



## CFD Analysis for Valve-Holding Camber Permanent Inhaler Spacer (AerospaAcer) with Different Valves

Riyadhthusollehan Khairulfuaad<sup>1</sup>, Norzelawati Asmuin<sup>1,\*</sup>, Juntakan Taweekun<sup>2</sup>, Azizan Ismail<sup>1</sup>, Nabil Izzuddin Shahhidan<sup>1</sup>

<sup>1</sup> Department of Aeronautical Engineering, Fakulti Kejuruteraan Mekanikal, Universiti Tun Hussein Onn Malaysia, 86400 Batu Pahat, Johor, Malaysia

<sup>2</sup> Department of Mechanical and Mechatronics Engineering, Faculty of Engineering, Prince of Songkla University, Hat Yai, Thailand

### ARTICLE INFO

#### Article history:

Received 17 October 2023

Received in revised form 19 November 2023

Accepted 15 December 2023

Available online 15 January 2024

#### Keywords:

Computational Fluid Dynamic (CFD);  
Flow characteristic; Metered- dose  
inhaler spacer; Valve-Holding Chamber

### ABSTRACT

During the COVID-19 pandemic, data statistics showed that patients with respiratory problems become infected. One of the therapy techniques for the respiratory condition was the use of a metered-dose inhaler and spacer. The objective of this paper is to determine the flow parameters of three types of valves which is duckbill valve, cross slit valve and umbrella valve in inhaler spacer to compare fluid flow between valve. Previous researchers chose the duckbill valve to control fluid flow in inhaler spacer. The flow characteristics are unaffected by the materials used in the new disposable inhaler spacers, such as paper and polylactic acid (PLA). Several design valves reduced the skewness below 0.94 by suppressing the fillet and chamfer. ANSYS Workbench Fluent 19.2 is used to calculate flow parameters such as turbulence kinetic energy (TKE), turbulence eddy dissipation (TED), velocity, particle velocity magnitude, streamline, and vector velocity. The setup input data is based on the previous researcher's specified parameters such as viscosity model, drug characteristics (salbutamol and propellant), discrete phase model (DPM) equal to 80, boundary condition model, and SIMPLE technique. For the three types of valves, the nozzle injection used a 0.50-millimetre dimension. The simulation work is cross-checked against the results of prior simulations. Within each iteration, the transient flow employed a time step size of 0.01 for 200 steps. The results show that computational analysis can distinguish between models of varying complexity. The TED, TKE, and velocity graphs showed the approximate value between the model geometries. Overall, the study was successful in achieving the desired velocity magnitude in terms of visual and graph representations of the various valve.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by the coronavirus 2 (SARS-CoV-2; formerly known as 2019-nCoV), which was originally discovered in Wuhan City, Hubei Province, China, during a respiratory sickness outbreak. It was announced to the World Health Organization for the first time on December 31, 2019. (WHO). COVID-19 was declared by the World

\* Corresponding author.

E-mail address: [norzela@uthm.edu.my](mailto:norzela@uthm.edu.my) (Norzelawati Asmuin)

<https://doi.org/10.37934/cfdl.16.6.5367>

Health Organization on January 30, 2020 [6]. In 2019, the coronavirus disease 2019 (COVID-19) first appeared in Wuhan, Hubei Province, China, and has since spread to over 100 countries worldwide. Coronavirus Disease 2019 (COVID-19) has been a big public health epidemic around the world since December. Since there are no pharmaceutical treatments for COVID-19, countries around the world are using non-pharmacological public health measures such as separation, quarantine, social distancing, and group containment. COVID-19 patients can be identified using diagnostic testing kits that detect the virus's presence. In COVID-19 patients, imaging procedures such as chest X-rays and pulmonary CT scans may be used to detect pneumonia. COVID-19 is divided into five therapeutic phases [2].

The people who infected positive COVID-19 must be isolated at special room or space about 14 days before continuing the work as usual. Commonly, the serious case placed in the intensive care unit (ICU) as soon as possible. The best practices for all those who to keep washing hand always and do not touch face skin with hand. Always compulsory to use the face mask at any assemblage place. If possible, prevent to come any assembly program [17].

COVID-19 outbreaks also affected asthma patient globally. Asthma respiratory disease are associated with human respiratory system which have similarities with COVID-19 disease. If a person having asthma disease is tested positive with COVID-19, the outcomes would be death. This is due to the extremely dangerous and critical condition of COVID-19 could cause to its victim especially asthma patient. Asthma attack often triggered by dust particle which enter patient's respiratory system through inhalation and exhalation process [12, 16, 18].

## **1. Introduction**

### *1.1 Human Respiratory System*

The respiratory system is made up of many organs that are engaged in ventilation. They include the nose, pharynx, larynx, trachea, bronchi, and lungs as shown in Figure 1. The respiratory system has two important functions: it transports oxygen into our bodies, which our cells require to survive and operate properly, and it helps remove carbon dioxide, which is a waste product of cellular function. The nose, throat, larynx, trachea, and bronchi all work together to filter air and deliver it to our lungs. The tiny air sacs known as alveoli pump oxygen into the bloodstream and push carbon dioxide up into the air. When something goes wrong in a component of the respiratory system, such as a pneumonia outbreak, getting the oxygen we need to remove the waste product carbon dioxide becomes more difficult. Common respiratory symptoms include shortness of breath, coughing, and chest pain [10].

Respiratory problem such as asthma had become the topic of discussion associated with human lung. Thus, an inhalation treatment using inhaler are often used to control the symptom [1, 7, 8]. Asthma could link to depression as it somehow lessens patient's everyday routine. Even though asthma not being classified as a chronic disease, but the effect could be fatal. Asthma is a systemic inflammatory condition of the lower respiratory tract caused by a combination of genetic predisposition and exposure to a variety of conditions in the climate. It's a long-term respiratory illness that causes morbidity, death, and a decline in health-related quality of life (HRQoL). Asthma affects an estimated 334 million people worldwide.

The COVID-19 outbreak is causing depression not only among healthy persons, but also among those who are ill. Excessive psychological stress (in terms of consistency, quantity, frequency, and/or duration) can lead to the development of clinical asthma in susceptible individuals. Asthma interfering with everyday life, breathlessness, night effects, use of bronchodilators, and inadequate adherence to medical care were all linked to depression.

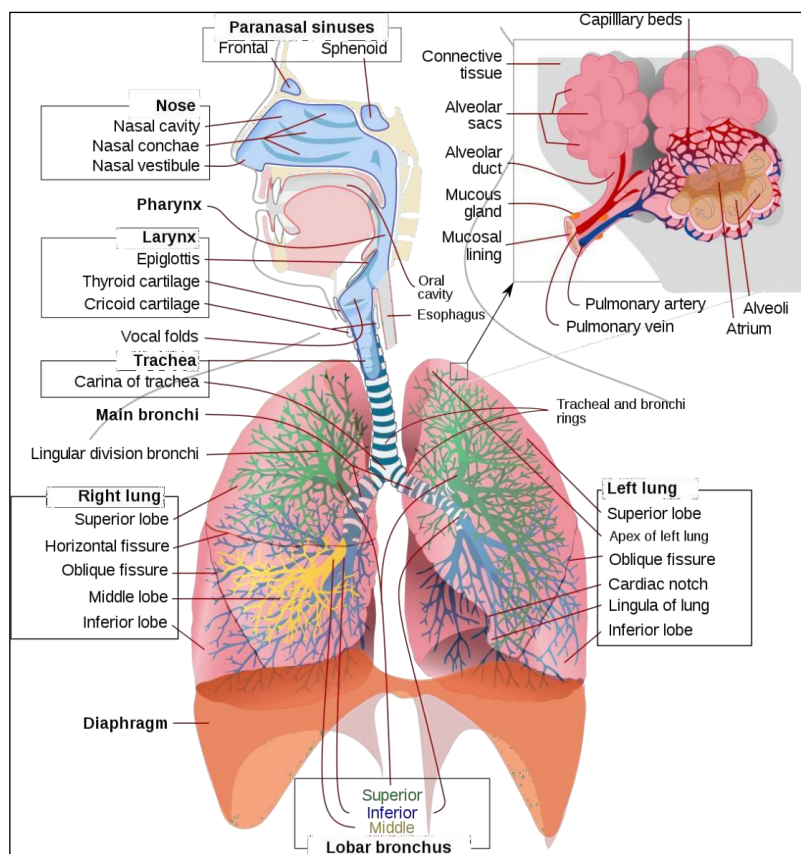


Fig. 1. Structure of respiratory system [3]

## 1.2 Inhaler Spacer

Inhaler is a medical device that releases drugs in the form of puffs into the lungs, allowing the user to breathe it in. Usually, patient would use inhaler directly without any additional device. However, a direct use of inhaler medication could create health complication to asthma patient. A technique in using inhaler must be correct otherwise it would produce ineffective medical treatment [1]. Hence, a spacer is recommended by many physicians as an alternative aid to ease the use of inhaler. Spacer is a tube made of plastic with a mouthpiece used by asthma patient to help contain drug medication from inhaler during asthma attack. Asthma patient may connect their inhaler with spacer as shown in Figure 2 to provide easy breathing while inhaling the drug medication from actuated inhaler. The unsteady tidal breathing of asthma patient during the attack could put them in a hard situation if they were not using the spacer. The time it takes for asthma patient during asthma attack to inhale the drug and allows it to reach the lungs is lengthened by using a spacer. This provides more efficient inhalation process in order to provide relax and relief effect on patient. In addition, the spacer concentrates the drug into a channel, preventing it from leaking into the atmosphere. Spacers are particularly useful for younger children or those who are only beginning to use an inhaler [10].



**Fig. 2.** Inhaler and spacer attached together

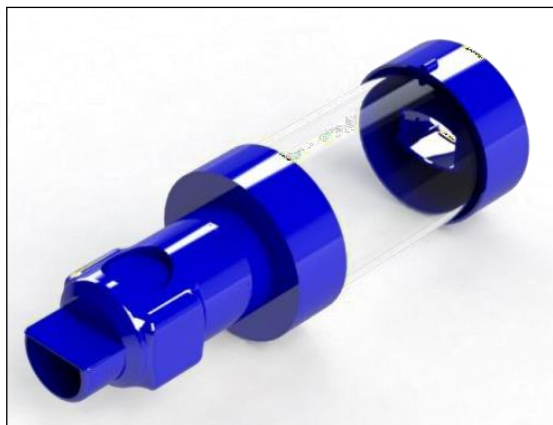
A spacer with a one-way valve at the mouthpiece is known as a valved-holding chamber. Like spacer, a valved-holding chamber is also a spacer but comes with more features. It is more than just a "space" between the mouth and medication [9]. The one-way valve act to guide the flow of drug medication from actuated inhaler directly towards patient mouth or nose as they inhale it. The valve also prevents exhalation air from patient to go inside the chamber of the valve-holding chamber. This feature of VHC helps patient to get more inhalation medication, prevent waste of drug medication, and avoid the drug medication intended for relief effect to be contaminated with exhalation air from themselves. Some VHC comes with more than just a one-way valve. It comes with a body made from electrostatic discharge (ESD) materials. These advantages prevent VHC from having an electrostatic effect which could cause the drug particle actuated from inhaler to be sticking to the wall of the chamber. Hence, provide more medication to patient to improves relief effect by maximizing the use of every single puff of the inhaler. Both valved chambers and spacers are silicone tubing that connect to the metered-dose inhaler.

Like many other medical devices, every features it provided has a significant effect toward patient. Thus, researcher comes with different approaches to understand the effect. Duke *et al.*, [4] focuses on the actuator orifice of the inhaler to better understand the effect of its diameter. The purpose of this research article was to identify the flow characteristics in the new VHC called AerospaAcer. The findings are related to streamline, velocity vector, turbulence kinetic energy, turbulence energy dissipation and velocity.

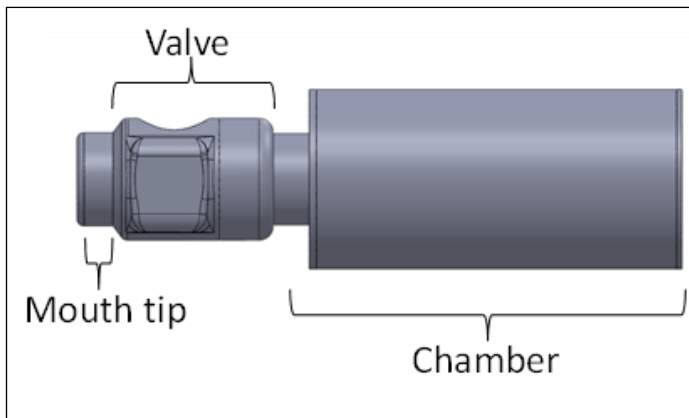
## **2. Methodology**

### **2.1 3D Geometry Model of AerospaAcer**

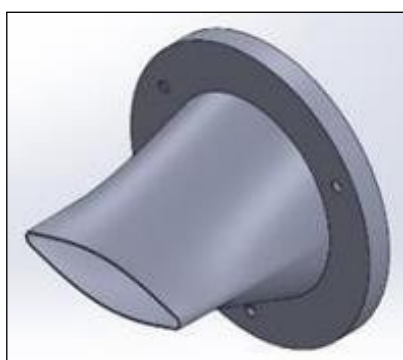
The 3D geometry of AerospaAcer was drawn based on earlier research (copyrighted with the number LY2020002678) using SOLIDWORK 2019. SOLIDWORK software is a computer aided design, CAD software which researcher nowadays used to draw 3D model for their research [5, 11, 13-15]. The 3D AerospaAcer model as shown in Figure 3 is drawn using some tool features provided in the software. AerospaAcer was design with three (3) section which is chamber, valve, and mouth tip as shown in Figure 4. In this research, three AerospaAcer model with three different type of inhalation one-way valve is modelled. The three types of valves are duckbill valve, cross slit valve, and umbrella valve as shown in Figure 5. All three types of valves have different geometry entirely. This would produce different analysis on the flow behavior of the drug particle. The valves are positioned at the same location inside the AerospaAcer which is at the valve section as shown in cross-section view in Figure 6.



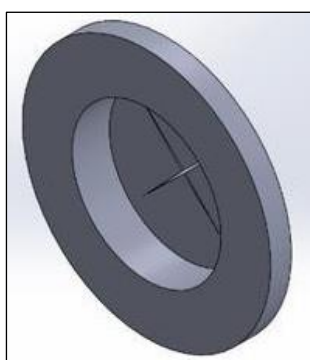
**Fig. 3.** The isometric view of AeroSpaAcer modelled with SOLIDWORK 2019 software



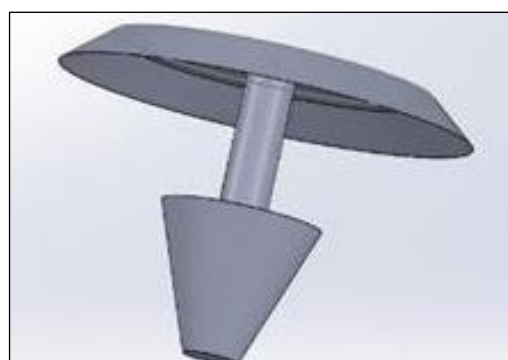
**Fig. 4.** Side view of AeroSpaAcer with three (3) section



(a)

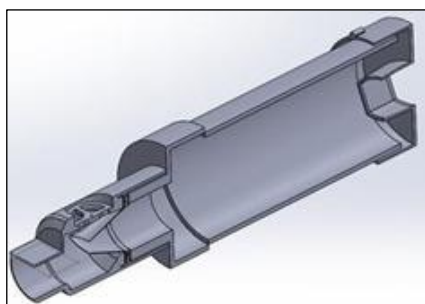


(b)

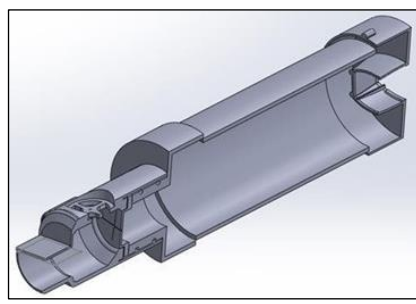


(c)

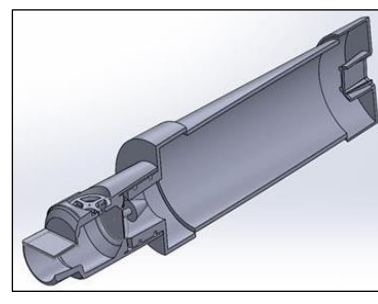
**Fig. 5.** Three types of valve (a) duckbill, (b) cross slit, and (c) umbrella valves



(a)



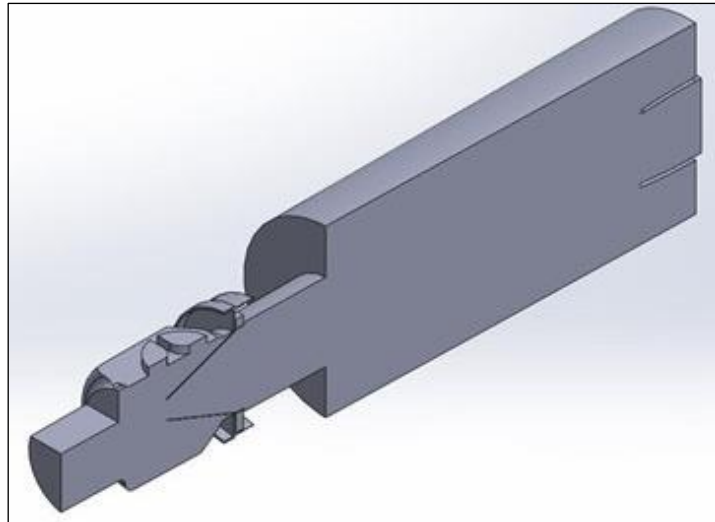
(b)



(c)

**Fig. 6.** Isometric cross-section view of AeroSpaAcer with (a) duckbill, (b) cross slit, and (c) umbrella valves

Numerical method is used to find the numerical approximations to the solution of ordinary differential equations (ODEs). Their use is also known as numerical integration. Hence, the commercial Computational Fluid Dynamic (CFD) ANSYS-Fluent Version 19.2 was used to analyse the distribution of flow in the AeroSpaAcer. The geometry in Figure 6 was intersected and subtracted inside SOLIDWORK 2019 software to create a fluid domain geometry for simulation purposes as shown in Figure 7.

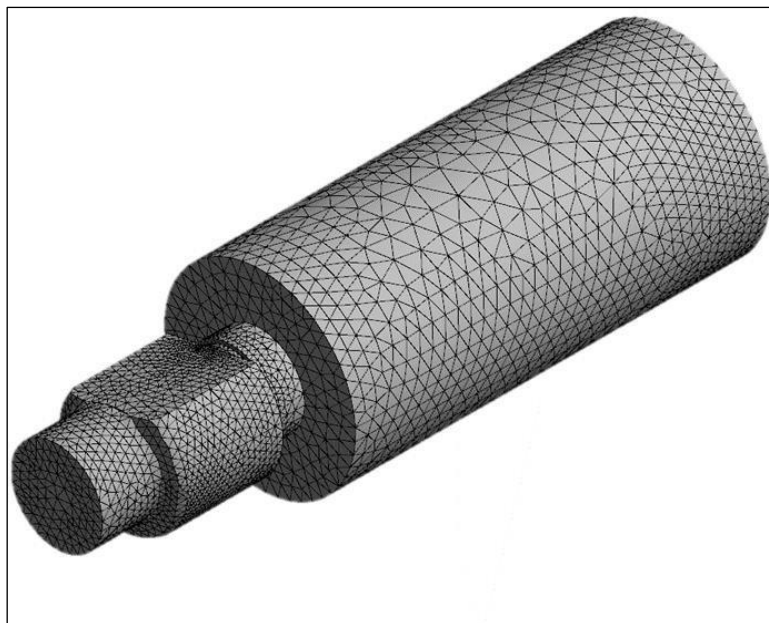


**Fig. 7.** Fluid domain of AerospaAcer model

## 2.2 Computational Fluid Dynamics Simulation using ANSYS Fluent Version 19.2

Based on previous investigations, the flow in the inhaler spacer was modelled using computational fluid dynamics, CFD analysis [11, 13]. In medical sectors of disease, the CFD has become a vital tool for medical engineering studies. CFD software such as ANSYS Fluent on the other hand, is a platform for solving and analyzing fluid flow problems. The computer serves in the simulation of gas and liquid interactions with surfaces determined by boundary conditions. It is extremely beneficial for engineers to be able to analyze data fast, easily, and at a minimal cost. The 3D model of AerospaAcer was solved and analyzed using ANSYS Fluent in this study. To generate further findings, the simulation's parameter was supplied. The data simulation in CFD is divided into three stages: pre-processing, solving, and post-processing. Pre-processing involved in 3D drawing and discretization meshing process. After pre-processing was done, the governing equation is solved with all parameter and boundary condition which was set earlier. Next, visualization of results with contour was done in post-processing steps.

After the 3D model file of AerospaAcer is inserted in the ANSYS Fluent version 19.2 software, discretization meshing process is done to the model as shown in Figure 8. Suitable skewness and orthogonal quality for all models were analyze. This process is called grid independent test, GIT. GIT is a process finding the most suitable mesh discretization method for fluid domain model. This process is compulsory to get the best data needed for analysis. By repeatedly changing and varying the element size in global mesh setup for fluid domain model, a series of skewness, orthogonal, and number of nodes for the model was constructed. Based on these data, one (1) mesh discretization setup is chosen and use as the most suitable setup for each fluid domain model. In this research, GIT for all model is done separately. Their number of elements is ranged from 2986220, 11033657, and 1713718 for duckbill valve, cross slit valve, and umbrella respectively. After getting the suitable value, setup the parameters such as model, material, boundary condition, discrete phase and more. Set the time steps and number of iterations as 0.01 and 1 before running the calculation. Next, extract the data of numerical simulation after completed. The simulation was done using Intel(R) Core (TM) i7th-Gen CPU and at 3.30 GHz processor with 16 GB of RAM, which run on Windows 10 with 64-bit Operating System.



**Fig. 8.** Discretization meshing process for AerospaAcer

The simulation was done with a boundary condition inserted in ANSYS Fluent version 19.2 software accordingly. In the meshing modeler, a boundary condition was applied to the chosen sections. Inlet, outlet, and wall are the three basic components in the model. The velocity magnitude was set to 0.8 m/s in the inflow boundary condition, and the gauge pressure was set to 75 psi. The temperature in the thermal tabs was set to 290K. 0.911, 0.085 and 0.004 were used to set the data input for HFA- 134a propellant, alcohol, and salbutamol. The outlet surface set by outflow, while the whole body (except inlet and outlet) set as escape wall. The drug properties of drug from inhaler was also consider following previous research by Rahman *et al.*, [13] as shown in Table 1.

**Table 1**  
 Properties of drug formulation in inhaler

Properties	Propellant-HFA	Ethanol	Salbutamol 134a
Density (kg/m <sup>3</sup> )	1311	790	1230
Specific Heat (j/kg-k)	982	2470	-
Thermal conductivity (w/m-k)	0.0857	0.182	-
Viscosity (kg/m-s)	0.000211	0.0012	-
Molecular weight (kg/kmol)	102.032	46.07	337.387

### 3. Results

#### 3.1 Simulation Analysis

The results and discussion section presents data and analysis of the study. This section can be organized based on the stated objectives, the chronological timeline, different case groupings, different experimental configurations, or any logical order as deemed appropriate. The results and discussion section presents data and analysis of the study. Comparison between valve in inhaler spacer were carried out. The velocity inlet was set as 100m/s in the setup. The particle velocity magnitude will be carried between duckbill valve, cross slit valve and umbrella valve. From previous researcher, particle velocity magnitude for duckbill valve was 15 m/s. For this research we want to find, is it any valve have better particle velocity magnitude other duckbill valve. The simulation will be carried out by ANSYS Fluent version 19.2

### 3.1.1 Velocity

The study on the velocity versus the position of Z axis. Based on the Figure 9, the duckbill valve started at the peak approximately  $0.28 \text{ (ms}^{-1}\text{)}$  designate as second highest flow velocity. The velocity was sharply fall from  $0.025\text{m}$  to point  $0.03\text{m}$ . The peak velocity for cross slit valve in Figure 10 at  $0.36\text{ms}^{-1}$ . The velocity was sharply fall at  $-0.03\text{m}$  and  $-0.01\text{m}$ . The peak velocity for umbrella valve in Figure 11 at  $2.9\text{ms}^{-1}$  and drop sharply at  $-0.004 \text{ m}$  and  $0.015\text{m}$ . Based on the result of velocity against the position of Z axis, the geometry influencing the velocity flow in the inhaler spacer.

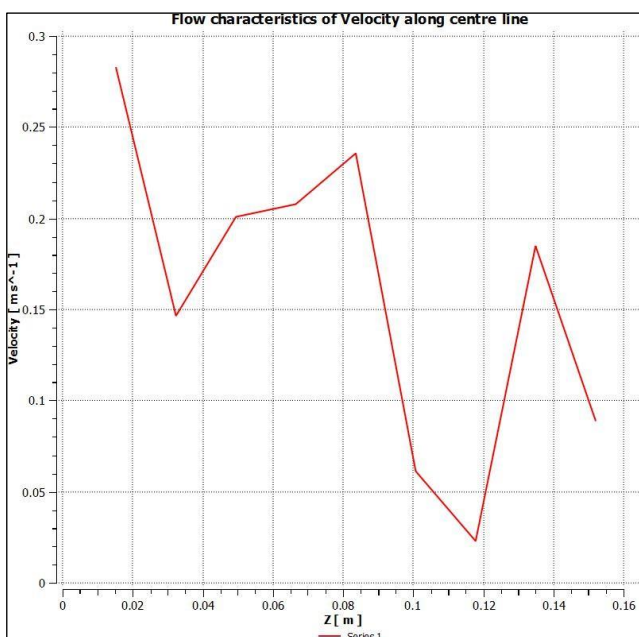


Fig. 9. Velocity flow characteristic for duckbill valve

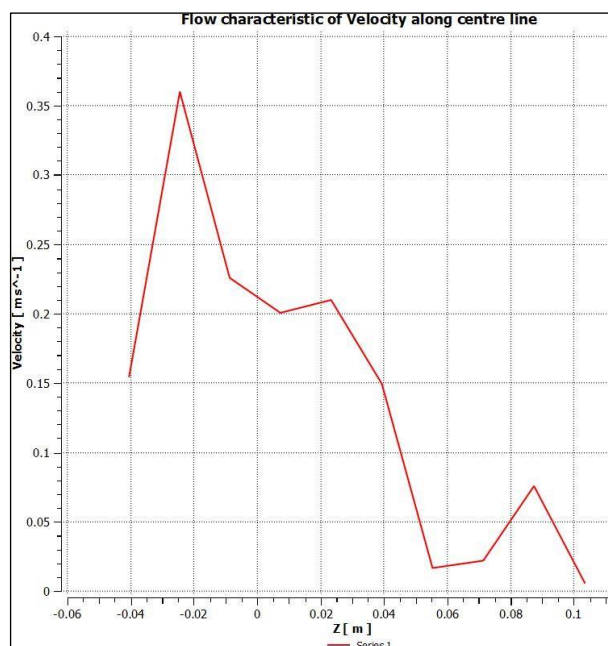


Fig. 10. Velocity flow characteristic for cross slit valve

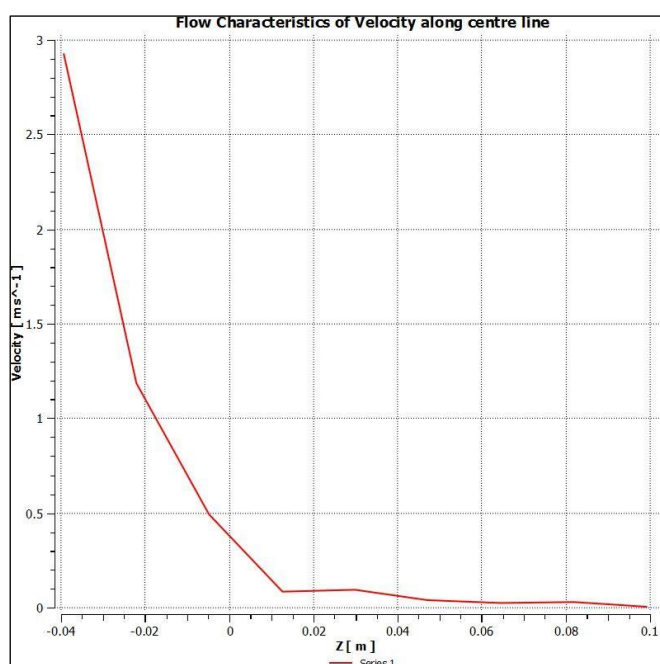


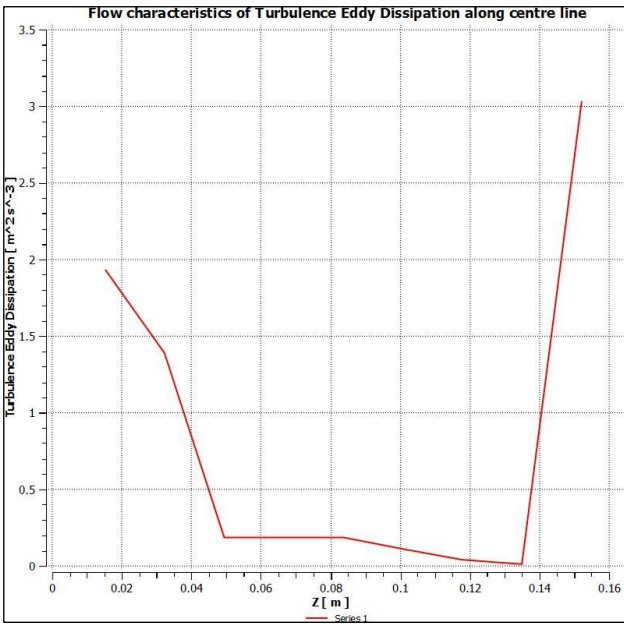
Fig. 11. Velocity flow characteristic for umbrella valve



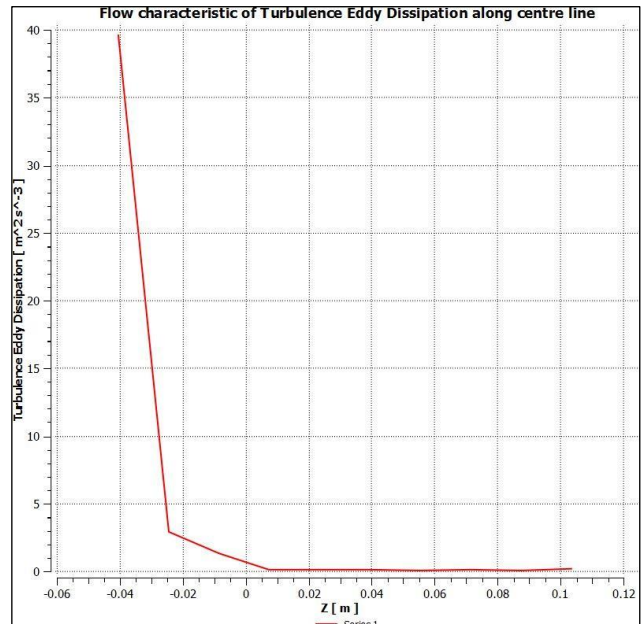
### 3.1.2 Turbulence Eddy Dissipation (TED)

Figure 12-14 displayed the graph turbulence eddy dissipation versus the position of Z axis for three unit of inhaler spacer. The interpretation begins with duckbill valve in Figure 12. It started at the peak about  $1.9 \text{ (m}^2\text{s}^{-3}\text{)}$ . The peak went down sharply at  $0.055\text{m}$  and constantly at  $0.3\text{(m}^2\text{s}^{-3}\text{)}$ . Point from  $0.055\text{m}$  until  $0.135\text{m}$  are steady. The trend for duckbill valve and umbrella valve (Figure 14) quite similar but the peak turbulence eddy dissipation for umbrella valve at  $8.0\text{(m}^2\text{s}^{-3}\text{)}$ . Trend chart for duckbill valve quite different from another valve. The peak turbulence eddy dissipation for cross slit valve in Figure 13 at  $40.0 \text{ (m}^2\text{s}^{-3}\text{)}$ . The peak turbulence eddy dissipation for umbrella valve was highest  $580.00 \text{ (m}^2\text{s}^{-3}\text{)}$  compared to duckbill the lowest peak at  $3.1 \text{ (m}^2\text{s}^{-3}\text{)}$  and cross slit valve at  $39.0 \text{ (m}^2\text{s}^{-3}\text{)}$ .

In a nutshell, the different of valve such as shape of duckbill valve, cross slit valve and umbrella valve influencing the value of turbulence eddy dissipation. When the area at valve is small, the velocity of fluid flow will fastest. This because area of valve that control fluid flow will influencing the velocity of fluid flow. In this situation the value of Turbulence eddy dissipation is smaller was cross slit valve



**Fig. 12.** Turbulence Eddy dissipation for duckbill valve



**Fig. 13.** Turbulence Eddy dissipation for cross slit valve

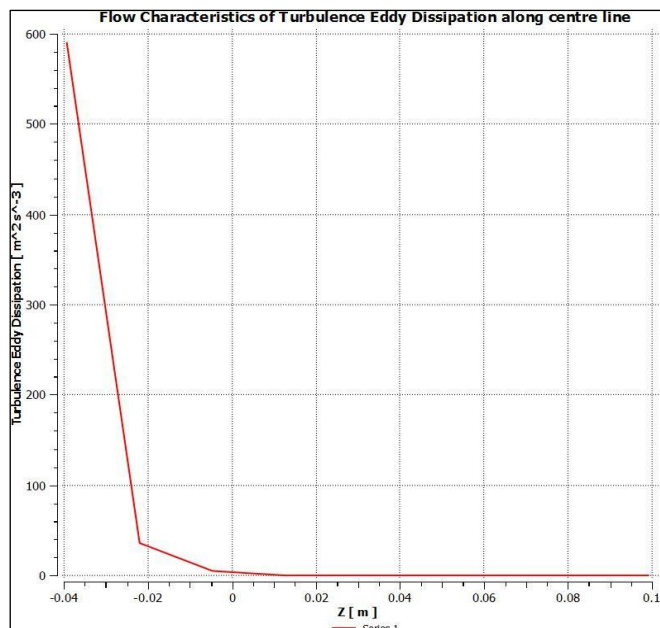


Fig. 14. Turbulence Eddy sissipation for umbrella valves

### 3.1.3 Velocity Vector

The study referred to velocity vector applied to the valve in AerospaAcer. The selection of vector has been made in the post-processing stage. The setup of velocity vector begins by selecting the vector. All fluid domains were selected with identify the vector at the middle plane (plane 1). The type of sampling as vertex with 1.0 reduction factor. The selected velocity as a variable, while arrowhead3D set as the arrow symbol. This setup was applied to all inhaler design valve. The velocity vector was shown in the Figure 15-17. Table 2 shown as result of velocity vector. The analyzed based on the maximum value in the middle plane of the AerospaAcer.

In according to velocity vector, the duckbill valve in Figure 15 shown the distribution of velocity vector along Z axis. The flow velocity at relatively low. The flow begins from the nozzle to the spacer. The flow collides with the wall then circulate and throughout any direction before reach to the outlet outflow.

The cross-slit valve (Figure 16) velocity vector equal to  $2.26657 \text{ ms}^{-1}$ . Umbrella valve in Figure 17 has  $1.39613 \text{ ms}^{-1}$  for amount of flow circulation while duckbill valve was  $2.14489 \text{e} +08 \text{ ms}^{-1}$ . The result of simulation velocity vector that have more recirculation was at umbrella and cross slit valve while duckbill valve was least recirculation so, duckbill valve was good design for control fluid flow in inhaler spacer.

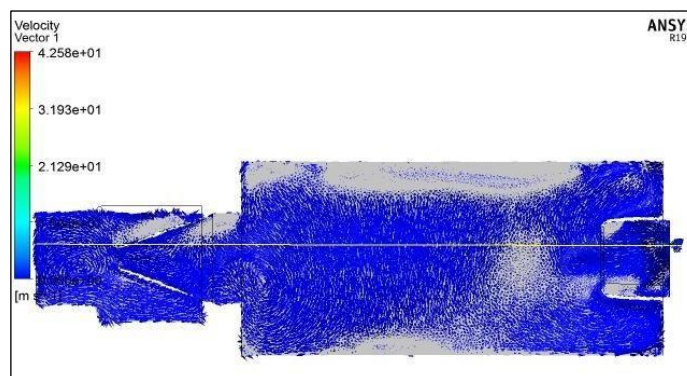


Fig. 15. Velocity vector flow characteristic

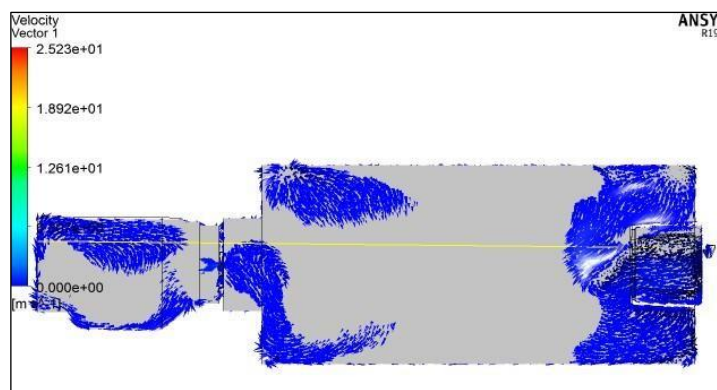


Fig. 16. Velocity vector flow characteristic

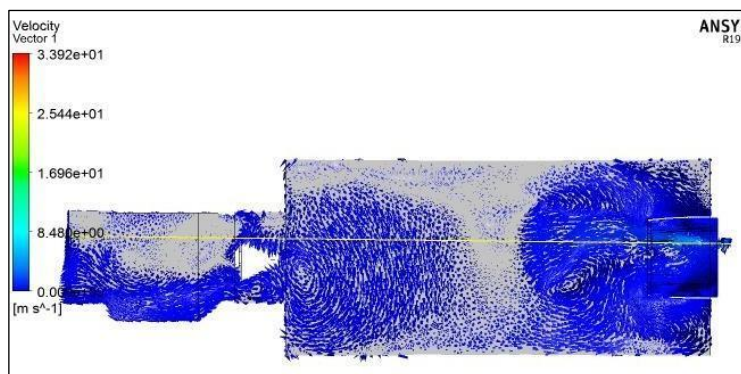


Fig. 17. Velocity vector flow characteristic

**Table 2**

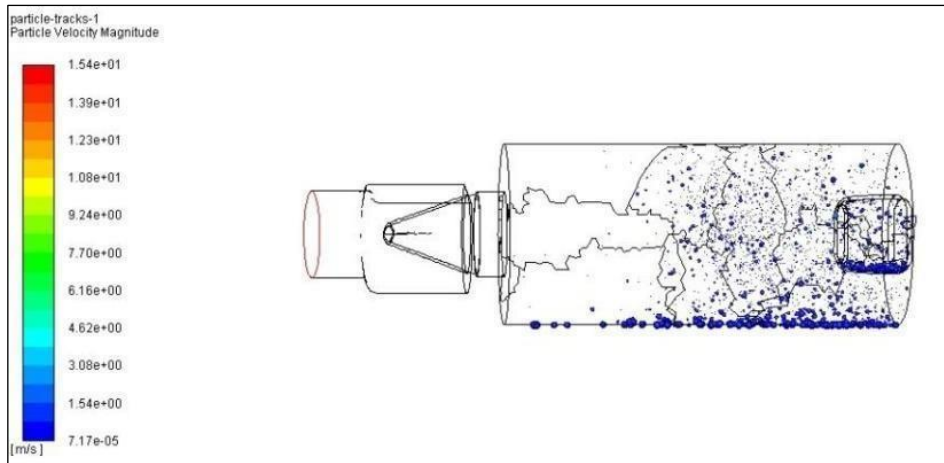
The velocity vector on cross section

Type of valve	Velocity vector (ms <sup>-1</sup> )
Duckbill	2.14489x10 <sup>8</sup>
Cross Lit	2.26657
Umbrella	1.39613

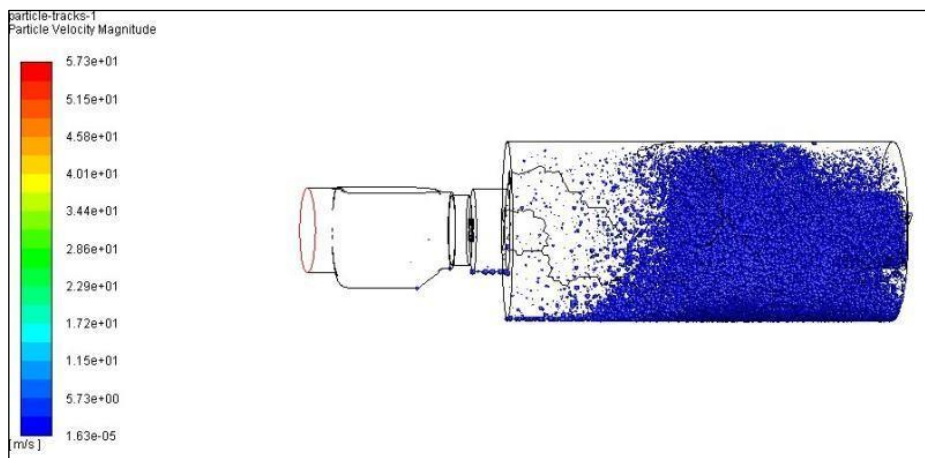
### 3.1.4 Particle velocity magnitude

The particle velocity magnitude can be selected in the graphic result after finished the simulation. The value of velocity magnitude is based on the discrete particle model (DPM). Based on the Figure 18-20, the particle velocity magnitude of drugs delivery for all design given as shown Table 3. The table was analyzed based on the maximum value in the middle plane of the inhaler AerospaAcer.

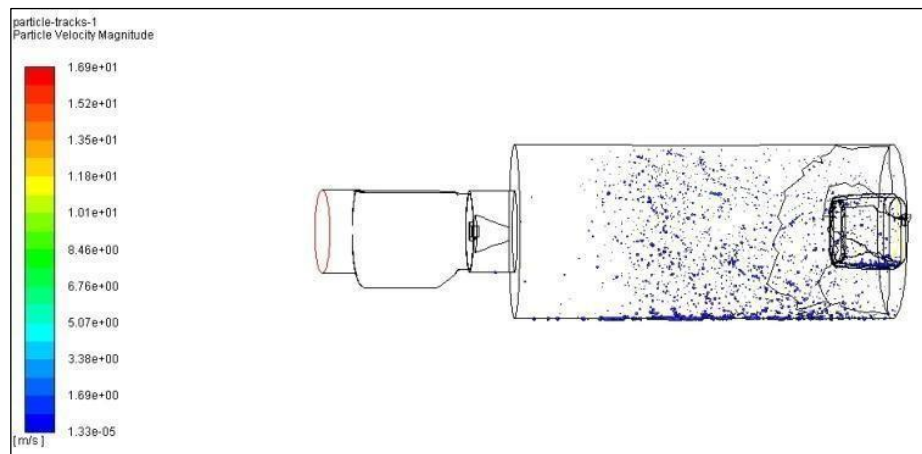
Duckbill valve shown the fully drug particle delivery at area mouthpiece and area of spacer has little drug particle. The maximum value of particle velocity at duckbill valve was 15.39 ms<sup>-1</sup>. The particle velocity of cross slit valve and umbrella valve equal to 57.2 ms<sup>-1</sup>, and 41.72 ms<sup>-1</sup>. The result shown the highest particle velocity was cross slit valve 57.21 ms<sup>-1</sup>.



**Fig. 18.** Particle velocity magnitude characteristic for duckbill valve



**Fig. 19.** Particle velocity magnitude characteristic for cross slit valve



**Fig. 20.** Particle velocity magnitude characteristic for umbrella valve

**Table 3**

The particle velocity magnitude on cross section

Type of valve	Particle velocity magnitude ( $\text{ms}^{-1}$ )
Duckbill	15.39
Cross Lit	57.26
Umbrella	41.72

### 3.1.5 Streamline

In this study, streamline referred as the flow of massless particle through the entire fluid domain. The previous research stated that the purpose of the streamline figures out the flow around and wake up the module. Table 4 was analyzed based on the maximum value in the middle plane of the inhaler AerospaAcer.

In the post-processing, the streamline can be setup with various variable. This study selecting streamline by using 3D streamline. All domains to be considered started from inlet to outlet. Velocity was set as variable as forward direction. The results shown in the Figure 21-23 were movement of streamline circulation due to the collision of flow to the wall in spacer. Most of the streamline in the chamber has the normal value of velocity depends on the colour of the streamline. At the begins of the nozzle, the velocity was high compared to after getting into chamber. The duckbill valve clearly visualizes the flow of streamline. The pattern quite similar with the cross- slit valve with velocity. Then, the umbrella valve followed with  $1.5597 \text{ ms}^{-1}$ . The internal position of duckbill valve achieved the higher velocity value of streamline compared to duckbill valve and cross slit valve. The result of simulation showed that valve that have many recirculation was at cross slit valve while duckbill was least circulation

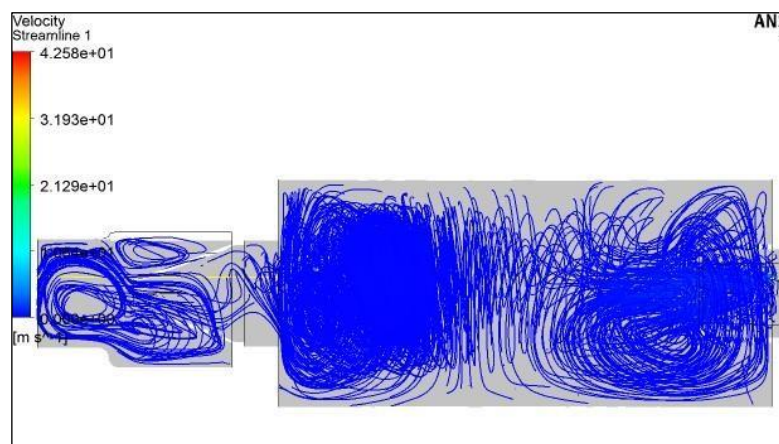


Fig. 21. Streamline flow characteristic for

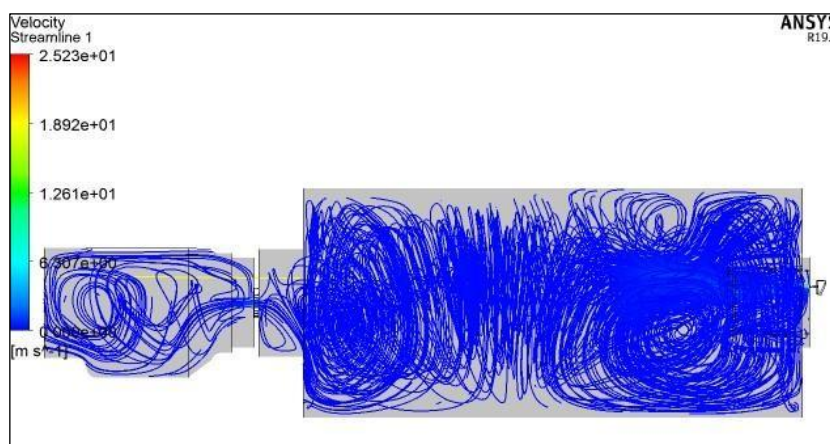
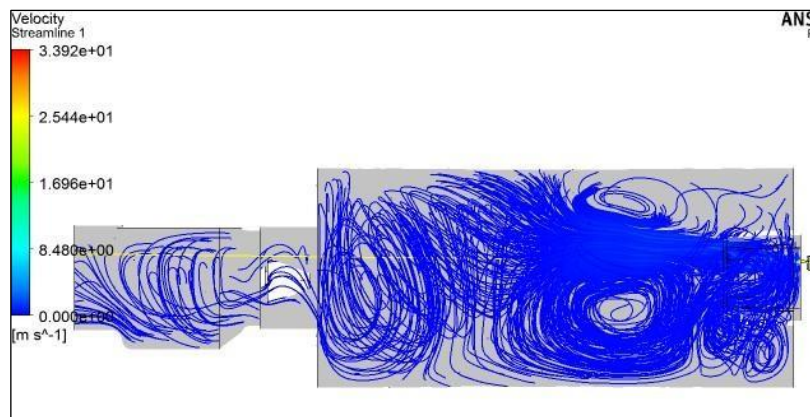


Fig. 22. Streamline flow characteristic for



**Fig. 23.** Streamline flow characteristic for

**Table 4**

The particle velocity magnitude on cross section

Type of valve	Streamline (ms <sup>-1</sup> )
Duckbill	2.42697 x10 <sup>11</sup>
Cross Lit	2.152
Umbrella	1.55597

#### 4. Conclusions

This study has already compared three main different designs which are to evaluate their fluid flow performance. This study was verified the flow characteristics between three types of valves in inhaler spacer. The study was use different valve in inhaler spacer to obtain desired velocity and identified the flow characteristics at the different valve. The result of present simulation was verified with the previous outlet velocity equal to 15 ms<sup>-1</sup>. There were use different valve into three types of valves. The flow characteristics such as turbulence kinetic energy (TKE), turbulence eddy dissipation (TED), velocity, particle velocity magnitude, streamline and vector velocity were obtained from the ANSYS Fluent 19.2 result in post-processing. The graphs and visualization were attached in the section 3.0. The result of TED for valve as follows; duckbill valve (6.9976e+31 m<sup>2</sup>s<sup>-3</sup>), cross slit valve (2.2701e+07m<sup>2</sup>s<sup>-3</sup>), umbrella valve (115.472 m<sup>2</sup>s<sup>-3</sup>), respectively. The different shape of visualization for particle velocity magnitude and vector field were based on the same value of velocity.

#### Acknowledgement

This research was funded by a grant from Ministry of Higher Education of Malaysia (RE-GG Grant Q047). This research also collaborated with FUJI DNDT Sdn. Bhd. as industry collaborator.

#### References

- [1] Amini, Shahideh, Arezou Ghasemi, Mohammad Solduzian, Besharat Rahimi, Kazem Heidari, Molouk Hadjibabaie, and Mona Kargar. "Is Inhaler Technique Associated with Quality of Life in Patients with Chronic Obstructive Pulmonary Disease?." *Current Therapeutic Research* 93 (2020): 100608. <https://doi.org/10.1016/j.curtheres.2020.100608>
- [2] Chen, Annie T., Shaoqing Ge, Susie Cho, Andrew K. Teng, Frances Chu, George Demiris, and Oleg Zaslavsky. "Reactions to COVID-19, information and technology use, and social connectedness among older adults with pre-frailty and frailty." *Geriatric nursing* 42, no. 1 (2021): 188-195. <https://doi.org/10.1016/j.gerinurse.2020.08.001>
- [3] Delikhoon, Mahdieh, Marcelo I. Guzman, Ramin Nabizadeh, and Abbas Norouzian Baghani. "Modes of transmission of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and factors influencing on the airborne transmission: A review." *International journal of environmental research and public health* 18, no. 2 (2021): 395.

- <https://doi.org/10.3390/ijerph18020395>
- [4] Duke, Daniel J., Dung T. Nguyen, Larissa Gomes Dos Reis, Dina M. Silva, Adrian Neild, Daniel Edgington-Mitchell, Paul M. Young, and Damon R. Honnery. "Increasing the fine particle fraction of pressurised metered dose inhaler solutions with novel actuator shapes." *International Journal of Pharmaceutics* 597 (2021): 120341. <https://doi.org/10.1016/j.ijpharm.2021.120341>
- [5] Abd Rahman, Muhammad Faqhrurrazi, Nor Zelawati Asmuin, Ishkrizat Taib, Juwaidi Nazar, Azizan Ismail, and Riyadhthusollehan Khairulfuaad. "Investigate flow characteristics of metered-dose inhaler (MDI) disposable inhaler spacer (AeroCup) for COVID-19 patient by using computational fluid dynamic (CFD)." *CFD Letters* 12, no. 12 (2020): 63-74. <https://doi.org/10.37934/cfdl.12.12.6374>
- [6] Jeswani, Harish Kumar, and Adisa Azapagic. "Life cycle environmental impacts of inhalers." *Journal of Cleaner Production* 237 (2019): 117733. <https://doi.org/10.1016/j.jclepro.2019.117733>
- [7] Kerwin, Edward M., Andrew Preece, Dimitra Brintziki, Kathryn A. Collison, and Raj Sharma. "ELLIPTA dry powder versus metered-dose inhalers in an optimized clinical trial setting." *The Journal of Allergy and Clinical Immunology: In Practice* 7, no. 6 (2019): 1843-1849. <https://doi.org/10.1016/j.jaip.2019.02.023>
- [8] Kesten, Steven, Elliot Israel, Guangxi Li, Jolyon Mitchell, Robert Wise, and Tom Stern. "Development of a novel digital breath-activated inhaler: Initial particle size characterization and clinical testing." *Pulmonary Pharmacology & Therapeutics* 53 (2018): 27-32. <https://doi.org/10.1016/j.pupt.2018.08.007>
- [9] Kofman, Carlos, and Alejandro Teper. "Usefulness of Nonvalved Spacers for Administration of Inhaled Steroids in Young Children with Recurrent Wheezing and Risk Factors for Asthma." *Canadian Respiratory Journal* 2018 (2018). <https://doi.org/10.1155/2018/3095647>
- [10] Lavorini, Federico, Celeste Barreto, Job FM van Boven, Will Carroll, Joy Conway, Richard W. Costello, Birthe Hellqvist Dahl *et al.*, "Spacers and valved holding chambers—the risk of switching to different chambers." *The Journal of Allergy and Clinical Immunology: In Practice* 8, no. 5 (2020): 1569-1573. <https://doi.org/10.1016/j.jaip.2019.12.035>
- [11] Mat, Mohamad Nur Hidayat, Nor Zelawati Asmuin, Nor Halim Hasan, Hanis Zakaria, Muhammad Faqhrurrazi Abd Rahman, Riyadhthusollehan Khairulfuaad, and Balasem Abdulameer Jabbar. "Optimizing dry ice blasting nozzle divergent length using CFD for noise reduction." *CFD Letters* 11, no. 6 (2019): 18-26.
- [12] Pope III, C. Arden, Joseph B. Muhlestein, Heidi T. May, Dale G. Renlund, Jeffrey L. Anderson, and Benjamin D. Horne. "Ischemic heart disease events triggered by short-term exposure to fine particulate air pollution." *Circulation* 114, no. 23 (2006): 2443-2448. <https://doi.org/10.1161/CIRCULATIONAHA.106.636977>
- [13] Abd Rahman, Muhammad Faqhrurrazi, Nor Zelawati Asmuin, Ishkrizat Taib, Mohamad Nur Hidayat Mat, and Riyadhthusollehan Khairulfuaad. "Influence of Actuator Nozzle Angle on the Flow Characteristics in Pressurized-Metered Dose Inhaler Using CFD." *CFD Letters* 12, no. 6 (2020): 67-79. <https://doi.org/10.37934/cfdl.12.6.6779>
- [14] Abd Rahman, Muhammad Faqhrurrazi, Norzelawati Asmuin, Nurul Fitriah Nasir, Ishkrizat Taib, Mohamad Nur Hidayat Mat, and Riyadhthusollehan Khairulfuaad. "Effect of Different Orifice Diameter on The Flow Characteristic in Pressurized Metered Dose Inhaler by Using CFD." *CFD Letters* 12, no. 3 (2020): 39-49. <https://doi.org/10.37934/cfdl.12.3.3949>
- [15] Abd Rahman, Muhammad Faqhrurrazi, Suzairin MD Seri, Nor Zelawati Asmuin, Ishkrizat Taib, and Nur Syakirah Rabiha Rosman. "Response Surface Methodology (RSM) Approach for Optimizing the Actuator Nozzle Design of Pressurized Metered-Dose Inhaler (pMDI)." *CFD Letters* 13, no. 7 (2021): 27-44. <https://doi.org/10.37934/cfdl.13.7.2744>
- [16] Torén, Kjell, Ingvar A. Bergdahl, Tohr Nilsson, and Bengt Järnholm. 2007. "Occupational Exposure to Particulate Air Pollution and Mortality Due to Ischaemic Heart Disease and Cerebrovascular Disease." *Occupational and Environmental Medicine* 64 (8): 515–19. <https://doi.org/10.1136/oem.2006.029488>
- [17] Wang, Sanwang, Xin Wen, Yingying Dong, Bin Liu, and Minghu Cui. "Psychological influence of coronavirus disease 2019 (COVID-19) pandemic on the general public, medical workers, and patients with mental disorders and its countermeasures." *Psychosomatics* 61, no. 6 (2020): 616-624. <https://doi.org/10.1016/j.psym.2020.05.005>
- [18] Wang, Xiao-Rong, and David C. Christiani. "Respiratory symptoms and functional status in workers exposed to silica, asbestos, and coal mine dusts." *Journal of occupational and environmental medicine* (2000): 1076-1084. <https://doi.org/10.1097/00043764-200011000-00009>