PARTICLE DEPOSITIONS IN MULTI STAGE LIQUID IMPINGER AS SIMPLIFIED LUNG MODEL USING COMPUTATIONAL FLUID DYNAMIC

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DEDICATION

Dedicated to

My beloved mother, Raudzah Binti Abdul Halim

My late father, Azmi Bin Mohamed

My soul-sisters and brothers, the Azmis

Musliha

Humaidah Amani

Amir Iskandar

Ikhwan Mukhlis

Nur Husna Umairah

My nephew, Ahmad Fawwaz Haqeem

A real blessing from God

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ABSTRACT

Inhaled medication is typically used to treat obstructive pulmonary disease and systemic diseases. The effectiveness of pulmonary drug delivery depends on the amount of drug deposited beyond the oropharyngeal region, the place where the deposition and the uniform distribution occurred. In this study, the performance of multistage liquid impinger (MSLI) simplified model which imitates the physiological lung in delivering the drug was analyzed. In order to achieve this main aim, the airflow patterns and particle depositions efficiency were evaluated in MSLI simplified model using computational fluid dynamic of COMSOL® software. The particle deposition efficiency is studied by varying flowrates (30.0 L/min, 60.0 L/min and 100.0 L/min) and particle sizes (0.1, 1.0, 3.0, 5.0, 10.0 μm) of salbutamol sulphate (density 20.0 kg/m^3). The highest particle deposition occurred at flowrate 100.0 L/min and particle size of 1.0 μm as the deposition yield was 15.55% compared to flowrate 60 L/min and 30 L/min which were 10.50% and 3.09% respectively. Previous studies claimed that higher inhalation flowrate generated dispersion forces for sufficient inhalation flowrate thus enhanced higher deposition efficiency. The paired-samples T-test shows there were significant different ($t= -15.400$, $df= 4$, $p <0.05$) in the performance of particle depositions in MSLI simplified model with different flow rates (60.0 L/min and 100.0 L/min). Thus, the efficient fine particle deposition was significantly contributed by higher flowrate. This study also revealed that particle size ranges from 1.0 to 3.0 μm was the most suitable for inhalation treatment. Smaller particle size less than 1.0 μm was not suitable as it tended to exhale before it deposit of while larger particle (more than 5.0 μm) was not suitable for inhaled drug. In conclusion, vigorous air flow pattern promotes higher particle deposition. For efficient fine particle depositions, it is important to consider not only the particle size distribution, but also the flowrate as vital aerosol transportation agent. Statistical analysis, two-way ANOVA indicated that there was a statistically significant interaction between the effect of flowrate and particle size on particle deposition efficiency, $F (8, 30)=5.857$, $p=0.00$.

ABSTRAK

Ubat sedutan kebiasaanya digunakan untuk merawat penyakit kronik pulmonari dan penyakit sistemik. Keberkesanan penghantaran ubat pulmonari bergantung kepada jumlah ubat yang termendap menjangkaui kawasan orofaring, tempat di mana pemendapan dan tabur seragam berlaku. Dalam kajian ini, prestasi model mudah cawangan cecair pelbagai peringkat yang menyerupai fisiologi paru-paru dalam penghantaran ubat telah dianalisa. Untuk mencapai matlamat utama ini, corak aliran udara dan kecekapan pemendapan zarah telah dikaji dalam model mudah MSLI menggunakan pengiraan dinamik bendalir iaitu melalui perisian COMSOL®. Kecekapan pemendapan zarah dikaji dengan perbezaan kadaralir (30.0 L/min, 60 L/min dan 100 L/min) serta berlainan saiz zarah (0.1, 1.0, 3.0, 5.0, 10.0 μm) salbutamol sulfat (ketumpatan 20 kg/m^3). Pemendapan zarah tertinggi berlaku pada aliran 100 L/min dan pada saiz zarah 1.0 μm dengan hasil mendapan 15.55%, berbanding dengan kadaralir 60 L/min dan 30 L/min iaitu masing-masing 10.50% dan 3.09%. Kajian terdahulu menyatakan kadaralir pernafasan yang tinggi menjana daya penyebaran kadaralir pernafasan yang mencukupi dan meningkatkan kecekapan pemendapan. Ujian-T-sampel berpasangan menunjukkan terdapat perbezaan yang ketara ($t=-15.400$, $df=4$, $p<0.05$) dalam prestasi pemendapan zarah dalam model mudah MSLI dengan kadaralir yang berlainan (60 L/min dan 100 L/min). Oleh itu, keberkesanan pemendapan zarah halus adalah penting disumbang oleh kadaralir yang tinggi. Kajian ini juga menunjukkan bahawa julat saiz zarah dari 1.0 hingga 3.0 μm adalah yang paling sesuai untuk rawatan pernafasan. Saiz zarah yang kecil kurang dari 1.0 μm tidak sesuai kerana ia cenderung terhembus keluar sebelum dapat mendap manakala zarah yang besar (lebih daripada 5.0 μm) tidak sesuai untuk ubat sedutan. Sebagai kesimpulan, corak aliran udara yang kuat menggalakkan pemendapan zarah yang tinggi. Bagi pemendapan zarah halus yang cekap, adalah perlu untuk mengambilkira bukan sahaja pengedaran saiz zarah, tetapi juga kadaralir sebagai ejen pengangkutan zarah yang penting. Analisis statistik, dua hala ANOVA menunjukkan terdapat interaksi ketara secara statistik antara kesan kadaralir dan saiz zarah ke atas kecekapan pemendapan zarah, $F(8, 30)=5.857$, $p=0.00$.

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LIST OF ABBREVIATIONS

ACI	-	Andersen Cascade Impactor
APIs	-	Active Pharmaceutical Ingredients
APSD	-	Aerodynamic Particle Size Distribution
CFD	-	Computational Fluid Dynamics
COPD	-	Chronic Obstructive Pulmonary Disease
DE's	-	Deposition Efficiencies
DEF	-	Deposition Enhancement Factor
DF	-	Deposition Fraction
dp	-	Drug Product
DPIs	-	Dry Powder Inhaler
FPF	-	Fine Particle Fraction
GSD	-	Geometric Standard Deviation
LD	-	Laser Diffractometry
MMAD	-	Mass Median Aerodynamic Diameter
MMI	-	Marple-Miller Impactors
MMD	-	Mass Median Diameter
MSLI	-	Multi-stage Liquid Impinger /
MOUDI	-	Micro Orifice Uniform Deposit Impactor
NGI	-	Next Generation Pharmaceutical Impactor
PDA	-	Phase-Doppler Particle Size Analysis
pMDIs	-	Pressurised Metered Dose Inhalers
QCM	-	Quartz Crystal Impactor
TI	-	Twin Impinger
TOF	-	Time-Of-Flight
WLAM	-	Whole-Lung-Airway Model

LIST OF SYMBOLS

°	-	Degree
%	-	Percent
<	-	Lesser than
≤	-	Lesser than and equal to
>	-	Bigger than
≥	-	Bigger than and equal to
=	-	Equal to
α	-	Womersley number
C	-	Celcious
dae	-	Aerodynamic diameter
dgeo	-	Geometric diameter
G	-	Generation
k	-	Kilo
Kg/m3	-	Kilogram per meter cube
mg	-	Miligram
s	-	Second
ρp	-	Particle
ρ0	-	Unit density
Pa	-	Pascal
χ	-	Dynamic shape factor
1-D	-	One-dimensional
3-D	-	Three-dimensional

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Inhaled drug therapy has gained extensive acceptance and has been used a long time ago as an effective non-invasive alternative for local and systemic medicine delivery of active pharmaceutical ingredients (APIs) (L. Chen, Okuda, Lu, and Chan, 2016; Kolanjiyil and Kleinstreuer, 2016). It does not only treat 'traditional diseases' such as asthma and other pulmonary disease, but it also capable to treat other systemic diseases like diabetes, migraine, angina pectoris, kidney failure, cancer, bone disorders, acute lung injury, tuberculosis due to an advancement in analysis technology (Lalas et al., 2017).

This route of drug delivery has many advantages compared to other non-invasive administration methods such as an oral, buccal, trans-dermal, vaginal, nasal or ocular administration as it allows the use of lesser doses and lower systemic side effects (Kolanjiyil & Kleinstreuer, 2016; Labiris & Dolovich, 2003a). This treatment also provides rapid absorption of the inhaled drug aerosol, especially nano-drugs due to unique features of lungs including highly vascularized surface area (80-100.0 m^2 for adult with 5.0 L/min blood flow) and thin alveolar-capillary membrane (0.1-0.5μm), low enzymatic activity (L. Chen et al., 2016; Depreter and Amighi, 2010), and result in rapid bio-distribution when targeting diseased organs (Kolanjiyil & Kleinstreuer, 2016). In addition, this treatment method allows systemic drug delivery without liver passage due to low metabolic activity in the lungs, thus avoiding first-pass metabolism in the liver. Hence, the lung provides a favourable environmental condition for therapeutic drugs and avoids for enzymatic and hepatic degradation in the gastrointestinal tract (Lalas et al., 2017).

For the past decade, investigations have been done to measure the inhaled drugs deposition in the human respiratory airways. Unlike in vivo experimental that using a whole or living organism in laboratory procedure only offer total or surface deposition data, mathematical simulations provide more meticulous information in terms of space and time which experimental observation fails to provide (Phuong & Ito, 2015). The most common mathematical modelling that applies to forecast fluid flow inside a system is Computational Fluid Dynamics (CFD). CFD can predict the deposition fraction and flow structure of the respiratory system (Saber and Heydari, 2012). Fluid flow characteristics can be determined by changing one or more input airflow parameters. Moreover, numerical simulation also permits study of different flow variables and forces of fluid flow in a specifics perspective (Rahimi-Gorji, Pourmehran, Gorji-Bandpy, & Gorji, 2015).

1.2 Problem Statement

It is challenging to capture the particle deposition for the entire pulmonary airways because of the complex structure of the lungs (Kolanjiyil & Kleinstreuer, 2013). Recent lung airway models are only restricted to the few upper airway generations. Due to limited resources of imaging technology and tiny branching structure of alveoli, lower part of airways are the hardest part to reconstruct (Lin, Tawhai, & Hoffman, 2013). Since it is difficult to simulate the three-dimensional (3-D) aerosol deposition for the whole lung airways, researcher has come out with simplified configuration as an alternative solution to overcome the limitation of computational of real lung geometry (Hansen & Ampaya, 1975; Horsfield & Cumming, 1968; Yeh & Schum, 1980). Simplified model which imitate the structure of human lung are easy implementation and low requirements of computational resources (Kolanjiyil & Kleinstreuer, 2016) and it has tendency to satisfy specific modelling requirement which can cover all 23-generation of lung airways that real human lung does not (Hofmann, 2011).

In laboratory procedure, it is difficult to obtain the detailed information of air behaviour or particle transport, local deposition patterns and surface densities of particle deposited in branching airways (Z Zhang, Kleinstreuer, & Kim, 2002). In vivo studies of aerosol deposition in the human lungs are also limited to human safety and by resolution limitation of current imaging technologies. In additions there were no clear studies that had been reported on the unsteady inhalation patterns and steady flow rates in pulmonary drug deposition analysis (Inthavong, Tu, & Heschl, 2011). The computed deposition also produced unpredicted result as the study was conducted based on simple inlet conditions and semi-analytical correlations for the deposition mechanisms (Hofmann, 2011).

Therefore, CFD simulation can fill the gap to achieve the deposition fraction and flow structure of the respiratory system (Saber & Heydari, 2012; Z Zhang et al., 2002) and provide unprecedented level of detail which experiment data cannot provide (Koullapis, Kassinos, Bivolarova, & Melikov, 2016). Furthermore, for every experimental data set it is important to validate the data using computer simulation models and gaining new physical perception, thus by applied CFD simulation can offer more detailed, accurate particle deposition studies with development of efficient, cost effective, and as an important component in industrial, academic research and preliminary design of a new product (Zhe Zhang, Kleinstreuer, & Kim, 2009).

Multi Stage Liquid Impinger (MSLI) is the most accurate impactor in evaluating the particle deposition of Dry Powder Inhaler (DPIs) in pharmaceutical industry. The system is compatible with human respiratory function as it consists five stages including filter, operates between air flowrate of 30.0 and 100.0 L/min and able to filter particles between 1.7 and 13.0 μm (Nichols, Mitchell, Shelton, & Roberts, 2013).

1.3 Research Objective

The main aim of the study is to analyse the performance of MSLI which imitate the physiological lung in delivering the drug. In order to achieve the aim, two objectives are set as follows:

i. To determine airflow patterns in the Multistage Liquid Impinger (MSLI) simplified model.
ii. To analyse particle depositions in the Multistage Liquid Impinger (MSLI) simplified model.

1.4 Scope of Study

The scopes of this study are:

i. To use the SOLIDWORK® software as a tool to develop the MSLI simplified model.
ii. To analyse the air flow patterns and particles deposition in MSLI simplified model by applying differences variables of particle sizes and air flow rate using COMSOL® software.
iii. The study done on modelling of the MSLI simplified model and does not covered the experimental works.

1.5 Significance of Study

Since many challenges in modelling human respiratory airway due to its complex structure and limited resources of imaging technology, thus a simplified model of MSLI which imitate the human lungs structure was implement in this study.

It is easy to implement because MSLI simplified model requires low computational resources and most importantly, it represents all 23-generation of lungs airways that human lungs model does not applied (Kolanjiyil & Kleinstreuer, 2013).

This is the first attempt to model the industrial pharmaceutical device of MSLI simplified model which is an accurate impactor that evaluates the particle deposition of DPIs in pharmaceutical industry. The system in MSLI is compatible with human respiratory function as it consist five stages including filter which can imitate the function of alveolus that filter the blood in human lungs. It operates between air flowrate of 30.0 L/min and 100.0 L/min indicating different human lungs activity and able to filter particles between 1.7 and 13.0 micron in the different of MSLI stages (Jolyon P. Mitchell & Nagel, 2003).

In laboratories procedures, there were no clear studies regarding the unsteady inhalation patterns and steady flow rates in pulmonary drug deposition analysis, especially in pharmaceutical industry device (Inthavong et al., 2011). Thus, CFD simulation in MSLI allow to capture the condition inside that model, the flow structure and deposition fraction thus produce detail insight flow the real respiratory system which experiment data cannot provided (Saber & Heydari, 2012; Z Zhang et al., 2002).

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