

Investigate Flow Characteristics of Metered-Dose Inhaler (MDI) Disposable Inhaler Spacer (AeroCup) for COVID-19 Patient by using Computational Fluid Dynamic (CFD)


 Open
Access

Muhammad Faqhrurrazi Abd Rahman^{1,*}, Nor Zelawati Asmuin^{1,*}, Ishkrizat Taib¹, Juwaidi Nazar², Azizan Ismail³, Riyadhthusollehan Khairulfuaad¹

¹ Department of Thermofluids Engineering, Faculty of Mechanical and Manufacturing Engineering, Universiti Tun Hussein Onn, 86400 Parit Raja, Johor, Malaysia

² FUJI DNDT SDN BHD, B-17-5 Block B, Megan Avenue II No 12 Jalan Yap Kwan Seng, 50450 Kuala Lumpur, Malaysia

³ Department of Multimedia, Faculty Of Computer Science And Information Technology, Universiti Tun Hussein Onn, 86400 Parit Raja, Johor, Malaysia

ARTICLE INFO

Article history:

Received 21 October 2020

Received in revised form 22 December 2020

Accepted 22 December 2020

Available online 30 December 2020

ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory coronavirus-2 syndrome (SARS-CoV-2) were first reported by officials in Wuhan City, China, in December 2019. COVID-19 patients have a symptom of respiratory pneumonia diseases which have difficulties in breathing normally. Previously, the nebulizer machine commonly used to treat respiratory pneumonia diseases. However, the usage for this machine was not suggested during this COVID-19 period because the virus will be spread off easily. To overcome these shortcomings, the uses of Metered-Dose Inhaler (MDI) with MDI disposable inhaler spacer is preferable. Besides, it had been known that the used of MDI disposable inhaler spacer helps to increase the uptaking of the drug into the lung. Besides that, the high demand for the MDI Disposable Inhaler Spacer in the hospital, causing a shortage of supply in Malaysia. Thus, this study aims to produce a new design of this spacer to full fill the market need. This new design of MDI Disposable Inhaler Spacer (AeroCup) was designed by using Solid Work 2018. Then, the parameters for flow characteristic such as particle velocity magnitude, velocity, Eddy viscosity, turbulence Eddy dissipation and turbulence kinetic energy (TKE) was successfully characterized and compared with commercial design A using ANSYS Fluent Version 19.2. The result showed that new design (AeroCup) had the desired characteristic, which was almost similar to commercial design A. This study can provide a piece of information to produce the low-cost metered-dose inhaler (MDI) disposable inhaler spacer to enlighten the burden shouldered by front liners, especially during the pandemic and also can scale-up the economic viability.

Keywords:

Disposable; spacer; metered-dose inhalers; simulation

Copyright © 2020 PENERBIT AKADEMIA BARU - All rights reserved

* Corresponding author.

E-mail address: hd170038@siswa.uthm.edu.my (Muhammad Faqhrurrazi Abd Rahman)

* Corresponding author.

E-mail address: norzela@uthm.edu.my (Nor Zelawati Asmuin)

<https://doi.org/10.37934/cfdl.12.12.6374>

1. Introduction

In late December 2019, an outbreak of mysterious pneumonia caused by severe acute respiratory coronavirus-2 syndrome (SARS-CoV-2) happened in a seafood wholesale wet market in Wuhan, Hubei, China [1]. This disease is known as Coronavirus disease 2019 (COVID-19). So far, the virus of this disease infected more than 64 million individuals and killed almost 1.6 million people worldwide [2]. The first case reported in Malaysia was on 25 January 2020 on traveller from China arriving via Singapore [3]. As of 5 December 2020, a total of 69 095 confirmed cases with 376 deaths nationwide as documented by the Ministry of Health (Malaysia) [4]. The virus was previously named as Wuhan coronavirus or 2019 novel coronavirus (2019-nCov) by the Chinese researchers. The name was then identified as SARS-CoV-2 and the disease as COVID-19 by the International Committee on Taxonomy of Viruses (ICTV) [5]. Coronaviruses belong to the Coronaviridae family in the Nidovirales order, got its name from the crown-like spikes on the outer surface of the virus. Coronaviruses are minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length [6]. This virus is a member of the β group coronaviruses that occurred 17 years ago. It believed that the virus is zoonotic, meaning it spread from animals to human [7]. According to Datuk Dr Noor Hisham, Malaysia's Health Director-General, coronavirus (SARS-CoV-2) infections develop through 5 different stages. Nearly 80% of patients in Malaysia who tested positive for COVID-19, displayed either mild symptoms, or none at all. The remaining 20% of patients were the ones who fell into the moderate and critical categories of positive coronavirus infections [8].

Ministry of Health (Malaysia) reported that the nebulizer previously used to treat pneumonia patients [9]. However, the use of nebulizer can increase the risk of infection transmission via droplet nuclei and aerosols [10]. Thus, the use of nebulizer is currently not suitable to treat pneumonia patients caused by COVID-19. Nevertheless, the use of metered-dose inhaler (MDI) could be considered as alternatives to flow driven nebulization [9]. The MDI inhaler potentially used for stage 4 patient as the symptom of the shortness breath, and it was easy to use. Nevertheless, MDIs has a vital weakness, such as their propensity, to be used in optimally and inaccurately [11]. The release of particles at high speed frequently trapped in the oropharynx and blocked from entering the lungs [12].

It was not easy to synchronize actuation and inhalation, where most children and 25–51% of adults have trouble with this technique [13]. Thus, the introduction of inhaler spacer can help to overcome this problem, which varies in their design features and benefit [14]. Spacers also minimize the need for patients to coordinate inhalation with MDI action and catch large particles that would typically accumulate mucosa in the mouth and throat by expanding the MDI mouthpiece and by providing additional volume for an aerosol catch [15]. This spacer significantly decreases the deposition of oropharyngeal drugs through the accumulation of large aerosol particles in the holding chamber, thereby decreasing the risk for local side effects associated with corticosteroids and systemic absorption [16]. Spacers were designed with one-way valves and holding chambers to optimize the drug delivery time and make spacers even easier to use. Valved spacers are a particular benefit to children and adults with inadequate inhalation techniques [17].

The spacers attached to MDIs as shown in Figure 1 at one end through a port and at the other end fitted with a face mask or mouthpiece, in practice, spacers extend the inhaler mouthpiece and channel the drug plume into the mouth. As the plume of actuated aerosol passes through the spacer, the particles lose momentum, causing the propellant to evaporate and the larger, non-breathing particles (created by drug particles coalescing) to settle [18]. The objective of this study is to modify the commercial MDI disposable inhaler spacers to create a new design of MDI disposable inhaler

spacers to full fill the market need. Another objective was to investigate the flow characteristic of the new design and compared with commercial design A of MDI disposable inhaler spacer.



Fig. 1. Disposable spacer attach with MDI inhaler [18]

2. Methodology

2.1 Geometrical Modelling

The 2-Dimensional view for the new design MDI disposable inhaler spacer (AeroCup) and commercial design A of MDI disposable inhaler spacer model attached with actuator nozzle design by using Solid Works 2018 shown in Figure 2.

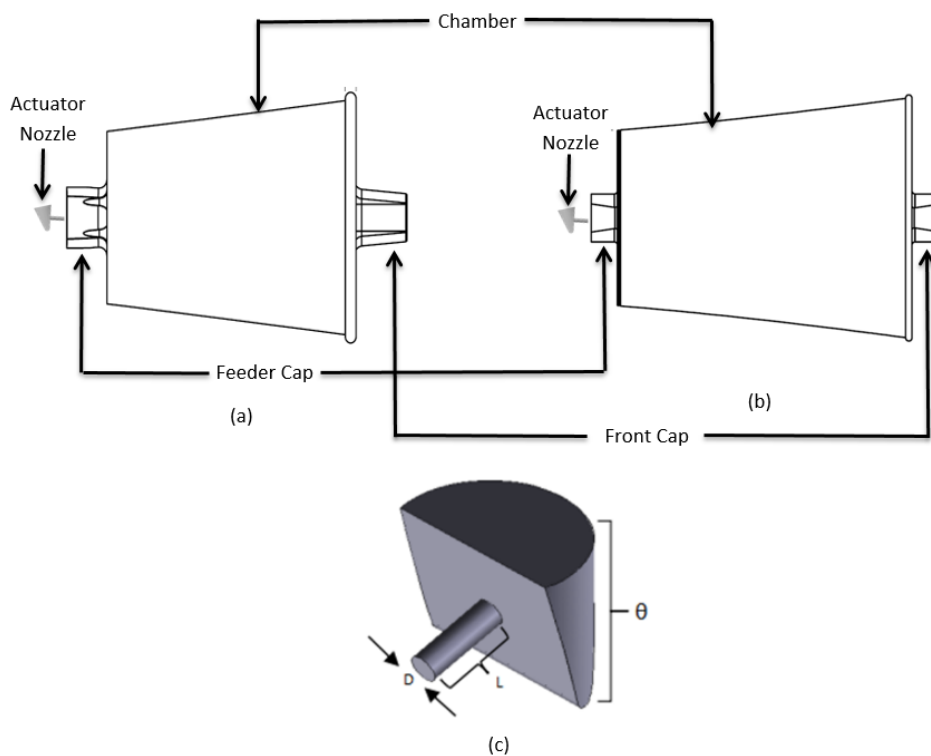


Fig. 2. Geometrical modelling of commercial design A and new design (AeroCup) for MDI disposable inhaler spacer (a) Right view of AeroCup (b) Right view of commercial design A (c) Schematic diagram of internal parts in the actuator nozzle

The geometrical modelling for the commercial design A created by using the real scale of the existing spacer. Actuator nozzle dimension designed according to previous literature [19]. AeroCup has been designed in this project to see if this design can be comparable to the commercial design in term of performance and flow characteristics. Based on the simulation results performed by Oliveira *et al.*, [20] it was possible to determine the base design diameter for MDI units, the diameter of the orifice is 0.49mm, the angle of the actuator being 165° and the length of the orifice being 1.50 mm. This actuator nozzle attached at the back of the feeder cap. A parameter used to define the geometry of the actuator nozzle was orifice diameter (D), length of the orifice (L) and angle of the actuator (θ) that shown in Figure 2(c).

2.2 Grid Independent Test for Commercial Design a Model of MDI Disposable Inhaler Spacer

The commercial design A of MDI disposable inhaler spacer redesigned from the real scale of the existing MDI disposable inhaler spacer. In this study, it was compulsory to maintain the model's precision by using the Grid-independent test. The grid-independent test value must remain as low as possible to maintain its accuracy. Nonetheless, in this GID series, the coarse, medium and fines meshed can be generated, and the solution can shift between the medium and fine mesh. Grid independent test for actuator nozzle, as shown in Table 1. There were nine (9) GID tests performed. The best GID obtained based on the lower skewness mesh metric value and the higher orthogonal mesh metric. It shows that number six (6) meets the selection of criteria for the GID. The GID already selected by selecting number six (6) for further analysis of simulation.

Table 1

Grid independent test for commercial design A model

No	Number of Nodes	Number of Elements	Skewness Mesh Metric	Orthogonal Mesh Metric
1	556325	831166	0.9563	0.9622
2	546123	863216	0.9254	0.9365
3	514865	832362	0.9165	0.9532
4	586326	798622	0.8962	0.9244
5	550032	873265	0.9321	0.9665
6	579313	816325	0.8831	0.9788
7	516186	896532	0.9365	0.9233
8	596265	963216	0.9254	0.9135
9	536181	886135	0.9623	0.9061

The main properties of drug formulation for propellant-HFA 134a, ethanol and salbutamol involved in this study a listed in Table 2

Table 2

Property of drug formulation [20]

Properties	HFA-134a	Ethanol	Salbutamol
Density (kg/m ³)	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

2.3 Meshing for New Design (AeroCup) and Commercial Design a Model of MDI Disposable Inhaler Spacer

The meshed model in mesh mode of ANSYS components systems shown in Figure 3. The infinite number of particles in the meshing process transformed into the finite number of particles. In the current study, an intelligent mesh tool is used, which generates the best possible precise and efficient mesh in a single click for the given geometry [21]. The mandatory measuring cell carried out with high efficiency and accuracy. The higher the number of elements, the more precise the results are. A higher number of elements, however, will result in a longer time required for the results of computing [22]. The refining mesh used in smaller cells was set up for an extensive solution gradient and fine geometric data. It was necessary to maintain the accuracy and stability of the solution to achieve a good mesh quality. In the ANSYS, there was four operation mesh mode can be done. The process was beginning with specifying the global mesh setting, inserting a local mesh setting, generating the mesh and checking mesh quality [23,24]. By using proximity and curvature, the curve object (cylinder) and square object (box) can be pick as the convergent segment. To select the meshing size, the Grid Independent Test was required.

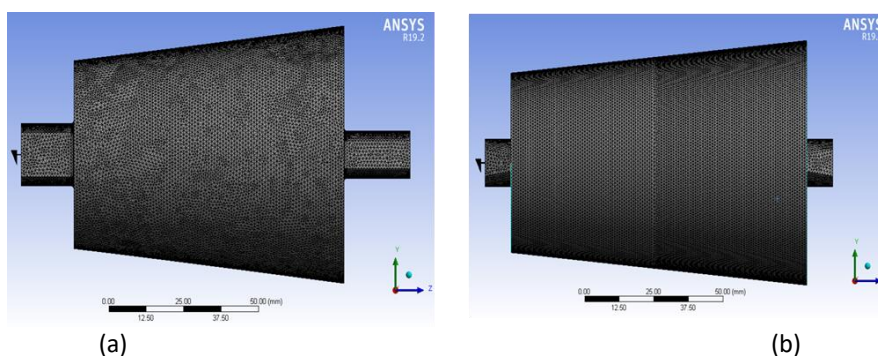


Fig. 3. Meshing process for MDI disposable inhaler spacer (a) AeroCup (b) commercial design A

2.4 CFD Simulation Method for New Design (AeroCup) and Commercial Design a Model of MDI Disposable Inhaler Spacer

The purpose of this simulation was to illustrate the configuration parameters better suited to the real-life case of a new design (AeroCup) and commercial design A model of MDI disposable inhaler spacer using commercially available computational fluid dynamic (CFD) software, such as ANSYS® Fluent version 19.2. Rosin-Rammler priorly selected as the diameter distribution in the discrete phase model. The CFD solver accepts this type of distribution by inserting its parameters in Table 3 [20].

The drug amount of puff (100µg) can be used and divided by the duration of a puff (0.1s). The spray flow rate can be determined using the puff quantity and puff duration. The solver spray configuration parameters showed as in Table 4 below.

Table 3
 Property of particle diameter [20]

Parameter	Value
Diameter distribution	Rosin-Rammler
Minimum diameter (µm)	1.22
Maximum diameter (µm)	49.50
Mean diameter (µm)	16.54
Spread parameter	1.86

Table 4
Property of spray configuration

Parameter	Value
Spray type	Solid-cone [25,26]
Angle (°)	10 [19]
Velocity (m/s)	100 [20]
Radius (m)	0.00025 [20,27]
Flow rate (kg/s)	1e ⁻⁶ [19]

Parameters for the discrete phase model previously evaluated in different configurations, and those described here seemed best suited for simulation purposes. The inject time step size (s) use for this DPM were particle time step. The unsteady particle tracking presently used because of the limited period time (0.1s) for the injection to occur. The spherical type used in this study as the drag law, and this simulation activated the two-way coupling turbulence [27].

2.5 Verification of Actuator Nozzle with Commercial Design Model of MDI Disposable Inhaler Spacer

In this verification system of MDI devices with commercial design model, four (4) parameters were selected from the previous literature analysis as shown in Table 5, which was particle velocity magnitude, velocity magnitude, air temperature and HFA mass. The reference model for verification obtained from Oliviera *et al.*, [28]. The previous model was simulated using version 14.0 of ANSYS Fluent. On the other hand, this analysis would use ANSYS Fluent version 19.2 to do the simulation. The highest relative error for geometric modelling shown in the table below was 6.2%. For the numerical simulation, the average limit for comparing two (2) simulated models was below 10% [29]. As the maximum value was below the average limit, and the geometric simulation was appropriate, and further simulation can proceed.

Table 5
Verification of based model geometry

Velocity Inlet (m/s)	Variable Parameters	Result by Fluent 14.0 [28]	Result by Fluent 19.2	Relative error (%)
100	Particle Velocity Magnitude (m/s)	29.298	28.421	3.6
	Velocity Magnitude (m/s)	10.29	10.91	6.0
	Air Temperature (K)	293.15	293.01	0.05
	HFA Mass Fraction	0.0029	0.0027	6.2

3. Results

3.1 Qualitative Analysis of Flow Characteristic of New Design (AeroCup) and Commercial Design A of MDI Disposable Inhaler Spacer Along the Axis of Center-line

Figure 4 illustrated the design of AeroCup and commercial design A. The X-axis (m) represented in the direction of the centre-line inside the chamber. It clearly can be seen that AeroCup design and commercial design A is different in term of their chamber length, the size of a mouthpiece and the size of universal backpiece. The difference in these properties might contribute to the difference in flow characteristics such as Eddy viscosity, turbulence Eddy dissipation, turbulence kinetic energy (TKE), and velocity.

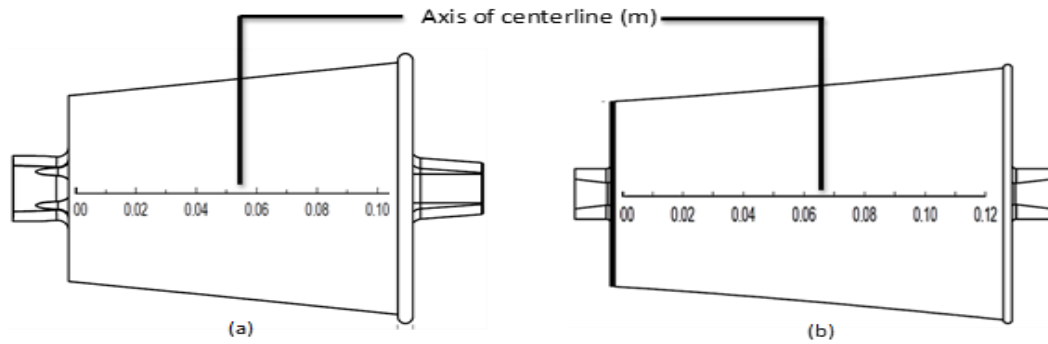


Fig. 4. Axis of centre-line inside the (a) AeroCup design (b) commercial design A

3.1.1 Eddy viscosity

Figure 5 displayed the graph of Eddy viscosity versus the position of x-axis along the centre-line. Eddy Viscosity was the proportionality factor describing the turbulent transfer of energy as a result of moving eddies, giving rise to tangential stresses. From Figure 5(a) graph, the results show that the pattern of the graph rapidly rise from 0 to 0.01m and after 0.02m, the graph was steadily increasing. The graph steeply decreased from 0.09 to 0.11m. This Figure 5(a) graph shows a similar trend to Figure 5 (b) graph.

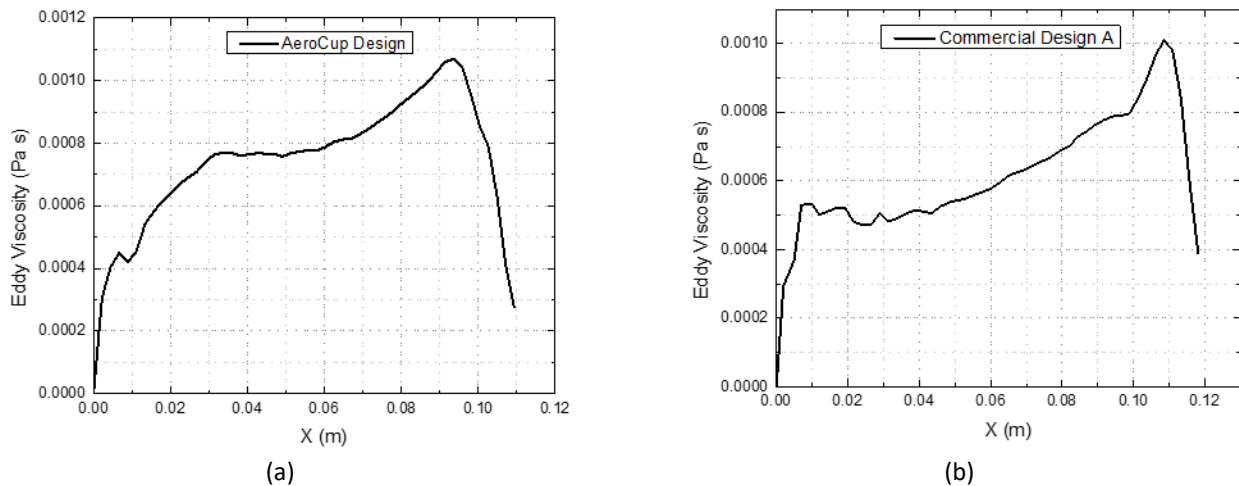


Fig. 5. Flow characteristic of Eddy viscosity along axis of centre-line (a) AeroCup design (b) Commercial design A

3.1.2 Turbulence eddy dissipation

Figure 6 displayed the graph of turbulence Eddy dissipation versus the position of x-axis along the centre-line. With the increment distance from 0 to 0.005m, the peak turbulence Eddy dissipation in Figure 6(a) rapidly increased, which was $9500 \text{ m}^2\text{s}^{-3}$. The peak went down sharply from 0.005m distance to 0.01m and remained steady at $0 \text{ m}^2\text{s}^{-3}$ afterwards until 0.11m. The trend of Figure 6(b) graph was quite similar to Figure 6(a), but, the peak turbulence Eddy dissipation for Figure 6(b) was $9000 \text{ m}^2\text{s}^{-3}$ which a bit lower.

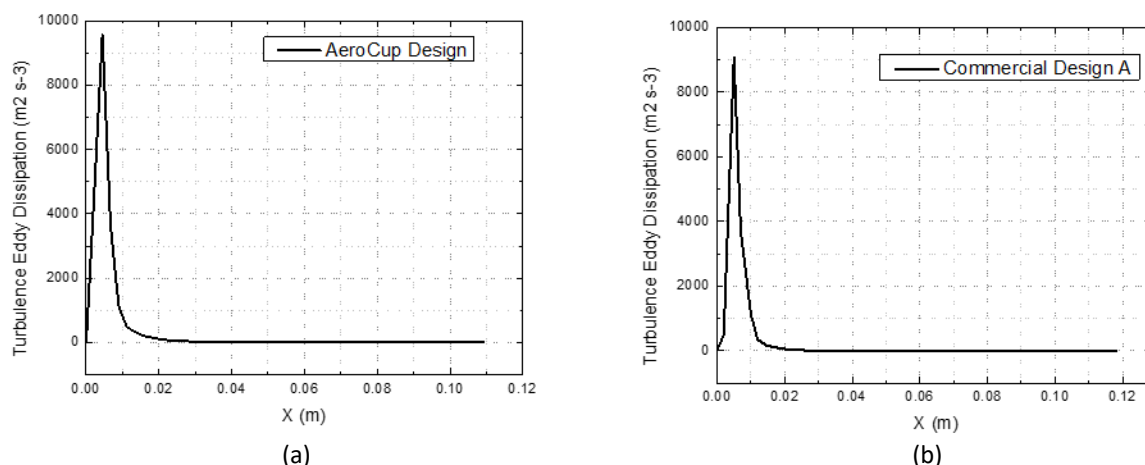


Fig. 6. Flow characteristic of turbulence Eddy dissipation along axis of centre-line (a) AeroCup design (b) commercial design A

3.1.3 Turbulence kinetic energy

Figure 7 presented the turbulence kinetic energy against the position along the x-axis of the centre-line. The value of TKE directly represents the 'strength' of the turbulence in the flow. The peak in Figure 7(a) showed a steep rise of TKE from 0 to 0.005m, producing a sharp peak which indicates the highest state of TKE ($3.0 \text{ m}^2 \text{s}^{-2}$). Then, the peak of TKE was dropping sharply at 0.01m and continue decreasing gradually. Interestingly, the trend of this result was in accord with the result, as shown in Figure 7(b). However, the peak produced in Figure 7(b) slightly lower compared to Figure 7(a). A possible explanation for these results might have resulted from the difference between the lengths of both chambers.

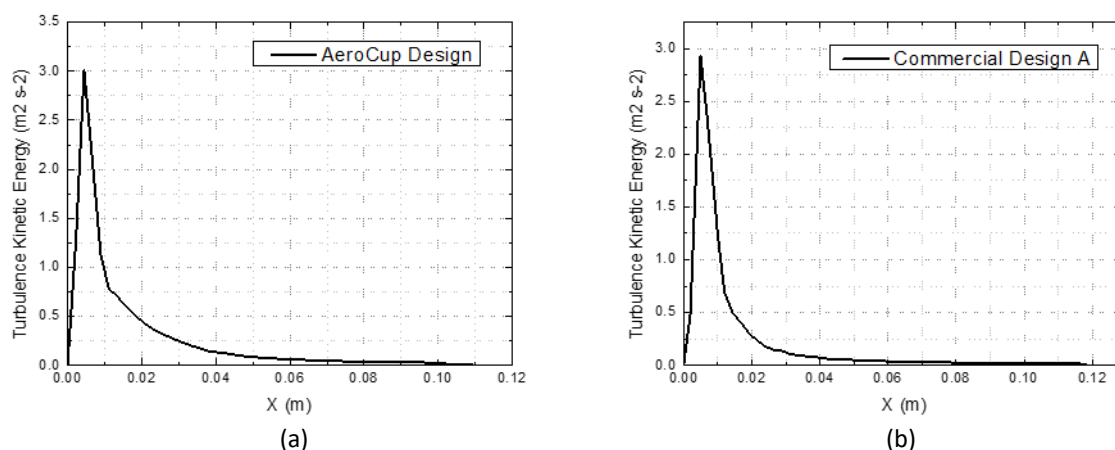


Fig. 7. Flow characteristic of turbulence kinetic energy along axis of centre-line (a) AeroCup design (b) commercial design A

3.1.4 Velocity

The study further analyzed the velocity of flow produced by both designs. Figure 8(a) shows a dramatically increased inflow velocity from 0 to 0.005m, producing a sharp peak that indicates the highest flow velocity at 4.7 m/s. However, the flow velocity sharply dropped at 0.01 m and gradually begins to decline. This result was in good agreement with Figure 8(b), which also showed a similar trend. Nevertheless, it clearly can be seen that the peak of Figure 8(b) slightly higher, which was 5.4

m/s. This result might have resulted from the difference of chambers length, which slightly shorter, but still, did not affect the function of the new design spacer (AeroCup).

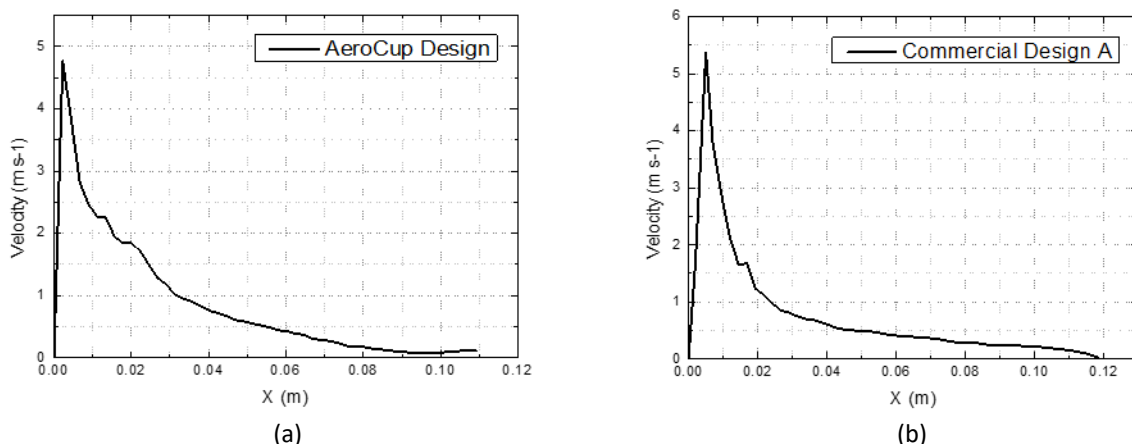


Fig. 8. The flow characteristic of velocity along the axis of centre-line (a) AeroCup design (b) commercial design A

3.2 Qualitative Analysis of Flow characteristic of New Design (AeroCup) and Commercial Design a of MDI Disposable Inhaler Spacer

In this study, the discrete phase model (DPM) was used to find the velocity magnitude of the drug particles for both AeroCup design and commercial design A. The results, as shown in Figure 9, showed the velocity magnitude of the drug particles for both spacers was almost similar. The velocity magnitude of drug particles for AeroCup was 28.01 m/s, whereas, for the commercial design A was 28.80 m/s. This result suggested that the speed of drug particles was not affected by the differences between the shape and the size of both design, AeroCup design and commercial design A.

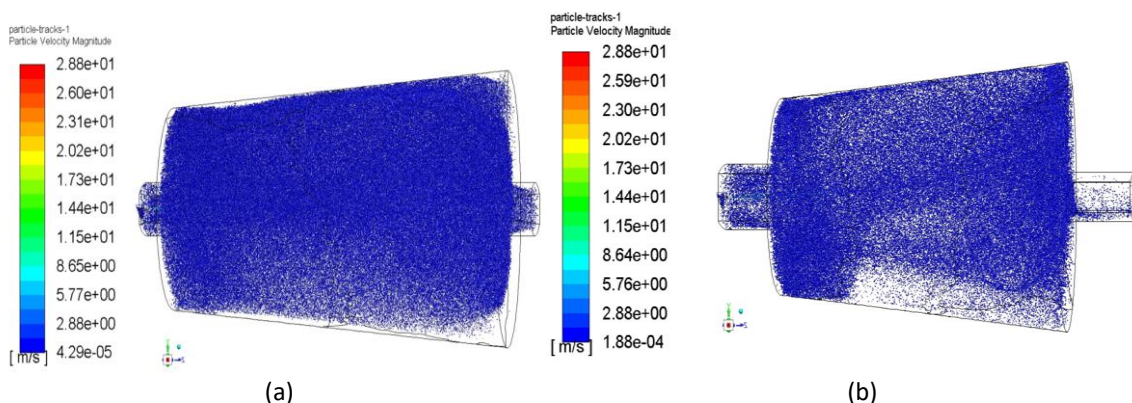


Fig. 9. Particle velocity magnitude by using the discrete phase model (a) AeroCup design (b) commercial design A

The flow characteristic further analyzed through the velocity vector. The velocity vector was crucial as it can provide excellent visualization of the flow around the module, depicting details of the wake structure. Figure 10 shows the velocity vector for the AeroCup design and commercial design A. The result showed that the AeroCup design has the lowest velocity vector compared to commercial design A. The velocity vector for the AeroCup design was 24.88 m/s, and commercial design A was 26.72 m/s.

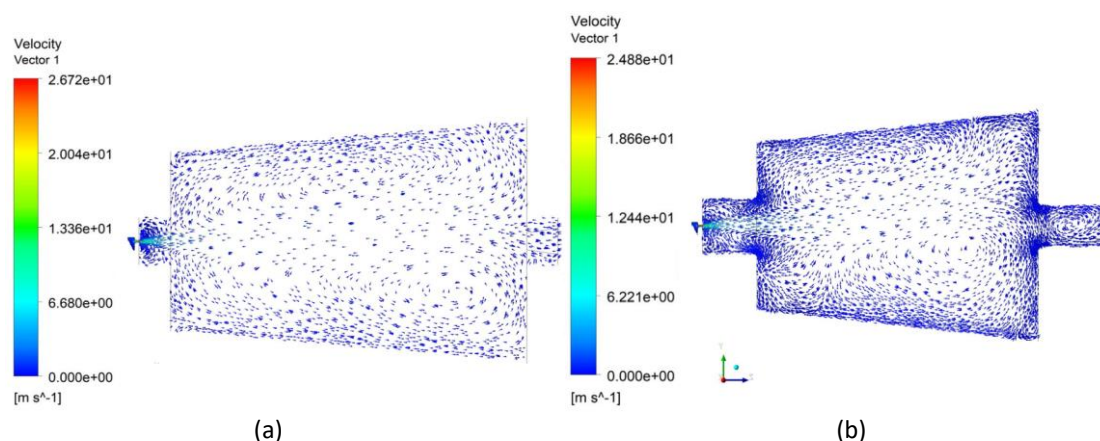


Fig. 10. Velocity vector for MDI disposable inhaler spacer (a) AeroCup design (b) commercial design A

Streamline are the lines travelled by neutrally buoyant particles in equilibrium with the fluid motion. It was an excellent tool for visualization of complex three-dimensional flows. In this study, the streamline used to examine the flow around and in the wake of the module. Figure 11 shows the streamline for the AeroCup design and commercial design A. The velocity streamlines for AeroCup design was 24.88 m/s, and for the commercial design A was 26.72 m/s.

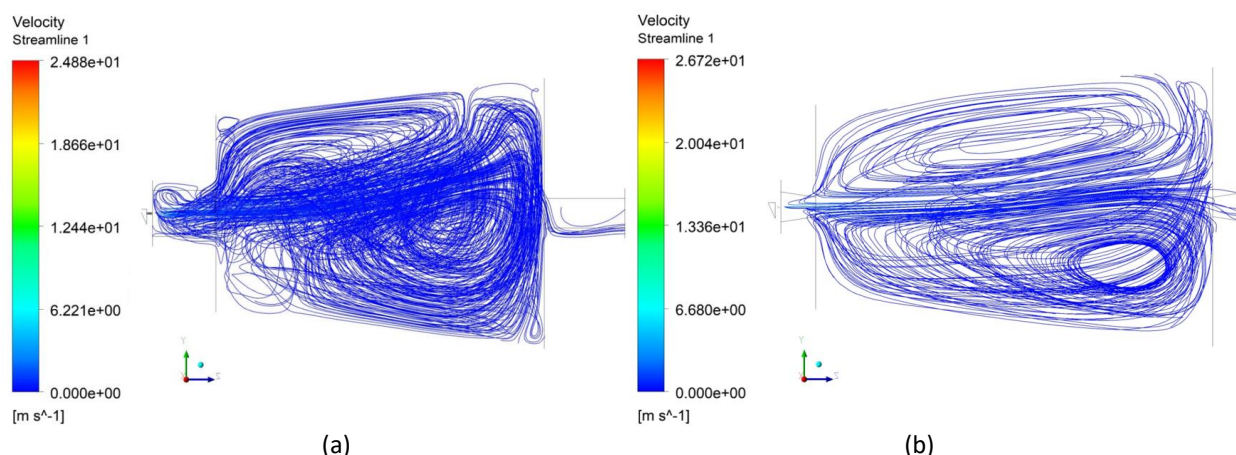


Fig. 11. Streamline for MDI disposable inhaler spacer (a) AeroCup design (b) commercial design A

4. Conclusions

This study was successful in producing a new design of MDI disposable inhaler spacers (AeroCup) that have desired characteristic which comparable to commercial design A. The pattern and particle flow characteristics of the new design (AeroCup) were analyzed and compared to commercial design A using the standard K-epsilon function wall and the Discrete Particle Model (DPM) mode. The parametric analysis found that there was slightly different in particle velocity magnitude for AeroCup and commercial design A. Further qualitative analysis also showed a slight difference in the Eddy viscosity, turbulent Eddy dissipation, turbulent kinetic energy (TKE) and velocity of the flow. This study can provide a piece of information to produce the low-cost MDI disposable inhaler spacer to enlighten the burden shouldered by front liners, especially during the pandemic and also can scale-up the economic viability. However, it recommended studying the design of the feeder cap further to make it more universal and user-friendly. Besides, the compatibility of the material used for the fabrication of the AeroCup should also be studied to avoid the uses of toxic material, especially for

health-care application. All the considerations outlined here was needed to provide a complete and profound understanding of AeroCup application in future.

Acknowledgement

The author would like to thank the Ministry of Higher Education Malaysia for supporting this research under the Centre of Graduate Studies, Universiti Tun Hussein Onn Malaysia, Postgraduate Research Grant (GPPS) H030, Product Development grant (GPP) B088 and B092 for sponsoring this project. This new design (AeroCup) was already patterned under LY 2020002678.

References

- [1] Shereen, Muhammad Adnan, Suliman Khan, Abeer Kazmi, Nadia Bashir, and Rabeea Siddique. "COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses." *Journal of Advanced Research* 24, (2020): 91-98. <https://doi.org/10.1016/j.jare.2020.03.005>
- [2] World Health Organization (WHO). "Coronavirus disease (COVID-19) pandemic." (2020).
- [3] Elengoe, Asita. "COVID-19 Outbreak in Malaysia." *Osong Public Health and Research Perspectives* 11, no. 3 (2020): 93. <https://doi.org/10.24171/j.phrp.2020.11.3.08>
- [4] Ministry of Health (MOH) Malaysia "(COVID-19) Malaysia." (2020).
- [5] Lai, Chih-Cheng, Tzu-Ping Shih, Wen-Chien Ko, Hung-Jen Tang, and Po-Ren Hsueh. "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges." *International journal of antimicrobial agents* 55, no. 3 (2020): 105924. <https://doi.org/10.1016/j.ijantimicag.2020.105924>
- [6] Moore, John B., and Carl H. June. "Cytokine release syndrome in severe COVID-19." *Science* 368, no. 6490 (2020): 473-474. <https://doi.org/10.1126/science.abb8925>
- [7] Peiris, Joseph SM, Kwok Y. Yuen, Albert DME Osterhaus, and Klaus Stöhr. "The severe acute respiratory syndrome." *New England Journal of Medicine* 349, no. 25 (2003): 2431-2441. <https://doi.org/10.1056/NEJMr032498>
- [8] Mashable Sea Asia. "These are the 5 stages of coronavirus infection according to Malaysia's Health Ministry". (2020).
- [9] Guidelines on the Paediatric Intensive Care Unit (PICU) Management of Children with COVID-19 from Kementerian Kesihatan Malaysia. KKM.600-27/6/1 (2020).
- [10] Amirav, Israel, and Michael T. Newhouse. "Transmission of coronavirus by nebulizer: a serious, underappreciated risk." *CMAJ* 192, no. 13 (2020): E346-E346. <https://doi.org/10.1503/cmaj.75066>
- [11] Lavorini, Federico. "The challenge of delivering therapeutic aerosols to asthma patients." *International Scholarly Research Notices* 2013 (2013): 1-17. <https://doi.org/10.1155/2013/102418>
- [12] Pauwels, Romain, S. Newman, and L. Borgstrom. "Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers." *European Respiratory Journal* 10, no. 9 (1997): 2127-2138. <https://doi.org/10.1183/09031936.97.10092127>
- [13] Price, David B., Miguel Román-Rodríguez, R. Brett McQueen, Sinthia Bosnic-Anticevich, Victoria Carter, Kevin Gruffydd-Jones, John Haughney et al. "Inhaler errors in the CRITIKAL study: type, frequency, and association with asthma outcomes." *The Journal of Allergy and Clinical Immunology: In Practice* 5, no. 4 (2017): 1071-1081. <https://doi.org/10.1016/j.jaip.2017.01.004>
- [14] Sanders, Mark, and Ronald Bruin. "A rationale for going back to the future: use of disposable spacers for pressurised metered dose inhalers." *Pulmonary medicine* 2015, no. 2 (2015): 1-6. <https://doi.org/10.1155/2015/176194>
- [15] Lavorini, F., and G. A. Fontana. "Targeting the drug to the lungs: effect of spacer devices." *Expert Opin Drug Deliv* 6 (2009): 91-102. <https://doi.org/10.1517/17425240802637862>
- [16] Levy, Mark L., P. N. R. Dekhuijzen, P. J. Barnes, M. Broeders, C. J. Corrigan, B. L. Chawes, L. Corbetta et al. "Inhaler technique: facts and fantasies. A view from the Aerosol Drug Management Improvement Team (ADMIT)." *NPJ primary care respiratory medicine* 26, no. 1 (2016): 1-7. <https://doi.org/10.1038/npjpcrm.2016.28>

- [17] O'CALLAGHAN, C. H. R. I. S., and PETER W. BARRY. "How to choose delivery devices for asthma." *Archives of disease in childhood* 82, no. 3 (2000): 185-187.
<https://doi.org/10.1136/adc.82.3.185>
- [18] Saeed, Haitham, Mohamed EA Abdelrahim, Hoda Rabea, and Heba F. Salem. "Evaluation of Disposable and Traditional Accessory Devices for Use With a Pressurized Metered-Dose Inhaler." *Respiratory care* 65, no. 3 (2020): 320-325.
<https://doi.org/10.4187/respcare.06835>
- [19] Oliveira, Ricardo F., Ana C. Ferreira, Senhorinha F. Teixeira, José C. Teixeira, and Helena C. Marques. "pMDI spray plume analysis: a CFD study." In *Proceedings of the World Congress on Engineering*, vol. 3. 2013.
- [20] Oliveira, Ricardo F., S. F. C. F. Teixeira, José C. Teixeira, Luís F. Silva, and Henedina Antunes. "pMDI sprays: Theory, experiment and numerical simulation." *Advances in Modeling of Fluid Dynamics* 300 (2012).
- [21] Uppu, Shiva Prasad, Dindigala Manisha, Gudey Dharani Devi, Pranav Chengalwa, and Boppana Vaishnavi Devi. "Aerodynamic analysis of a dragonfly." *Journal of Advanced Research in Fluid Mechanics and Thermal Sciences* 51, no. 1 (2018): 31-41.
- [22] Dahalan, Md Nizam, Ahmad Fitri Suni, Iskandar Shah Ishak, N. A. R. Nik Mohd, and Shabudin Mat. "Aerodynamic study of air flow over a curved fin rocket." *Journal of Advanced Research in Fluid Mechanics and Thermal Sciences* 40, no. 1 (2017): 46-58.
- [23] Mat, Mohamad Nur Hidayat, and Norzelawati Asmuin. "Optimizing Nozzle Geometry of Dry Ice Blasting Using CFD for the Reduction of Noise Emission." *International Journal of Integrated Engineering* 10, no. 5 (2018): 1-9.
<https://doi.org/10.30880/ijie.2018.10.05.019>
- [24] Mat, Mohamad Nur Hidayat, Nor Zelawati Asmuin, Md Faisal Md Basir, Marjan Goodarzi, Muhammad Faqhrurrazi Abd Rahman, Riyadhthusollehan Khairulfuaad, Balasem Abdulameer Jabbar, and Mohd Shareduwan Mohd Kasihmuddin. "Influence of divergent length on the gas-particle flow in dual hose dry ice blasting nozzle geometry." *Powder Technology* 364 (2020): 152-158.
<https://doi.org/10.1016/j.powtec.2020.01.060>
- [25] Leach, Chet L., Patricia J. Davidson, Bruce E. Hasselquist, and Robert J. Boudreau. "Influence of particle size and patient dosing technique on lung deposition of HFA-beclomethasone from a metered dose inhaler." *Journal of aerosol medicine* 18, no. 4 (2005): 379-385.
<https://doi.org/10.1089/jam.2005.18.379>
- [26] Cheng, Y. S., C. S. Fu, D. Yazzie, and Y. Zhou. "Respiratory deposition patterns of salbutamol pMDI with CFC and HFA-134a formulations in a human airway replica." *Journal of aerosol medicine* 14, no. 2 (2001): 255-266.
<https://doi.org/10.1089/08942680152484180>
- [27] Clark, Andrew R. "MDIs: physics of aerosol formation." *Journal of aerosol medicine* 9, no. s1 (1996): S-19.
<https://doi.org/10.1089/jam.1996.9.Suppl.1.S-19>
- [28] Oliveira, Ricardo F., Senhorinha Teixeira, Luís F. Silva, José Carlos Teixeira, and Henedina Antunes. "Study of a pressurized metered-dose inhaler spray parameters in fluent." In *Proceedings of the World Congress on Engineering*, vol. 2. 2010.
- [29] Goswami, Mayank, Sanjeev Kumar, and Prabhat Munshi. "Correlation between numerical simulation and limited data experimental technique for estimation of nitrogen flowing in LMMHD loop." *Flow Measurement and Instrumentation* 46 (2015): 80-86.
<https://doi.org/10.1016/j.flowmeasinst.2015.10.002>