THE IMPROVEMENT OF PRESSURIZED METERED-DOSE INHALER AND SPACERS FOR TREATING RESPIRATORY DISEASES

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A thesis submitted in
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Doctor of Philosophy of Mechanical Engineering

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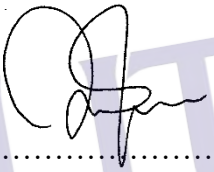
Supervisor : 
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This thesis is dedicated to:

For the sake of Allah, my Creator and my Master,

My great teacher and messenger, Muhammad S.A.W (May Allah bless and grant him), who taught us the purpose of life,

My great parents, Abd Rahman Hasan and Fatimah Sham Matt@Ahmad, who never stop giving of themselves in countless ways,

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My cute little baby girl Nur Ayra Zhafira who always replaces my tears with laughs and smiles,

My beloved sibling for her endless love,

My friends who encourage and support me,

All the people in my life who touch my heart,

I dedicate this research.

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ABSTRACT

The burden of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) is constantly increasing. The symptoms can be alleviated using a pressurized metered-dose inhaler (pMDI). However, poor inhalation technique incorporation with a high initial velocity of pMDI may compromise treatment efficacy. This problem can be tackled by optimizing the pMDI actuator nozzle and using a spacer. Thus, this research aims to improve drug deposition in the lower respiratory tract using an optimized pMDI actuator nozzle and spacers. This study employed computational fluid dynamic (CFD) to predict particle tracking, particle deposition, and spray plume characteristics. Three designs of actuator nozzle (Design A, Design B, and Design C), two designs of disposable spacers (AeroCup Design D and AeroCup Design E), and two designs of the valved-holding chamber (VHC) (AerospaAcer Design F and AerospaAcer Design G) had been studied. The selected designs were fabricated using a three-dimensional (3D) printer. Lastly, the simulation results were validated with particle imaging velocimetry (PIV). Based on these results, actuator nozzle Design C was selected due to the highest injection particle with a maximum velocity magnitude of 35.67m/s. Moreover, actuator nozzle Design C improved the drug deposition in the lower respiratory tract to 21.80% compared to the commercial pMDI (16.90%). AeroCup Design D shows outstanding performance by trapping the highest injection particle and reducing the particle velocity to the air velocity. The particle deposition in the lower respiratory tract improved up to 54.7%. Lastly, AerospaAcer Design G shows a promising result by trapping the highest injection particles and reducing the particles' velocity to the air velocity. AerospaAcer Design G further improved the particle deposition in the lower respiratory tract up to 69.8%. Overall, the spray plume analysis of the actuator nozzle in pMDI, disposable spacer, and VHC showed a similar trend with a percentage error below 5%.

ABSTRAK

Bebanan penyakit pernafasan seperti asma dan penyakit pulmonari obstruktif kronik (COPD) sentiasa meningkat. Gejala ini boleh dikurangkan menggunakan ubat sedut dos bermeter (pMDI). Namun, teknik penyedutan salah disamping halaju awal pMDI tinggi boleh menjejaskan keberkesanan rawatan. Masalah ini boleh diatasi dengan mengoptimum muncung aktuator pMDI dan corong sedut. Oleh itu, penyelidikan ini bertujuan untuk menambahbaik pemendapan ubat dalam saluran bawah pernafasan menggunakan muncung aktuator pMDI teroptimum dan corong sedut. Kajian ini menggunakan pengiraan dinamik bendalir (CFD) untuk mensimulasi pengesanan partikel, pemendapan partikel, dan ciri-ciri kepulan semburan. Tiga jenis reka bentuk muncung aktuator (Reka Bentuk A, Reka Bentuk B, dan Reka Bentuk C), dua jenis reka bentuk corong sedut pakai buang (AeroCup Reka Bentuk D dan AeroCup Reka Bentuk E), dan dua jenis reka bentuk rongga penyimpan berkatup (VHC) (AerospaAcer Reka Bentuk F dan AerospaAcer Reka Bentuk G) telah dikaji. Reka bentuk terpilih difabrikasi menggunakan mesin pencetak tiga dimensional (3D). Akhir sekali, dapatan simulasi disahkan menggunakan halaju pengimejan partikel (PIV). Berdasarkan dapatan ini, muncung aktuator Reka Bentuk C terpilih kerana bilangan partikel tertinggi dengan magnitud halaju maksimum 35.67m/s. Selain itu, muncung aktuator Reka Bentuk C meningkatkan pemendapan ubat dalam saluran bawah pernafasan sebanyak 21.80% berbanding pMDI komersil (16.90%). AeroCup Reka Bentuk D menunjukkan prestasi cemerlang dengan memerangkap partikel tertinggi dan mengurangkan halaju partikel kepada halaju udara. Pemendapan partikel dalam saluran bawah pernafasan bertambah baik sehingga 54.70%. Akhir sekali, AerospaAcer Reka Bentuk G menunjukkan hasil memberangsangkan dengan memerangkap partikel tertinggi dan juga berjaya mengurangkan halaju partikel ke halaju udara. AerospaAcer Reka Bentuk G meningkatkan lagi pemendapan partikel dalam saluran bawah pernafasan sehingga 69.80%. Keseluruhannya, analisis kepulan semburan muncung aktuator dalam pMDI, corong sedut pakai buang dan VHC menunjukkan arah aliran sama dengan peratusan ralat bawah 5%.

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LIST OF SYMBOLS AND ABBREVIATIONS

°	-	Degree
°C	-	Degree Celcius
ρ	-	Fluid Specific Mass
ū	-	Mean Velocity
σ_k	-	Mean Velocity Gradients
µg	-	Microgram
µm	-	Micrometers
Ø	-	Minuscule
%	-	Percentage
τ_{ij}	-	Reynold's Stress Tensor
μi	-	Time-Averaged Velocity
ε	-	Turbulent Dissipation of Energy
ω	-	Turbulent Dissipation Rate
σ_ε	-	Turbulent Prandtl Numbers
μ_t	-	Turbulent Viscosity
μ	-	Viscosity
3D	-	Three-Dimensional
A	-	Ampere
AC	-	Alternative Current
amf		Additive Manufacturing File Format
API	-	Active Pharmaceutical Ingredient
$C_{1\varepsilon}$ & $C_{2\varepsilon}$	-	Model Constants
CAD	-	Computer-Aided Design
CCD	-	Charge-Coupled Device
CFC	-	Chlorofluorocarbon
CFD	-	Computational Fluid Dynamic
cm	-	Centimetre

COPD	-	Chronic Obstructive Pulmonary Disease
COVID-19	-	Coronavirus Disease 2019
CSR	-	Corporate social responsibility
DC	-	Direct Current
DPI	-	Dry Powder Inhaler
DPM	-	Discrete Phase Model
F	-	Momentum Equation
FASTREG	-	Flow Analysis, Simulation, Turbulence, Research Group
FDA	-	Food and Drug Administration
FDM	-	Fused Deposition Modeling
FPF	-	Fine Particle Fraction
g	-	Gram
g	-	Gravitational Acceleration
GIT	-	Grid-Independent Test
G_k	-	Generation Of Turbulent Kinetic Energy
HFA	-	Hydrofluoroalkane
Hz	-	Hertz
ICU	-	Intensive Care Units
IV	-	Invasive Ventilation
j/kg-k	-	Joule per Kelvin per Kilogram
k	-	Kinetic Energy
K	-	Kelvin
KEGA	-	Key Economic Growth Activities
k-ε	-	K-epsilon
kg	-	Kilogram
kg/kmol	-	Kilogram per Kilomol
kg/m^3	-	Kilogram per Cubic Metre
kg/s	-	Kilogram per Second
kHz	-	Kilohertz
k-ω	-	K-Omega
L/min	-	Litres per Minute
m	-	Meter
ml	-	Milliliter

mm	-	Millimetre
mm/s	-	Millimeters per Second
MMAD	-	Mass Median Aerodynamic
m/s	-	Meter per Second
MT	-	Mouth-Throat
NIV	-	Non-Invasive Ventilation
OBJ	-	Geometry Definition File Format
p	-	Static Pressure
PIV	-	Particle Imaging Velocimetry
PLA	-	Polylactic Acid
pMDI	-	Pressurized Metered-Dose Inhaler
psi	-	Pounds per Square Inch
PVA	-	Polyvinyl Alcohol
RAM	-	Random Access Memory
RANS	-	Reynolds-Averaged Navier–Stokes
RSM	-	Response Surface Method
s	-	Second
SABA	-	Short-Acting β2-Agonists
SARS-CoV-2	-	Severe Acute Respiratory Syndrome Coronavirus 2
SD card	-	Secure Digital Card
STL	-	Standard Triangle Language
TB	-	Trachea-Bronchial
TPU	-	Thermoplastic Polyurethane
UDF	-	User-Defined-Function
USB	-	Universal Serial Bus
UTHM	-	Universiti Tun Hussein Onn Malaysia
v	-	Kinematic Viscosity
V	-	Volts
VHC	-	Valved Holding Chambers
VMD	-	Volume Median Diameter
vT	-	Turbulent Kinematic Viscosity
WHO	-	World Health Organization
w/m-k	-	Watts per Metre Kelvin

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CHAPTER 1

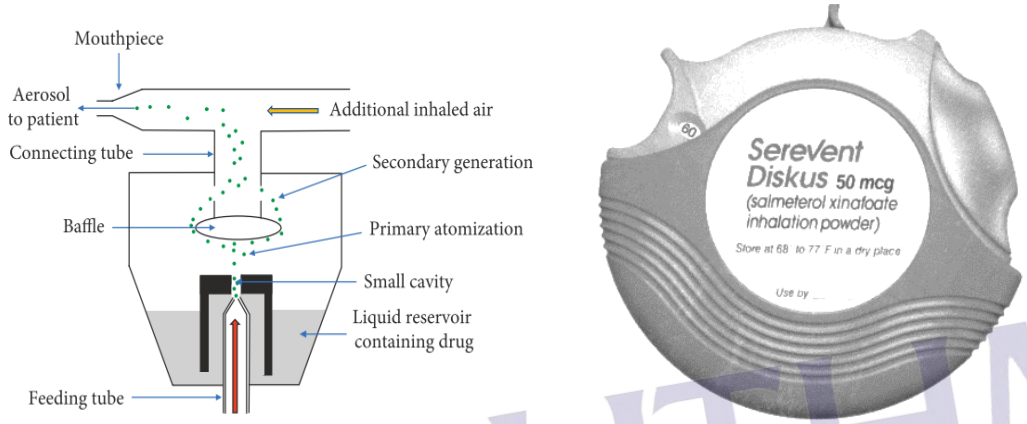
INTRODUCTION

1.1 Research background

Respiratory problems such as asthma and chronic obstructive pulmonary disease (COPD) inflict an immense worldwide health burden. Over 1 billion individuals worldwide suffer from acute or chronic respiratory conditions, which account for 7% of all mortality (4.2 million deaths) (Marciniuk *et al*., 2017). Respiratory problems are characterized by chronic airways inflammation that induces bronchial hyperresponsiveness and decreased lung function. Approximately 97.2 million individuals globally suffer from moderate to severe COPD. About 3 million individuals die each year, making it the third leading cause of mortality — and the numbers are increasing (Li *et al*., 2020). Nearly 334 million individuals worldwide have asthma, the most prevalent chronic disease of childhood, affecting 14% of children (Enilari & Sinha, 2019).

Typically, respiratory problems are treated using a nebulizer, a dry powder inhaler (DPI), and the pressurized metered-dose inhaler (pMDI) (Ibrahim *et al*., 2015). However, the situation has been exacerbated because the nebulizer is not recommended during the current coronavirus disease 2019 (COVID-19) pandemic (Fink *et al*., 2020; Mei-Zahav & Amirav, 2020). Individuals with respiratory problems, particularly asthma and COPD, are more susceptible to the severe repercussions of COVID-19 as viral infections may result in pneumonia, affecting the respiratory system (Rabe & Watz, 2017; Leung *et al*., 2020). Due to their ease of use and cost-effectiveness, DPIs and pMDIs became some of the most popular and common methods of delivering pharmaceutical drugs, substituting the nebulizer. Despite that, the primary disadvantage of DPIs is their high surface-free energy, which causes them

to bind together cohesively (Shetty *et al*., 2020). Consequently, it has a poor flow and aerosolization efficiency and tends to accumulate within the inhaler. Moreover, some patients with nerve or muscle weakness might have difficulty inhaling DPI forcefully. Poor coordination, such as blowing and exhaling directly into the device, might potentially result in medicine scattering prior to inhalation (Levy *et al*., 2019). Figure 1.1 shows the image of the nebulizer and DPI.



(a) (b)

Figure 1.1: Device to treat respiratory problems. a) nebulizer, b) dry powder inhaler (Atkins *et al*., 2005; Santati *et al*., 2019)

In contrast to DPIs, pMDIs have a canister that aids medication delivery to the lung. Thus, pMDI is more suitable for individuals with nerve or muscle weakness, such as the elderly and children. Figure 1.2 shows the components of pMDI. Previous studies have demonstrated that pMDI decreased the drug deposition in the pharynx, boosting the drug deposition in the lower respiratory tract (Vincken *et al*., 2018). The geometry of the actuator nozzle inside pMDI is one of the factors affecting drug deposition in the lower respiratory tract (McKiernan, 2019; Abd Rahman *et al*., 2020). The pMDI actuator nozzle is a vital subsystem that directly impacts the pMDI's distribution properties. The diameter, length, and actuator angle of the orifice might significantly affect the atomization of particles. Furthermore, pMDI contains hydrofluoroalkane (HFA) as an inhaler propellant, obviating the need for harmful chlorofluorocarbon (CFC). HFA, with much smaller particle size, delivers more than 10% to 15% of drugs to the lower respiratory tract (Stein & Thiel, 2017).

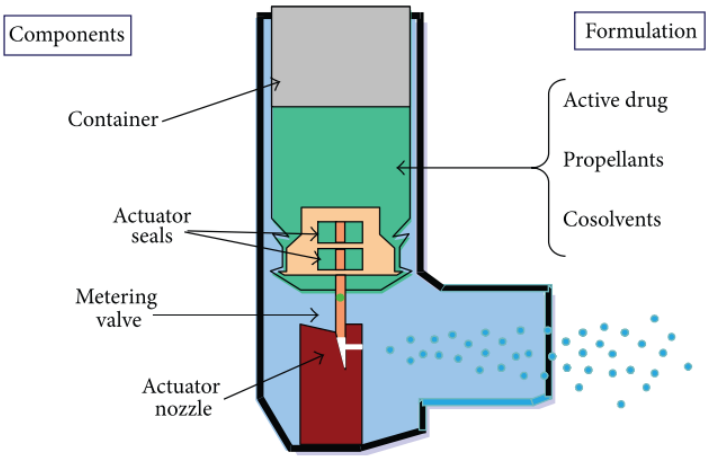


Figure 1.2: The components of pMDI (Lavorini, 2013)

The proper use of pMDI is challenging, with the most critical problem being synchronizing actuation and inhalation. A spacer is designed to assist patients with difficulty with their inhaler techniques. In general, the spray plume generated by the pMDIs is faster than the patient's inhalation. Children and the elderly confront the challenge of coordinating device actuation with patient inhalation when using pMDIs. Additionally, the patient's breathing pattern influences the effectiveness of pulmonary delivery. Rapid inspiration is not recommended when using pMDIs because it results in turbulent airflow and high velocity, increasing impaction deposition in the upper airways (Lavorini *et al*., 2017). In these scenarios, most drugs are deposited in the upper respiratory tract. The drug delivery efficiency of pMDIs in the lower respiratory tract can be increased by utilizing spacers and valved holding chambers (VHCs) (Vincken *et al*., 2018).

A spacer is a tube or extension device placed at the interface between the patient and the pMDI. There are two types of spacers available in the market: a simple spacer, and a VHC, as shown in Figure 1.3. A simple spacer is usually disposable and for short-term usage. It is made from plastic bottles, Styrofoam or paper cups, plastic baggies, or even toilet paper rolls (Lavorini *et al*., 2020). On the other hand, VHC has a one-way valve at the mouthpiece end to allow inhalation and prevent exhalation into the chamber (Vincken *et al*., 2018). It is reusable and easy to clean, ideal for long-term use. Spacers enable the patients to breathe from a "standing aerosol cloud" that does not require breath coordination (Chandel *et al*., 2019). These inhalation aids slow down the spray plume production, allowing the propellant to evaporate from the larger

droplet, increasing lower lung deposition and decreasing oropharyngeal deposition (Ibrahim *et al*., 2015).

(a) (b)

Figure 1.3: Two types of spacers. a) simple spacer and b) VHC (Dissanayake & Suggett, 2018; Thong *et al*., 2021)

Experimentally developing and optimizing inhalation devices will be costly and time-intensive. The rapid development of innovative devices might be critical for their thriving market penetration in a highly competitive environment. This drawback can be resolved by decreasing the number of experiments and trials using computational models. Computational fluid dynamic (CFD) models may substantially reduce the time to develop new inhalation products (Milenkovic *et al*., 2017). For optimizing drug delivery, CFD models have been employed to predict injection particle number, particle velocity magnitude, particle deposition patterns, and spray plume characteristics (Raman *et al*., 2018).

This study first designed the three-dimensional (3D) model of pMDIs, disposable spacers, and the VHCs through SOLIDWORKS 2019. The best design was selected according to injection particle number and maximum particle velocity magnitude in ANSYS Fluent version 19.2. This study also investigated the percentage of drug deposition in the lungs of selected designs using scFLOW software. Next was fabricating the chosen designs using a fused deposition modeling (FDM) 3D printer. Following that, the spray plume characteristics of the new design actuator nozzle in pMDI, disposable spacer, and VHC were observed using particle imaging velocimetry (PIV). Finally, the spray plume characteristics results were validated by comparing the simulation study with the experimental. This research established that the new design actuator nozzle in pMDI, disposable spacer and VHC contributed significantly to enhancing the drug deposition in the lower respiratory tract.

1.2 Problem statement

Drug delivery to the lungs has emerged as a crucial process in treating respiratory problems. Despite this, poor inhalation techniques may compromise treatment efficacy. The inhaler's improper use reduced the amount of drugs delivered to the lungs due to direct flow toward the throat (Chongtu *et al*., 2017). Even with a good inhalation technique, most pMDIs only deposit 10% to 20% of the dosage in the lungs (Lavorini *et al*., 2017). Furthermore, the high initial velocity produced by common pMDIs, in conjunction with the larger particle sizes, resulted in a sizeable proportion of particles impacting the mouth and throat prior to the propellant evaporating, decreasing the number of particles available for inhalation (Fonceca *et al*., 2019). Thus, reducing the maximum particle velocity and increasing injection particles number may affect the drug deposition in the lower respiratory tract. Several initiatives have been taken to address this shortcoming. This problem can be addressed in two ways: 1) optimizing the actuator nozzle and 2) using a spacer. Despite several studies being available, research into optimizing the actuator nozzle remains limited and underexplored. Additionally, previous research indicated that many spacers were made from bottomless plastic bottles and toilet paper rolls, increasing the concern that the drugs administered to the lungs may not be optimum to alleviate symptoms (Vincken *et al*., 2018; Lavorini *et al*., 2020). Thus, this study aimed to investigate the potency of a novel actuator nozzle design in pMDIs and spacers to improve drug particle deposition in the lower respiratory tract by decreasing the particle velocity magnitude but increasing the number of injection particles.

1.3 Research objectives

The general objective of this study was to improve drug deposition in the lower respiratory tract by using a novel actuator nozzle design in pMDIs and spacers to alleviate respiratory symptoms (asthma, COPD and COVID-19).

The study objectives were as follows:

1. To analyze the particle tracking (injection particles and maximum velocity magnitude) in pMDIs, disposable spacers, and VHCs using ANSYS Fluent version 19.2, while actuator nozzle (orifice diameter, length of orifice and angle of actuator) been analyze in pMDIs only.
2. To examine the percentage of drug deposition in the lower respiratory tract for the selected new design of pMDI, disposable spacer, and VHC using scFLOW software.
3. To investigate the spray plume characteristics (spray penetration, spray cone angle and spray plume width) of the new design pMDI, disposable spacer, and VHC using ANSYS Fluent version 19.2 and experimental PIV.

1.4 Scope of study and limitation

The scope of the study was limited to:

1. Commercial products:
   a) Pressurized metered-dose inhaler (pMDI)
   b) DispozABLE spacer (disposable spacer) from Clement Clarke International, United Kingdom
   c) AeroChamber (valved holding chamber) from Allergan Sales, LLC, an AbbVie company, United States
   d) AngelBiss (valved holding chamber) from AngelBiss Medical Technology, China
2. The simulation employed the ANSYS software version 19.2 and scFLOW software, conducted in the Computational Fluid Dynamic (CFD) laboratory at Universiti Tun Hussein Onn Malaysia (UTHM). The following were the simulation properties:

   a) ANSYS software version 19.2
      i. Optimization of pMDI actuator nozzle (Design A, Design B, Design C, and commercial pMDI) using response surface method (RSM)
      ii. Three (3) designs were selected for disposable spacer (Design D, Design E, and commercial disposable spacer)

iii. Four (4) designs were selected for VHC (Design F, Design G, commercial VHC 1, and commercial VHC 2)
iv. K-epsilon for turbulence modeling
v. Pressure inlet = 5.2 bar (More *et al*., 2014)

b) scFLOW software

i. Two (2) designs were selected for pMDI (Design C and commercial pMDI)
ii. Two (2) designs were selected for disposable spacer (Design D and commercial disposable spacer)
iii. Four (4) designs were selected for VHC (Design F, Design G, commercial VHC 1, and commercial VHC 2)
iv. K-omega for turbulence modeling
v. Recommended inhalation flowrate for pMDI = 30 L/min (Haidl *et al*., 2016)
vi. Pressure inlet = 5.2 bar (More *et al*., 2014)

3. An experiment using PIV has been conducted at the Aerodynamic laboratory, UTHM. The simulation result was validated by experimental results regarding spray penetration, spray cone angle, and spray plume width.
4. The materials used as filament in 3D printing are polylactic acid (PLA), thermoplastic polyurethane (TPU), and polyvinyl alcohol (PVA). PLA material was used to print the actuator nozzle in the pMDI (Design C), the disposable spacer Design D components, and the VHCs (AerospaAcer Design F and AerospaAcer Design G). TPU was used to print the universal backpiece, duckbill, and flap valve for AerospaAcer Design G. PVA functions as a support, printing the PLA without any damage, particularly in the hollow parts.
5. This study employed two (2) FDM 3D printing machines: a) Creality Ender 3 Pro (the single extruder machine used to print the PLA and TPU materials) and b) Flashforge Creator Pro (the only double extruder used to print the PLA and PVA materials simultaneously).
6. This study utilized a) SOLIDWORKS 2019 to design the components of the actuator nozzle in the pMDI, disposable spacer, and VHCs, b) FlashPrint version 4.1.0, and c) Ultimaker Cura version 4.6.2 software in a 3D printing

machine to print the materials, d) ImageJ to measure the spray penetration, spray cone angle and spray plume width for the new design pMDI, disposable spacer, and VHCs, e) scFLOW software to discover the percentages of the particle's deposition in the lungs of new design pMDI, disposable spacer, and VHCs, and f) ANSYS Fluent version 19.2 to determine particle tracking (injection particles, maximum velocity magnitude, and axial distance) and RSM optimization.

1.5 Significance of the study

Developing the actuator nozzle of pMDI and spacers will benefit society, especially individuals diagnosed with respiratory problems such as asthma, COPD, and COVID-19, by increasing the drug deposition in the lower respiratory tract. These prototypes are made from non-toxic and environmentally friendly materials, eliminating the environmental issues in response to the government's call (The 12th Malaysia Plan) to adopt green technology. It also enhances expertise and local technology vital for national development per Malaysia's Science and Technology Development Plan 2021 - 2030 (15 KEGA). Moreover, it is less expensive, more convenient, portable, and relatively maintenance-free than nebulized therapy. Furthermore, studying spacer's development will boost demands for local products and economic circulation in the local market. It could substitute for the inhaler spacer imported from abroad, which is much less costly, alleviating the burden of purchasing an expensive spacer. Interestingly, over 1000 of the new disposable spacers have been distributed to the healthcare centers across Malaysia, including Hospital Universiti Kebangsaan Malaysia, Hospital Putrajaya, Batu Pahat Health Clinic, and Ayer Hitam Health Clinic, as part of the company's corporate social responsibility (CSR) initiative to eliminate the burden shouldered by frontliners during the pandemic (**APPENDIX A**).

1.6 Outline of the thesis

The thesis was divided into five (5) chapters, which were as listed below:

CHAPTER 1 Introduction: Provides context for this study by outlining the research background, problem statement, research objectives, study scopes, limitations, and study significance.

CHAPTER 2 Literature Review: Provides background information on the pMDI, disposable spacer, and VHCs, as well as pertinent information about the study's objectives and scopes of study, which includes a fundamental principle of operation, the performance of the pMDI's actuator nozzle features (diameter of the orifice, angle of the actuator, and length of the orifice), and the research gap in pMDI and spacers research.

CHAPTER 3 Methodology: Covers development of the 3D designs for actuator nozzle in pMDI, disposable spacer, and VHCs geometry employing SOLIDWORKS 2019. This chapter also discusses the fabrication setup procedures utilizing 3D printing machines, experiments utilizing PIV, and simulation employing ANSYS Fluent version 19.2 and scFLOW software.

CHAPTER 4 Results and Discussion: Explanation of the optimization results for the various parameters: diameter of the orifice, angle of the actuator, and length of the orifice for the pMDI. The number of injection particles, maximum particle velocity, axial distance, and drug particle deposition of the pMDI, disposable spacer, and VHCs were determined and discussed. In addition, this chapter includes a discussion of the validation result obtained from experimental work.

CHAPTER 5 Conclusion and Recommendation: Summarizes and concludes the research output and recommends future research.

CHAPTER 2

LITERATURE REVIEW

2.1 Respiratory system

The respiratory system is primarily responsible for supplying oxygen to body tissues for cellular respiration, removing waste products such as carbon dioxide, and maintaining acid-base balance (Patwa & Shah, 2015). The respiratory system is divided into two zones; conducting zones (nose to bronchioles) which form a path for conduction of the inhaled gases, and respiratory zone (alveolar duct to alveoli), where the gas exchange takes place (Meyerholz *et al*., 2018). The respiratory system is divided anatomically into the upper and lower respiratory tracts. Figure 2.1 shows the schematics diagram of the human respiration system.

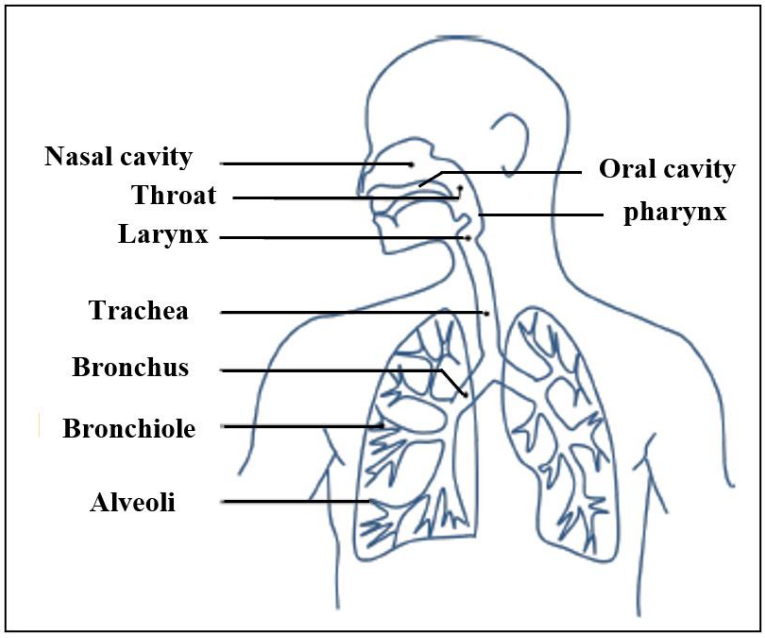


Figure 2.1: Human respiration system (Han & Hirahara, 2016)

2.1.1 Upper respiratory tract

The first section of the upper respiratory tract is called the extra-thoracic region, which includes the pharynx, oral cavity, nasal cavity, and larynx. The pharynx is a tube-like passage connecting the posterior nasal and oral cavities to the larynx and esophagus. It is divided into the nasopharynx, oropharynx, and laryngopharynx. This region serves as the first barrier in the human respiratory system against inhaled particles (Gulati & Cullen, 2017). This region plays a crucial role in improving drug delivery to the human lung. Most of the time, inhaled particles are trapped in this region. Geometrical complexities, including airway bends and sudden cross-sectional changes, can influence the turbulence level of inhaled air (Lizal *et al*., 2020).

2.1.2 Lower respiratory tract

The second section of the lower respiratory tract, referred to as the trachea-bronchial (TB) region, resembles an inverted tree composed of trachea, bronchi, bronchioles, and alveoli (Gulati & Cullen, 2017). As shown in Figure 2.2, the tracheobronchial tree is a complex system that transports gases from the trachea down to the acini, exchanging the gases. It is partitioned into 23 generations of dichotomous branching, extending from the trachea (generation 0) to the last order of terminal bronchioles (generation 23) (Patwa & Shah, 2015). At each generation, each airway is split into two smaller daughter airways. The airways are purely known as conducting pipes from the trachea (generation 0) to the terminal bronchioles (generation 5 to 16). Due to the absence of gas exchanges in this region, the volume in these pipes is called the dead space volume (average 150 ml) (Han & Hirahara, 2016). The terminal bronchioles (generation 16) divide into respiratory or transitional bronchioles (generations 17 to 19) with occasional alveoli at the walls. These respiratory bronchioles divide further into alveolar ducts (generations 20 to 22), wholly lined with alveoli. This region is referred to as acinus (generations 16 to 23). Moreover, the acinus comprises respiratory airways and forms functional tissues of the lung. The oxygen and carbon dioxide gas exchanges occur in this region. It has the most complex structure compared to other regions (Patwa & Shah, 2015; Han & Hirahara, 2016). Lastly, the distal ends of alveolar ducts open into the alveolar sac made up of alveoli.

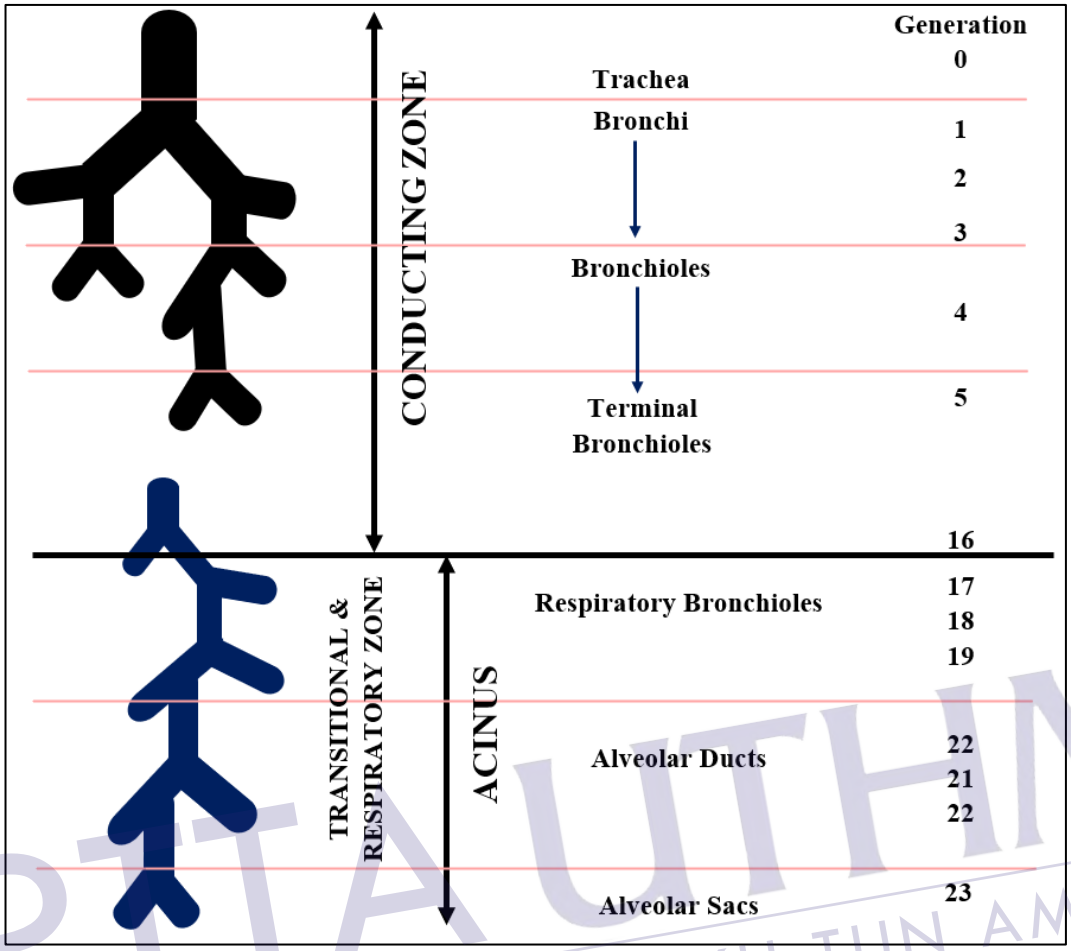


Figure 2.2: Tracheobronchial tree showing 23 generations (Patwa & Shah, 2015)

2.2 Respiratory problem

The respiratory problem refers to any disorder of the airways and lungs that affects human respiration (Kim *et al*., 2018). Lower respiratory system problems are less prevalent than upper respiratory system problems. However, lower respiratory problem symptoms are usually more severe than the symptoms of an upper respiratory problem. Coughing is a particularly acute symptom of all diseases affecting any part of the bronchial tree (Bouazza *et al*., 2021). The second most crucial symptom of lung disease is dyspnea, or shortness of breath (Bello *et al*., 2018). This sensation may arise acutely upon inhalation of foreign particles into the trachea. Chest pain may be an early symptom, but it is most often associated with an attack of pneumonia. It is due to an inflammation of the pleura following the onset of the pneumonic process (Miravitlles

& Ribera, 2017; Yadav & Gumber, 2017). Figure 2.3 shows the respiratory problems considered in this study.

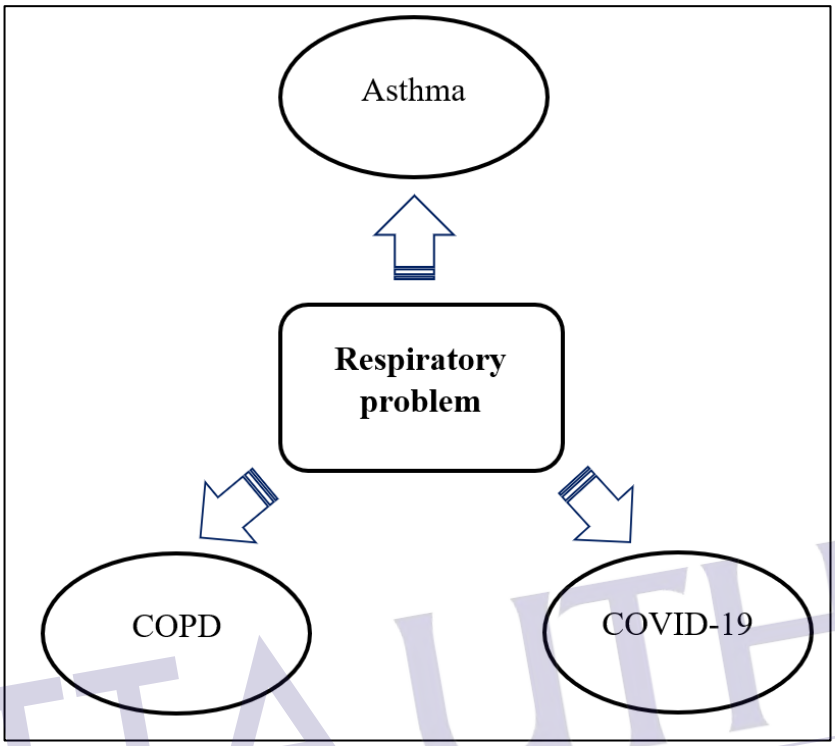


Figure 2.3 Respiratory problems

2.2.1 Asthma

Asthma is defined as a chronic inflammatory disease of the airways. Chronic inflammation is associated with airway hyperresponsiveness, which is an exaggerated airway-narrowing response to specific triggers by exposure to certain allergens such as weeds, pollen, pets, dust, and mites, among others (Naclerio *et al*., 2020). Some irritants in the air, such as smoke, chemical irritants, certain odors, extreme weather conditions, or the presence of sulfites in particular foodstuffs, may also cause or trigger asthma (Yadav & Gumber, 2017). Certain conditions, such as respiratory illness, exercise, and flu, predispose individuals to asthmatic attacks (Panagiotou *et al*., 2020). An outburst of specific emotions, such as shouting, crying, and laughing, may also trigger an asthmatic episode (Lumb, 2017). Wheezing, breathlessness, chest tightening, and coughing are common symptoms, especially at night or early morning

(Lumb, 2017). The airflow limitation is responsible for airway tissue reactions due to smooth muscle contractions, edema, and hypersecretion.

These symptoms are generally associated with extensive but varying airflow obstruction within the lungs that is usually reversible either spontaneously or with appropriate asthma medications, such as a fast-acting bronchodilator short-acting β_2-agonists (SABAs) (Quirt *et al*., 2018). Short-acting β2-agonists (SABAs) such as salbutamol are the most frequently prescribed medications in developing countries for children and adults with respiratory problems (Muneswarao *et al*., 2019). Some inhaled asthma medications are pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs). SABAs such as salbutamol are commonly prescribed to patients with asthma as the preferred reliever for treating acute symptoms. This SABA has no anti-inflammatory properties (Chin *et al*., 2017). Nevertheless, it can relax the muscles lining the airways that carry air to the lungs (bronchial tubes) within five minutes, increasing airflow and making breathing easier. It may provide relief from asthma symptoms for three to six hours.

2.2.2 Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease. COPD is characterized by persistent airflow limitation that is usually progressive, caused by an enhanced chronic inflammatory response in the airways and lungs due to noxious particles or gases (Weinberger *et al*., 2019). COPD patients face a variety of symptoms daily. Dyspnea, coughing, and sputum production are the most prevalent symptoms (Miravitlles & Ribera, 2017). Wheezing, chest tightness and chest congestion are less prevalent; nevertheless, symptoms are bothersome (Miravitlles & Ribera, 2017). Several risk factors and triggers, including smoking, severe airflow limitation, bronchiectasis, bacterial and viral infections, as well as comorbidities, exacerbate COPD (Viniol & Vogelmeier, 2018).

COPD is often treatable with β_2-agonists and anticholinergics as well as systemic corticosteroids. SABAs and short-acting anticholinergics are the initial treatment for COPD exacerbations. Systemic corticosteroids have been a standard treatment for exacerbations for decades (Crisafulli *et al*., 2018). It has been shown to improve lung function and oxygenation, minimize the recovery and hospitalization

time and duration, and reduce treatment failures. COPD patients may also be susceptible to bacterial infection in certain circumstances, and these patients will receive antibiotic medication (Miravitlles & Anzueto, 2017). Besides, non-invasive ventilation (NIV) and invasive ventilation (IV) can be used to treat COPD. In COPD patients with acute respiratory failure, NIV is considered the standard of care (Walter *et al*., 2018). However, severe or chronic COPD patients who need hospitalization or emergency room access require intubation with IV and intensifying pharmacologic therapies such as bronchodilators, inhaled corticosteroids, phosphodiesterase-4 inhibitors, long-term antibiotics, and mucolytics (Viniol & Vogelmeier, 2018). Lastly, smoking cessation is critical for patients with COPD to prevent further morbidity and mortality (Viniol & Vogelmeier, 2018).

2.2.3 Coronavirus disease 2019 (COVID-19)

On 12th January 2020, the World Health Organization (WHO) announced the epidemic outbreak of coronavirus disease 2019 (COVID-19). It is caused by a novel, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Elengoe, 2020). SARS-CoV-2 may be transmitted by respiratory droplets up to a distance of 2m or by contaminated surfaces, resulting in infection through contact transmission (Peng *et al*., 2020). Patients infected with the SARS-CoV-2 are at risk of developing and suffering acute respiratory failure, which may result in death (Mohanty *et al*., 2020). COVID-19 symptoms are divided into systemic and respiratory disorders. Fever, headache, coughing, fatigue, diarrhea, sputum production, hemoptysis, dyspnoea, and lymphopenia are common disorders of COVID-19. The respiratory disorders of COVID-19 include rhinorrhea, sneezing, sore throat, pneumonia, ground-glass opacity, and acute respiratory distress symptoms (Law *et al*., 2020).

As hospitalization rates rise due to the spread of COVID-19, salbutamol has become the first-line defense in the emergency room for COVID-19 patients with respiratory distress. Special groups such as elderly patients with asthma or chronic obstructive pulmonary disease (COPD) and premature infants with compromised lungs due to the respiratory syncytial virus rely heavily on salbutamol (Elbeddini *et al*., 2020). Additionally, some hospitals use nebulizers to treat COVID-19 patients (Sethi *et al*., 2020). Another treatment option is administering anti-inflammatory drugs to reduce the symptoms (Creeden *et al*., 2021).

COVID-19 may cause severe respiratory symptoms and an inability to breathe in an adequate amount of oxygen if left untreated. Ventilators may save COVID-19 patients' lives by supporting their lungs until their bodies are able to fight the virus (Dondorp *et al*., 2020). Approximately 96 COVID-19 vaccines are currently at various clinical development stages, offering hope for a better future (Olliaro *et al*., 2021). Preventive measures such as frequent handwashing with soap or sanitizer, avoiding handshakes, wearing masks and gloves, maintaining a social distance of 1m to 2m, coughing into disposable tissues, and avoiding gatherings in affected areas can help to prevent viral infection from spreading (Elengoe, 2020).

2.3 Medical inhalation therapy

Drugs and medication must be targeted and administered to the appropriate therapeutic or biological site of action to manage these respiratory problems effectively. The suitable action site is the lungs' small airways in many cases. Inhaled drug products are exceedingly popular for delivering drugs through the lungs or nasal mucosa for local or systemic therapy. Inhaled bronchodilators and corticosteroids are the mainstays of treating respiratory diseases (Alharbi *et al*., 2021). There are currently four (4) major medical inhalation devices: nebulizer, ventilator, DPI, and pMDI. Each of them has its advantages and drawbacks. The example of medical inhalation therapy is shown in Figure 2.4.

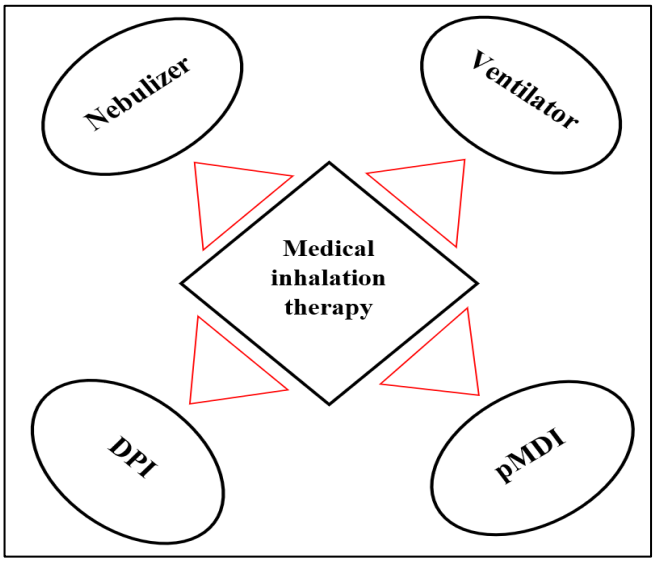


Figure 2.4 Examples of medical inhalation therapy

2.3.1 Nebulizer

A nebulizer is a device that converts liquids into aerosols for inhalation into the lower respiratory tract. Nebulizers produce and deliver a polydisperse aerosol in the range of 1µm to 5µm (Pleasants & Hess, 2018). While most nebulizers use compressed air for atomization, some use ultrasonic energy. Nebulizers can deliver bronchodilator (airway-opening) medications such as albuterol, Xopenex, or Pulmicort (steroid) to treat respiratory problems (Dhand, 2017). A liquid solution or suspension is added to the nebulizer for each treatment (Pleasants & Hess, 2018). The three significant nebulizers are jet nebulizers, ultrasonic nebulizers, and mesh nebulizers (Figure 2.5). Jet nebulizers are capable of nebulizing all drugs in solution or suspension form. In contrast, ultrasonic nebulizers can only nebulize aqueous solutions and may produce heat during the nebulization process. Similarly, mesh nebulizers can nebulize aqueous solutions but are less efficient at nebulizing suspensions formulation (Prajapati *et al*., 2019).

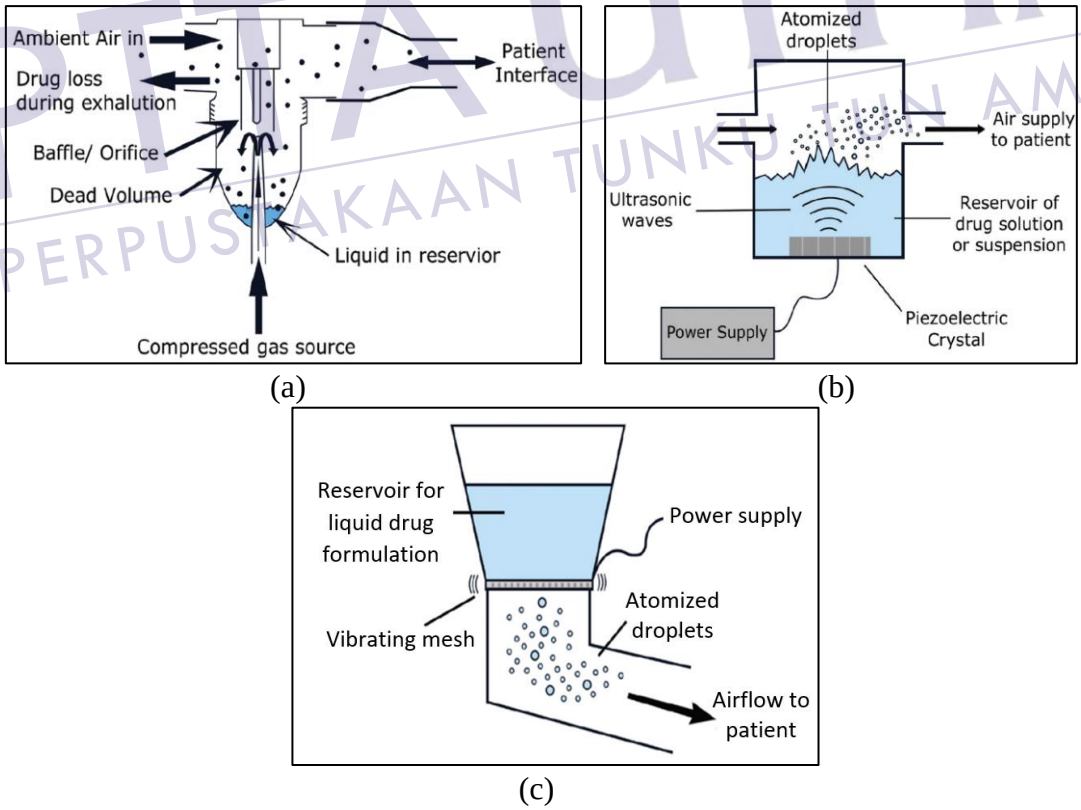


Figure 2.5: Three types of nebulizers. a) jet nebulizer, b) ultrasonic nebulizer and, c) mesh nebulizer (Alharbi *et al*., 2021)

The advantages of nebulizers include that they do not require patient synchronization between inhalation and actuation; it is beneficial for pediatric, elderly, ventilated, and non-conscious patients and those unable to operate pMDIs or DPIs (Barjaktarevic & Milstone, 2020). Nebulizers can deliver higher doses than other aerosol devices, albeit at the expense of lengthier administration timeframes. Certain severe respiratory conditions benefit more from nebulized medicines than standard inhaler devices (Tashkin, 2016). One disadvantage of nebulizers for users is that they must be assembled and loaded with medicine prior to each usage. Then, if the nebulizer is to be reused, it must be disassembled and cleaned (Ibrahim *et al*., 2015). These steps may be challenging and troublesome for untrained and inexperienced patients. Additionally, nebulizers are costly, bulky, require oxygen and electricity, deliver a high dosage, and produce less pulmonary deposition (Prajapati *et al*., 2019). They transmit infection from unsterile chambers or tubing into the lungs, particularly during prolonged usage. Finally, nebulizers waste a significant amount of medication vaporizing from the outside (Amirav & Newhouse, 2020).

2.3.2 Ventilator

A ventilator is a device that supports or recreates the breathing process by pumping air into the lungs. Ventilators were used to support those unable to breathe adequately by supplying oxygen into the lungs and removing carbon dioxide. Their breathing inability might result from general anesthesia or a respiratory issue (Hossain *et al*., 2018). Ventilator support is classified into non-invasive ventilator (NIV) and invasive ventilator (IV). The NIV is also referred to as a face mask ventilator in which the breathing support is administered through a face mask, nasal mask, or a helmet (Bahammam *et al*., 2018). IV is classified into two types: mechanical ventilator and tracheostomy ventilator. Mechanical ventilators operate via a tube inserted into a person's throat, pumping air into the lungs and removing carbon dioxide.

In contrast, a tracheostomy ventilator involves the creation of an incision in the windpipe and the insertion of a tube that allows air to flow in and out (Walter *et al*., 2018). The use of NIV is associated with a marked reduction in the need for endotracheal intubation, a decrease in complication rate, reduced duration of hospitalization, and a substantial decrease in in-hospital mortality (Cortegiani *et al*., 2017). However, a ventilator might damage the lung tissue if excessive pressure is

applied for an extended period. In certain pulmonary obstruction diseases, the ventilator is required to assist the lungs in processing oxygen (Crisafulli *et al*., 2018). Figure 2.6 shows the current-generation ventilators used in the intensive care unit.

Figure 2.6: Current-generation intensive care unit ventilators (Puritan Bennett 840) (Srinivasan *et al*., 2020)

2.3.3 Dry powder inhaler (DPI)

DPIs have been used extensively to treat various local and systemic diseases and are superior to other formulations. This feature is attributed to the active substance's solid form that provides enhanced stability, ease of use, and ability to administer high dosages (Akdağ, 2019). Despite their apparent simplicity, DPIs are sophisticated devices. In order to deliver the active drug to the respiratory tract, users must inhale through the device. This inhalation provides energy that breaks up the compacted drug powder, a process known as de-agglomeration. It transports the de-agglomerated drug into the lungs (Levy *et al*., 2019).

There are four main types of DPI systems, as shown in Figure 2.7. The single-unit dose inhaler requires the patient to load the device with a single hard gelatine capsule containing the powder formulation prior to usage. This is the most common type of DPI device currently available. The second type is the single-unit disposable dose DPI. It contains a pre-metered amount of a single dose that can be discarded following use. The third type is the multiple-unit DPI. It delivers individual doses from pre-metered replaceable blisters, disks, dimples, or tubes. Another type of DPI is a

multiple-dose reservoir inhaler with a bulk amount of drug powder in the device with a built-in mechanism to meter a single dose (Lavorini *et al*., 2017).

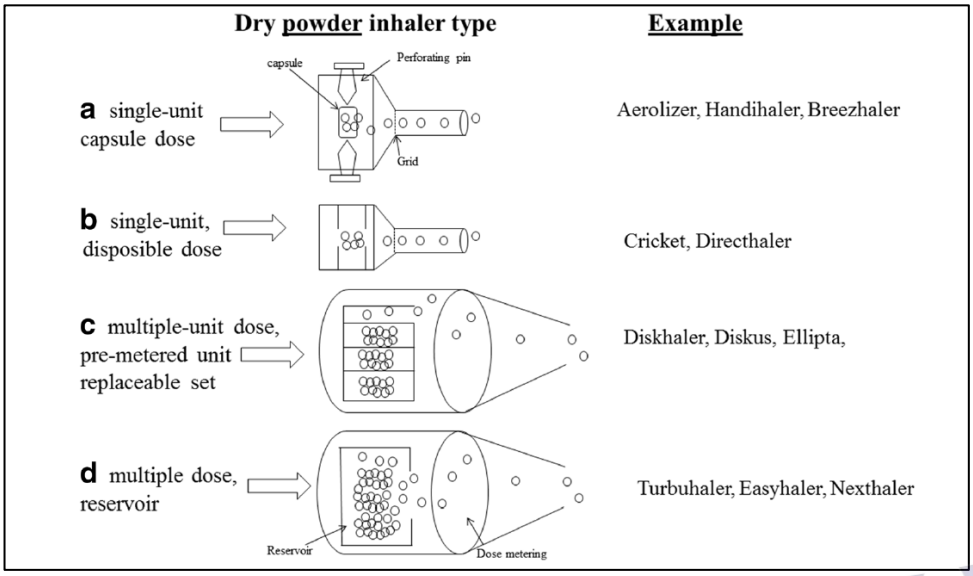


Figure 2.7: Examples of DPIs devices (Lavorini *et al*., 2017)

The efficacy of DPIs can be enhanced by developing novel drug delivery systems that optimize aerodynamic parameters, formulation stability, and drug physicochemical properties (Shetty *et al*., 2020). DPIs are actuated and driven by a patient's inspiratory flow. It does not require propellants to generate the aerosol or coordination of inhaler actuation with inhalation (Lavorini *et al*., 2017). Patients occasionally report that they are unsure whether or not they have taken their dose and that devices are discarded before they are completely empty (Alharbi *et al*., 2021). Micronization results in the formation of particles with a mass median aerodynamic (MMAD) of less than 5 μm that readily deposit in the lungs. Due to the strong, cohesive forces between such fine particles, disaggregation is complex, requiring large carrier particles such as lactose to assist in particle separation (Peng *et al*., 2016). Finally, to achieve deposition in the lungs, an inspiratory flow rate between 30 L/min to 120 L/min is required to separate the drug particles from the lactose carrier. Additionally, DPIs are not recommended for children, the elderly, and those severely ill as they often cannot provide a high enough respiratory flow rate (Shetty & Srinivasan, 2017).

2.3.4 Pressurized metered-dose inhaler (pMDI)

A pMDI is the first inhaler device commercially available to treat airway diseases. It is a cost-effective inhaler device that is easy to handle, reliable, and extensively utilized (Rogliani *et al*., 2017). A pMDI device consists of a metering valve and stem, a mouthpiece actuator, and a pressurized canister containing a medication suspended within a propellant (Gumani *et al*., 2017). Moreover, Figure 2.8 illustrates the schematic diagram of pMDI. The propellant is a compressed liquefied gas capable of maintaining a constant vapor pressure, essential for proper device functionality. It maintains a consistent suspension pressure regardless of the volume remaining in the canister. Otherwise, the pressure would fluctuate with each use of the inhaler, significantly limiting the device's effectiveness (Ruwaida *et al*., 2020).

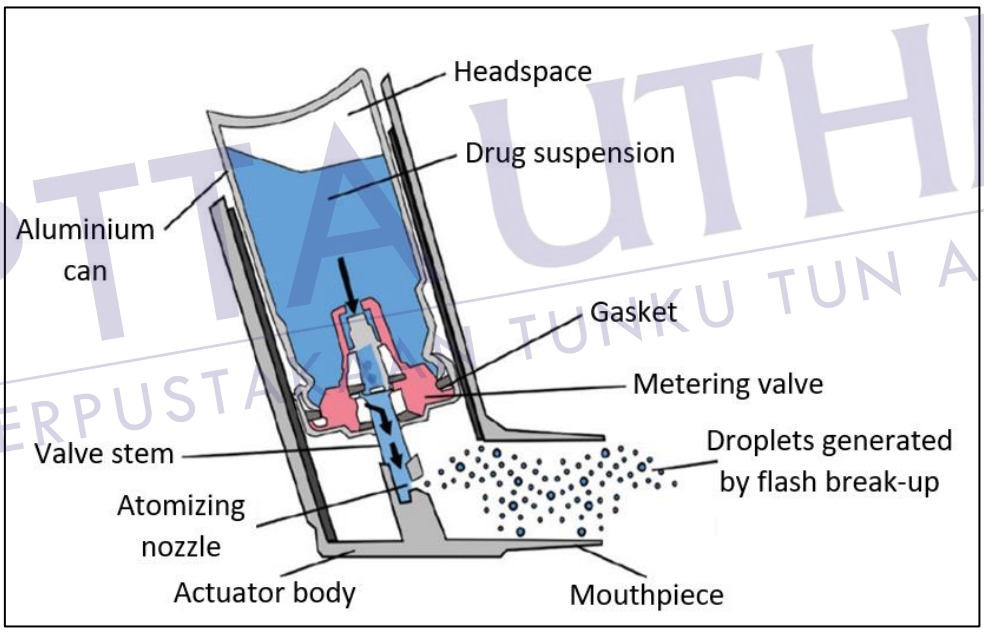


Figure 2.8: Pressurized metered-dose inhaler (pMDI) (Alharbi *et al*., 2021)

Initially, pMDI devices contained chlorofluorocarbons (CFCs) as a propellant. However, it has been phased out in favor of the CFC-free propellant hydrofluoroalkane (HFA) following the implementation of the 1987 Montreal Protocol — an international agreement to ban CFCs due to their documented role in ozone depletion (Andersen *et al*., 2018). However, this propellant switch has had no adverse effect on the capability of pMDI devices to adequately deliver inhaled medications to the lungs (Gumani *et al*., 2017). Instead, HFA-pMDI has been developed to deliver smaller particles with a

higher fine particle fraction (FPF) than CFC-pMDIs. (Roche & Dekhuijzen, 2016). These properties explained why pMDIs sparked unprecedented interest in lung drug delivery.

The HFA-containing pMDIs tend to produce much softer and warmer plumes, resulting in less oropharyngeal deposition (Gumani *et al*., 2017). Moreover, the warmer plume decreases the number of patients experiencing a phenomenon known as the 'cold freon' effect, a cold sensation felt at the back of the throat following device actuation. This is most certainly a result of the forceful plume impacting the back of a patient's throat. The ethanol-HFA-134a formulation delivered through a fine actuator orifice was warmer than the 100% HFA-134a formulation delivered through an orifice (Rogliani *et al*., 2017). However, pMDIs emit the dose at a high velocity, increasing the likelihood of premature deposition in the oropharynx. Thus, pMDI is limited to treating upper airway conditions due to low lung drug deposition. Only 10% to 15% of the dose reaches the lung. Furthermore, it requires careful coordination of actuation and inhalation (Kadu *et al*., 2018).

2.4 Challenges in treating respiratory problems during the pandemic

In most countries, most hospital resources are being allocated to COVID-19 management. Patients with asthma and COPD are at a significantly higher risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) amidst the current pandemic (Bouazza *et al*., 2021). Overburdened healthcare systems are experiencing a shortage of medical devices. Additionally, there are restrictions on using nebulizers to limit the transmission of SARS-CoV-2 infection (Fink *et al*., 2020). These factors combined make the current pandemic one of the biggest healthcare crises.

Although there is minimal data regarding the risks of transmitting viral infection with nebulized treatment, it has been a significant concern since the COVID-19 outbreak. There is compelling evidence that nebulization is associated with increased coronavirus transmission (Amirav & Newhouse, 2020). The jet nebulizer with the face mask possibly increased the risk of transmission due to the possibility of viral secretions entering the nebulizer's reservoir. In addition, this therapy is not

recommended for COVID-19 patients owing to the risk of virus transmission (Sethi *et al*., 2020).

Individuals with severe respiratory illness may need mechanical ventilation during a pandemic of COVID-19 (Attaway *et al*., 2021). Patients who develop severe respiratory conditions require oxygen therapy, with most of them needing ventilator support. Depending on the extent of the outbreak, there may be insufficient capacity in intensive care units (ICUs) to provide ventilator support to all the rapidly increasing cases (Buheji *et al*., 2020). Hospitals are rapidly running out of ventilators as the number of patients infected with COVID-19 increases. This unprecedented demand for ventilators puts immense pressure on governments and directs many resources toward a single goal. Additionally, the ventilator cost per unit is prohibitively high, limiting its use to severely sick patients exclusively.

When choosing a drug delivery device, the most crucial consideration is ensuring that the patients use it appropriately (Waller & Sampson, 2018). Some patients may have difficulty inhaling DPI forcefully, as it may be particularly challenging for those with nerve or muscular weakness (Ibrahim *et al*., 2015). Poor coordination, such as blowing and exhaling directly into the device, might potentially result in medicine scattering prior to inhalation (Levy *et al*., 2019). Young, elderly, or chronically ill patients with poor coordination may have difficulty using DPIs (Lavorini *et al*., 2017; Shetty & Srinivasan, 2017). As a matter of fact, individuals who suffer from respiratory problems are unable to inhale appropriately.

Several reports concluded that pMDI was most likely applicable and effective in the current situation. It was affordable, portable, and as effective as other aerosol generation systems for drug delivery when properly used (Shetty *et al*., 2020). The multi-dose capability ensures that a dose is immediately available whenever required to treat a respiratory condition (Rogliani *et al*., 2017). Unlike nebulizer therapy, which typically takes between 5 and 30 minutes, a dose can be delivered in a matter of seconds (Zhao & Yu, 2019). As a result of the pandemic, the utilization of metered-dose inhalers (MDIs) as an alternative to nebulized therapy has increased substantially (Sethi *et al*., 2020). However, a lack of coordination between inhaler actuation and pMDI inhalation might decrease drug deposition in the lung, only around 10% to 15% (Kadu *et al*., 2018). Further improvement in pMDI may result in the most optimal and desirable drug delivery to the lungs.

2.5 Factors enhancing the performance of pMDI

The performance of the pMDI is determined by its velocity and particle size, which contribute to increased drug deposition in the lung. The geometry and design of the actuator nozzle in pMDI are two factors that impact these properties. Additionally, the actuator nozzle design significantly impacts the spray characteristics of the pMDI (Wilkinson & Anderson, 2020). The combination of nozzle parameters, including orifice diameter, length of the orifice, and actuator angle inside the actuator nozzle, influence spray patterns, spray plume, particle velocity, particle size, and drug deposition (McCabe *et al*., 2012; Copellia *et al*., 2016). Reduced particles' velocity and drug particle size may decrease oropharyngeal deposition and increase the inhalation success rate (Gumani *et al*., 2017).

2.5.1 Diameter of the orifice

The actuator design is critical because the orifice diameter partially determines the aerosol particle size, which varies between 0.14mm and 0.60mm (Zhu *et al*., 2015). Aerosol particle size is proportional to the diameter of the orifice, and particle size affects lung deposition (Hou *et al*., 2015). Particles with an aerodynamic diameter of 1µm to 5µm are deposited in the airways and alveoli. Most particles>10µm are deposited in the oropharynx and subsequently swallowed, whereas particles <1µm are mostly exhaled. In general, drugs should have a diameter of <5µm to decrease oropharyngeal deposition (Bake *et al*., 2019). Figure 2.9 illustrates the various sizes of drug particles that enter the specific area. The dosage and proportion of fine particles may be enhanced using actuators with smaller orifice diameters. More precisely, improved atomization accomplished via a smaller nozzle orifice results in more excellent dispersion of the smaller droplets throughout the airways (Carvalho & McConville, 2016).

LIST OF PUBLICATIONS

1. **Abd Rahman, M. F**., Seri. S.M., Asmuin, N.Z., Taib, I., and Rosman, S.R. (2021). Response surface methodology (RSM) approach for optimizing the actuator nozzle design of pressurized metered-dose inhaler (pMDI). CFD Letters an International Journal, 13(7), 27-44.
2. **Abd Rahman, M. F**., Asmuin, N.Z., Taib, I., Nazar, J., Ismail, A., and Khairulfuaad, R. (2021). Investigate flow characteristics of metered-dose inhaler (MDI) disposable inhaler spacer (Aerocup) for COVID-19 patient by using computational fluid dynamic (CFD). CFD Letters an International Journal, 12(12), 63-74.
3. **Abd Rahman, M. F**., Asmuin, N.Z., Taib, I., Mat, M.H., and Khairulfuaad, R. (2020). Influence of actuator nozzle angle on the flow characteristics in pressurized-metered dose inhaler using CFD. CFD Letters an International Journal, 12(6), 67-79.
4. **Abd Rahman, M. F**., Asmuin, N.Z., Nasir, N.F., Taib, I., Mat, M.H., and Khairulfuaad, R. (2020). Effect of different orifice diameter on the flow characteristic in pressurized metered dose inhaler by using CFD. CFD Letters an International Journal. 12(3), 39-49.
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