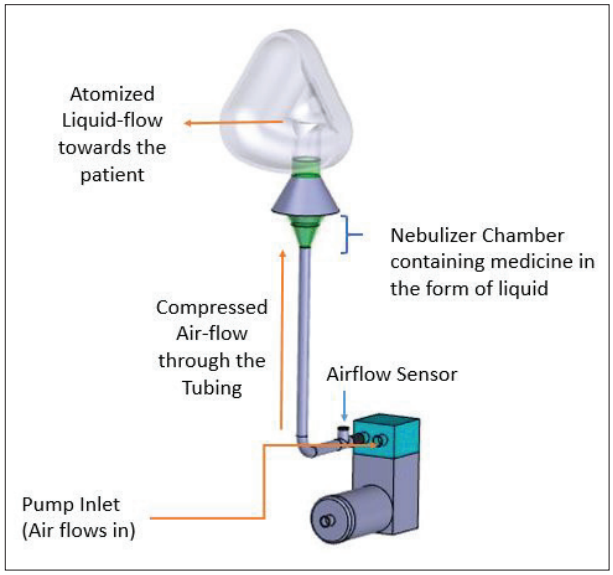

Figure 6: SOLIDWORKS model of the pump assembly

chamber, and nebulizer tubing were drawn as per the dimensions of the pre-existing nebulizers.

Analysis of the safety requirements and circuitry designing

Each subsystem of the overall system is a part of an integrated safety system. The system software can manage routine error handling and communicate the state of the system to the user. For example, the airflow sensor in combination with the PID function integrated within the controlling unit ensures that the patient does not receive an airflow of higher flow rate than the desired flow rate. In addition to that, the device is of unobtrusive and non-invasive type.

The circuit was designed using the "schematic capture" feature of the Proteus Design Suite. The power supply converts 230V AC to a 12V DC and 5V DC. The 12V DC supply is for powering up the motor controller and the three solenoid driver circuits, and the 5V DC supply is for powering up the display unit. The 12V and 5V requirements were fulfilled by the use of a 12V regulator (7812) and a 5V regulator (7805), respectively. The required components were selected from the Proteus library whilst referring to their datasheets. The components were placed in the workspace, and were routed to the Arduino as necessary.

Monitoring of the volumetric breathing rate and dynamic flow regulation of the compressor

The temperature is read through the analog input. It is then matched with the immediately previous value, to see if the value reaches a maxim or minimum If the value of the temperature increases and suddenly decreases, or vice versa, a peak is reached. The peak could be either positive or negative.

On either of these peaks, a count is set as a value, so that the order can be checked to measure the time gap between two adjacent crests and a trough. Then this particular time difference is used to derive the breathing rate of the patient.

As the controller gets the flow rate set by the user, simultaneously the airflow sensor starts monitoring the airflow produced by the diaphragm pump. The flow rate entered by the user and the current flow rate are compared and the difference is calculated as an error. In accordance with that, the PWM signal given to the L298N IC for driving the motor through Arduino Mega 2560 is varied. The two pins are used as output for the motor driving, and the enable pin in the motor driver is supplied by the PWM signals from the Arduino. By supplying a high signal level to the enable (ENA) pin on the L298N, the motor driver provides the 12V supply to the motor, so by varying the signal to the enable pin, the motor speed will be varied. As shown in the above circuit diagram, ENA is connected to pin 11 of the Arduino, which serves as one of the output pins for its PWM function. The difference is counted as an error and from there onwards, PID calculation starts in the program. During the next step, the values of proportional, integral, and derivative errors are determined.

Performance evaluation of the nebulizer

Assessing the nebulizer motor performance

The motor function is a vital factor for the performance of the proposed nebulizer. Therefore, the motor control circuit was simulated using Matlab & Simulink (R2016b) software.

Since the PID control was to be applied for the DC brushed motor integrated within the micro diaphragm pump, the transfer function of the motor was chosen accordingly.

$$G(s) = \frac{\omega_n^2}{s^2 + 2\zeta\omega_n s + \omega_n^2} \quad ...(1)$$

The above general equation (1) describes the behaviuor of a typical second-order function with no zeros. Here ζ and ω_n are the damping ratio and the natural frequency respectively. The PID controller block was created within the controller subsystem and the output of the PID controller was connected to the input of the pump motor. The PID controller block output is a weighted sum and the weights are the proportional, integral, and derivative gain parameters. Then the inputs from the temperature sensor were added to the motor controlling circuitry. The MATLAB function contains the program for how the pump speed has to be varied according to the volumetric breathing rates of the patient. The pump speed has to be varied among 10, 8, and 6 L/min with the change of the volumetric breathing rate of the patient.

The PID controller was tuned automatically with the aid of the Control System Toolbox™. The goals of the motor controlling circuit were to achieve a settling time of less than 5 s and to get a zero steady-state error to the step reference input.

Circuitry simulation and experimental analysis

The circuitry simulation was run on Proteus 8.0 software. By way of checking the Arduino program for errors, and specifically, to check the functioning of the breath rate monitoring coding, an experimental setup was built using the hardware components mentioned under 'conceptual design and hardware components' setion. However, due to the unavailability of the diaphragm pump, in place of it, a normal DC motor was used. The DC motor was checked for the RPM values corresponding to the flow rates of the pump.

CFD simulation of the compressed airflow

In order to incorporate design considerations into a prototype device consistent with project goals, an iterative design process was implemented. For this purpose, computational fluid dynamics simulation was performed on the conceptual device solid model. SOLIDWORKS Flow Simulation and ANSYS Fluent software were utilized.

The values given in Table 1 were entered under the properties option of the two software programs.

Table 1: Parameter characterization

Parameter	Value
Velocity	1.02 m/s, 1.36 m/s, 1.7 m/s
Flow rate	6 L/min, 8 L/min, 10 L/min
Pressure	101, 325 Pa
Fluid Type	Normal Air

RESULTS AND DISCUSSION

PID controller simulation on Matlab and Simulink

Since PID tuning is an iterative process, obtaining gain values using automated tuning of the linearized model and testing the entire Simulink model via simulation were carried out a few times till the desired results were obtained. After performing a series of simulations and comparing them using Simulink, the most appropriate system response was chosen. Thus, Figure 7 denotes the response of the entire closed-loop system. It fulfills the design requirements. With the change of the volumetric breathing rates, the flow rates of the pump change smoothly without any unrealistic spikes, in a settling time of 2.63 seconds. There is only a slight difference between the control input and the measured output.

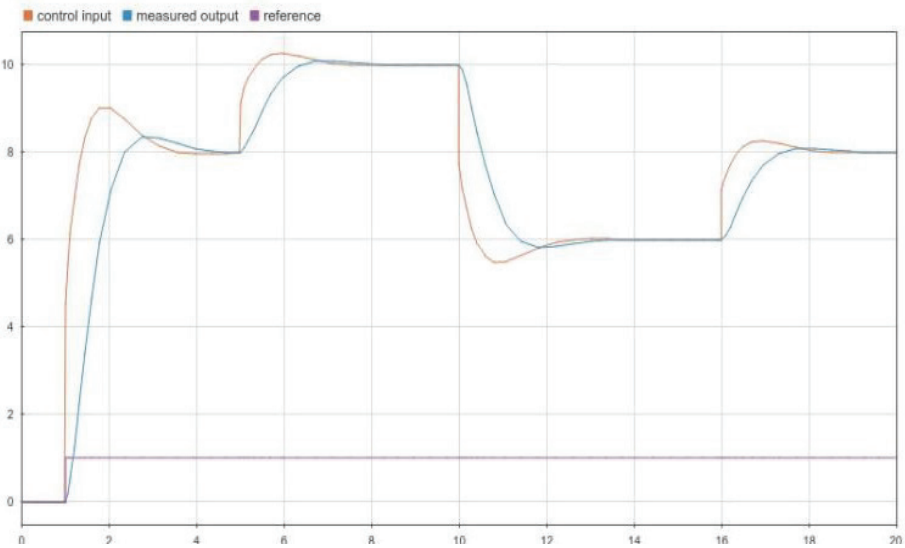

Figure 7: Closed loop system response (Flow rate vs time)

Circuitry simulation and experimental analysis

Due to the complexity of the circuitry, it was hard to simulate the entire circuit on Proteus software. Therefore, two errors were encountered: '[SPICE] transient GMIN stepping at time = 2.19633e-006' and 'Simulation is not running in real-time due to excessive CPU load.' However, when the power supply-motor controller circuit was simulated separately, correct voltage values were displayed on the DC voltmeters. The terminal voltage of the motor were shown as 12V. Thus, there were no errors in the power supply nor with the motor controller circuitry.

All the components that were used in the experimental setup functioned according to the uploaded program. The DC motor speed was regulated as per the rpm values specified in the Arduino program. The respiratory monitoring coding functioned successfully. The DS1835 temperature sensor was able to detect the small fluctuations of temperature between inhalation and exhalation. This particular experiment suggested that there were no shortcomings in the coding.

CFD simulations carried out on SOLIDWORKS

SOLIDWORKS flow simulation

The simulation was turbulent and laminar, and time-independent with air as the fluid. Therefore, the airflow through the pump assembly was modelled and assessed using the flow trajectories generated as a result. At the pump, a turbulent flow was to be seen, as presented in Figure 8.

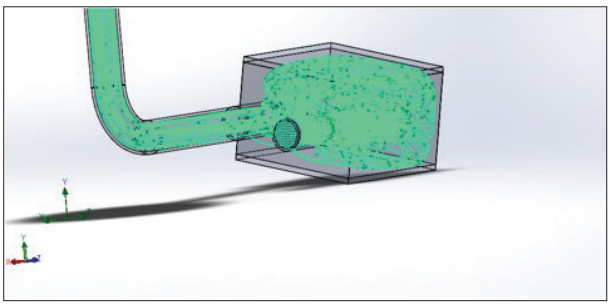

Figure 8: Flow trajectories within the pump

The flow generated from the outlet of the pump towards the nebulizer tubing shows the characteristics of laminar flow as depicted in Figure 9. The flow was steady. In addition to that, the flow of air through the nebulizer tubing was also examined and found to be uniform and laminar without any excessive turbulent flow or rotational flow pattern. The presence of rotational flow pattern is considered unacceptable because it imposes a restriction at recruiting drug particles and dispersing them through the mask, and dispositioning them within the airways.

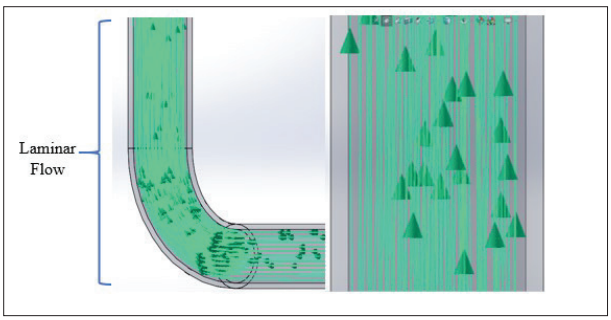

Figure 9: Flow trajectories within the nebulizer tubing

Within the nebulizer chamber, pressurized atomization air is discharged from an orifice and directed against baffles, which causes the air to flow with swirling turbulence over the orifice. The turbulent swirling flow of the atomization air is what causes the droplets to decrease in size. The flow path of the aerosol through the nebulizer chamber towards the mask shows a rapid change of direction to facilitate condensation of any large droplets in the aerosol, as presented in Figure 10 below.

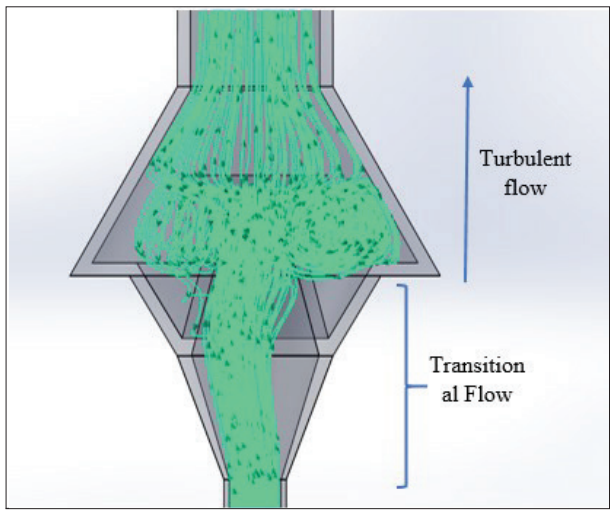

Figure 10: Flow trajectories within the nebulizer chamber

CONCLUSION

Due to the pervasive nature of respiratory diseases and the manner in which they are treated, the market for aerosol drug delivery devices is high. Despite the large market, insufficient drug delivery is a common issue associated with some of the conventional nebulizers. This particular issue is addressed by the current research. The reason for optimizing the control unit of the nebulizer was because the dynamic flow of compressed air is unidirectional and constant, whereas the breathing pattern of a patient is bidirectional. In the first phase of the research, the development of the temperature sensor-based algorithm for volumetric breathing rate detection, and implementation of the compressor control circuitry (PID) were completed successfully. All the objectives were met. The simulation results obtained from Simulink validated the performance of the PID control unit. In addition to that, the results gained from the physical simulations carried out on SOLIDWORKS and ANSYS Fluent 16, were satisfactory. No substantial amount of turbulent flow or rotational flows were detected within the device.

However, according to section VIII of us Food and drug Administration (FDA)1993, regulations 1993, *in vitro* testing is required prior to completing the product development. For this purpose, techniques like laser

scattering or cascade impactor need to be incorporated to determine, the size of the respirable droplet produced by the nebulizer and the amount of drug deposition (FDA, 1993). In addition to that, the device has to be tested for the available drug types.

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