



## Numerical modeling and Optimization of Respirational Emergency Drug Delivery Device using Computational Fluid Dynamics and Response Surface Method

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### ABSTRACT

Studies have shown that most of the particles sprayed on emergency respirational patients, accumulate inside the endotracheal tube and its connector. In this paper, applying Computational Fluid Dynamics (CFD) and Response Surface Method (RSM), an optimized geometry is introduced for higher efficiency of the drug delivery for patients with emergency respiratory diseases. In CFD modeling, finite volume method and for two-phase flow modeling, Lagrangian method is used. Reynolds averaged Navier–Stokes equations with Reynolds stress turbulence model are solved using SIMPLE pressure correction algorithm within the computational domain. The velocity fluctuations are simulated using the Discrete Random Walk (DRW). For optimization process, six different parameters including three dimensions of the connector of the tube: connector length, connector diameter and injection diameter, injection velocity of the drug particles, air flow velocity and particle size are investigated. Using Design of Experiments (DOE) and RSM, the output efficiency of the model and second-order regression equation model are derived and accuracy of the model is confirmed. Then the effect of each input parameter on the efficiency is investigated. Dringer algorithm is applied to optimize the process and the best combination of input parameters yielding the highest efficiency is introduced.

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## 1. INTRODUCTION

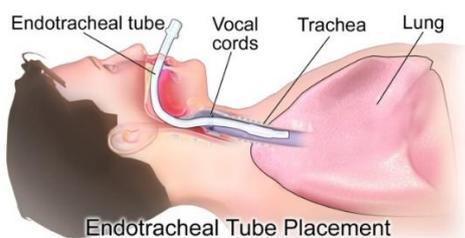
Today, human activity on the planet has caused the production of dangerous chemicals into the atmosphere which are inhaled by humans every day and cause different damages to the human digestive system. Chronic Obstructive Pulmonary Diseases (COPD) including emphysema, chronic bronchitis, asthma, when there is a blockage in the path of the air entering the lung. Bronchitis is when inflammation occurs in bronchi. In emphysema, very tiny air pockets at the end of the lung's air path are gradually dead. Diseases like severe asthma, COPD and recently emerged COVID-19 adversely affect the lung's tissue and obstacle the natural respiration. In such cases generally mechanical ventilators are implemented to assist breathing. It is vital, however,

sometimes, in addition to help patients in breathing, there is a need to send some drugs to the respiration system of the patients. Such drugs, generally in the form of suspension, including salbutamol, hydrofluoroalkane (HFA) and/or chlorofluorocarbon (CFC) particles. It is evident that such drug delivery system, through respiration, is quite effective in healing respiratory conditions [1-3]. In this state, drug after being sprayed builds up a two-phase flow with the oxygen flow and can directly find access to the infected areas of the lung. Treating patient using such a direct method would require lower dosage of drug and eliminate possible side effects as it is directly headed to the area where it is needed [4-6]. Nowadays different respiratory sprays like Nebulizers, dry powder inhalers and Metered-Dose inhalers (MDIs) are commercially available. Such sprays

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are suitable for patients who are breathing naturally and are physically able to put the spray in their mouth [7, 8].

At emergency condition for sending oxygen and drug to the lungs by an artificial air path, Endotracheal tube (ETT), is used. ETT is a flexible plastic tube and through the mouth it is mounted on the windpipe and it can transfer the oxygen and anesthetizers to the lung when patients are in a coma. For drug injection such a tube is equipped with spray-producing mechanism for drug injection which is connected to the tube with a connector. Figure 1 illustrates the schematic of such a system. The application of such tube system improves the respiration of patients as it keeps the breathing path opened and delivers oxygen to the lungs [9]. Such tubes have length of 160 to 300mm and internal diameter of 3 to 9 mm based on the application and age of the patients. When drug is sprayed evidently enormous amount of its particles is blocked in the tube, connector and connections and this remarkably reduces the efficiency of drug delivery. The lower amount of particles occupying the tube system means that higher dosage of drug was delivered to the lung and desirable efficiency is achieved. Mazela et al. [10] reported that the efficiency of particle delivery through such a system is heavily dependent upon the size of the particle; it is 100% for small particles and almost 0% for particles bigger than 7 micrometers. Ahrens et al. [11] investigated the blockage of the drug particles in tube system with different tube diameters of 3, 6 and 9 mm. They used a tube system where drug was delivered to the lung through a T connector connected to the tube. They reported that when size of the particles was smaller, about 0.54 micrometer, the blockage in the system remarkably decreased. However, it was evident that the distribution of the particles in two-phase flow and also properties of the flow are more important in delivery of the particles than the tube diameter. The effect of tube diameter was also examined and it was found that no remarkable change in delivery would occur with altering tube diameter from 7 mm to 9 mm [12]. Generally, though tube diameter is effective in the performance of drug delivery system, this effectiveness is varied in different systems and there exist other more influential parameters. Fuller argued that type of the spray: Nebulizers or MDI is influential over drug delivery [13].



**Figure 1.** Schematic application of endotracheal tube in emergency respiratory patients

Many reports have been released on the influence of the type of the spray which confirms better performance of the MDIs and chambers than nebulizers. Although both nebulizers and MDIs similarly function in terms of delivering the drug, the dosage required by nebulizers is considerably higher than that for MDIs. Yousefi [14] improved drug delivery using a one-way chamber with MDI. Later in 2017 using an acoustic wave surface they altered the creation of the particles in the chamber and then suggested the optimum condition of the chamber [15]. In another study, Yousefi et al. [16], investigated the effect of different parameters like particle velocity, particle distribution, particle injection angle and air flow rate. They reported an effectiveness on drug delivery to the lung. Very few studies are available concerning the design of the ventilator especially the connector to minimize the blockage of the drug in the system. It is expected that maximum blockage occurs in the area where path of the flow suddenly alters (change in the diameter of the path or the direction) [17]. In ventilator circuit maximum blockage would occur in the ETT and collector. The size of ETT is limited to the anatomy of the patient though tubes with higher diameter are more successful in delivering particles [10, 18]. Ivri [19] proposed connector angles less than  $16^\circ$  to improve through-ventilator drug delivery. This, however, would require longer connections in ventilator circuit. Recently, Mazela et al. [20] re-designed a Y shape connector. But the blockage of particles increased in modified design. Longest suggested a linearized connector where no abrupt changes existed in the path of the flow using gradually smoothing sections and they successfully reduced the blockage of particles from 30% to 5% for a T connector [16]. They examined their linearized connector for a Y shape connector and found that output particles increased from 40% to 70% using flow of 30 l/min of air and particle size of 4 micrometers [20, 21]. Also, in recent years, many researchers have conducted effective and relevant research in this field [22-29].

In this paper using Computational Fluid Dynamics (CFD) and Response Surface Method (RSM) an optimized geometry for better drug delivery performance of ventilator considering six different parameters including three dimensions of collector, particle injection velocity, flow rate and particle size is derived. For numerical modeling, finite volume method and for modeling two-phase flow, Lagrangian method is used. To evaluate the effect of each parameter on drug delivery and in order to validate the numerical model, design of experiments and response surface method are applied and then governing second order regression equation is derived. Finally using Dringer algorithm an optimum combination of parameters yielding the highest drug delivery performance and lowest blockage of the particle is investigated.

TABLE 1. Design variables

Design Variable	Symbol	Unit	From	To
Connector length	L	mm	10	30
Connector diameter	d1	mm	10	20
Injection diameter	d2	mm	2	6
Particle diameter	dP	µm	1	9
Particle velocity	VP	m/s	100	150
Air velocity	Va	m/s	4	8

2. MATHEMATICAL MODELING

The data required for optimization is extracted from numerical modeling. The detail of numerical modeling is elaborated in this section.

**2.1. Geometry** Figure 2 schematically illustrates the geometry of the system. This system includes an Endotracheal tube (ETT) entering the patient mouth, the connector with two opening: one through which drug is sprayed and the other is connected to the ventilator. For optimization purpose particle injection speed, particle size, air flow and three dimensions of the connector are taken into account. The variables range used in optimization is listed in Table 1.

**2.2. Governing Equation** The air flow is assumed to be incompressible and Newtonian. Moreover, 3D continuity and momentum conservation equations and Reynolds-averaged Navier-Stokes equations are solved using *k-ϕ* turbulence method as follows:

$$\frac{\partial \bar{u}_i}{\partial x_i} = 0 \tag{1}$$

$$u_j \frac{\partial u_i}{\partial x_j} = -\frac{1}{\rho_f} \frac{\partial p}{\partial x_j} + \frac{\partial}{\partial x_j} \left[ (v_f + v_T) \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) \right] \tag{2}$$

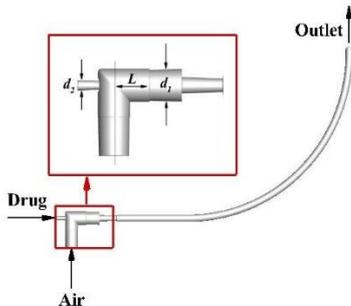


Figure 2. Details of endotracheal tube and definition of geometrical design variables

Discrete phase model and Lagrangian particle tracking approach are used for particle movement simulation. In this method to track each particle from equilibrium condition, integration is performed.

$$\bar{F} = m_p \cdot \frac{d\bar{u}_p}{dt} \tag{3}$$

where  $u_p$  is particle velocity,  $t$  is time and  $F$  is the force, constitute of 12 different components presented in Equation (4):

$$\begin{aligned} \bar{F} = & \bar{F}_D + \bar{F}_b + \bar{F}_g + \bar{F}_{Saffman} \\ & + \bar{F}_{virtualmass} + \bar{F}_{p.gradient} + \bar{F}_{Faxen} \\ & + \bar{F}_{Basset} + \bar{F}_B + \bar{F}_T + \bar{F}_m + \bar{F}_M \end{aligned} \tag{4}$$

Where components are drag, Buoyancy, gravity, Saffman lift, virtual mass, pressure gradient, facen, basset, Brownian, thermoforsis, Magnus and magnetic forces respectively. Many of these components are negligible. For instance, since the density of the particles is much higher than that of the fluid, buoyancy and basset forces are negligible. Gravity forces, also, are prominent only for lower flow rates. Brownny movement and saffman lift forces are applicable for sub-micron particles [30, 31]. Magnetic force can be discarded as no magnetic field exists over the path of the particle. Finally, Fax force can be ignored because its value is remarkable only when length scale of the particle and the system possess the same order. Thus the equilibrium equation of the particle can be rewritten as presented in Equation (5):

$$\bar{F} = m_p \cdot \frac{d\bar{u}_p}{dt} = \bar{F}_D \tag{5}$$

Stocks drag force over a smooth spherical particle is presented in Equation (6) [32]:

$$\bar{F}_D = \frac{18\mu m_p f Re_p}{\rho_p d_p^2} (u_f - u_p) \tag{6}$$

where drag coefficient is computed in Equation (7):

$$f = a_1 + \frac{a_2}{Re_p} + \frac{a_3}{Re_p^2} \tag{7}$$

where  $Re_p = \frac{\rho_f d_P |u_P - u_f|}{\mu_f}$  is Reynolds number for

each particle and  $a_1, a_2$  and  $a_3$  are empirical constants which are applicable in the range of  $0 \leq Re_p \leq 5 \times 10^4$  [33]. Moreover, for the sake of simplification, the effect of particle evaporation or particle concentration and also electrostatic charge of the walls were neglected.

**2.3. Boundary Condition** For numerical simulation, equations derived in the previous section should be solved with appropriate boundary conditions. Air with a certain flow rate enters the connector and exits the end of the ETT. On the walls of connector and ETT,

no-slip condition is considered and it is assumed that particles stick to the wall right away after coming into contact with the wall for the first time. At the end of the ETT it is assumed that air flow rate remains constant. All particles are assumed to enter the ETT particles with certain speed and size.

**2. 4. Numerical Method** Here, numerical method is based on finite volume method. Second order upwind was used to divide different variables. SIMPLE algorithm is used to solve the couple of the velocity and pressure fields. To ensure the accuracy of the results independent from the discretization, different mesh sizes are used and in each case the optimum grids with acceptable accuracy and low computational cost are selected. An essential assumption in DPM model is that the second phase of the two-phase flow, here is the particle size, possesses negligible volume fraction even for the high flow rates. Therefore, it seems necessary to check this volume fraction in each element to be less than 12% because the proposed model is only valid when this condition is satisfied. One-way coupling is defined so that the collision of each particle to the flow field and also to other particles is neglected.

On average, 500000 elements are used. A sample of generated mesh is shown in Figure 3. Mesh independence is examined for proposed model in Figure 4 are mesh networks with 170000, 270000, 490000 and 923000 elements made readily slight variation in flow rate values. Finally, total number of elements equal to 490000 is used for the further investigation.

**2. 5. Modeling of Spray Particles** The distribution of the particles in the input of the ETT should have no influence over the convergence of the results. For example, if a distribution with concentration towards the center of the tube's cross section exists, it would lead to a premature convergence which yields fallacious results. Therefore, a uniform distribution of the particles in the entrance of the ETT is necessary. Here a computer code

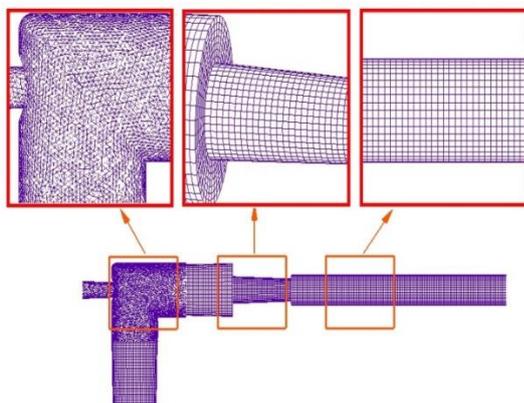


Figure 3. A sample of generated mesh using in CFD process

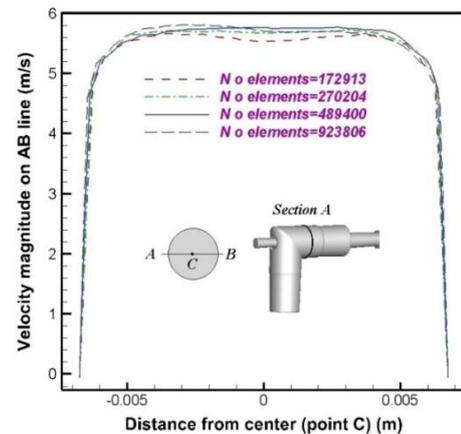


Figure 4. Results of grid independency test

to produce a uniform distribution has been used. Figure 5 compares the uniformity in the article distribution before and after using this computer code. Total 6000 particles are injected into the connector with 120 m/s velocity in the entrance cross section with diameter of 2.4 mm.

**2. 6. Validation of Numerical Results** To validate numerical results, comparisons should be made with reliable data. Since experimentation for drug blockage in the ventilator system is astronomically costly, there is no reported data available. Therefore, comparison of derived data here with results of the ETT with a 90-degree elbow reported elsewhere is followed [34]. Figure 6 shows the blockage value in a 90-degree-elbow ETT reported elsewhere [35] which affirm great correlation. The discrepancy in the results is attributed to the assumed condition of with-a-first-contact absorption of the particles to the wall and also one-way coupling condition which are different with what would happen in real experimentation setting.

### 3. RSM AND DATA ANALYSIS

Using DOE and RSM, six different parameters of air flow rate, particle injection velocity, particle size and three

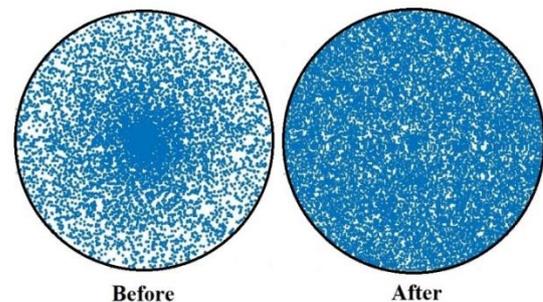
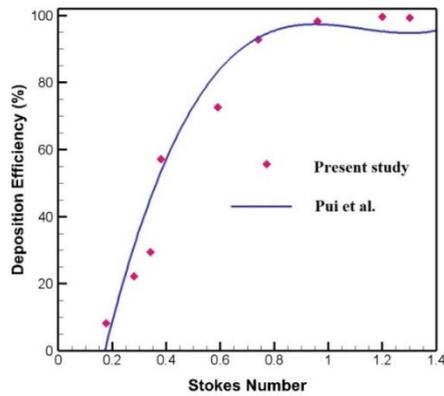


Figure 5. Details of endotracheal tube and definition of geometrical design variables



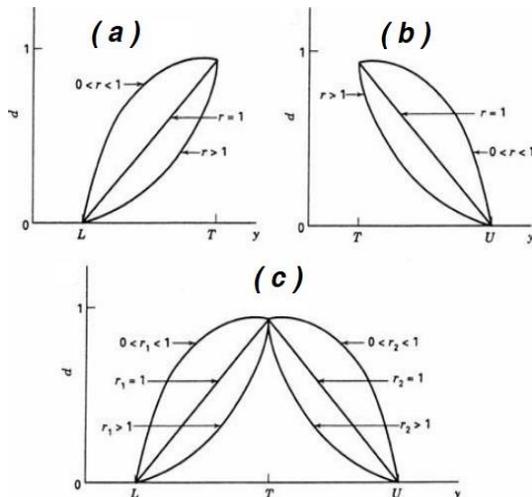
**Figure 6.** Details of endotracheal tube and definition of geometrical design variables.

dimensions of connector (Table 1) are considered as influential parameters. Governing equation of the fitted model are derived and then the model accuracy is confirmed. Then, in addition to studying the effect of each individual parameter, Dringer method is used to obtain optimum combination of input parameters to maximize drug delivery and minimize drug blockage within the ETT system.

In this method, the overall goal is to convert response ( $y_i$ ) to a dimensionless unique utility function ( $d_i$ ) that changes over the entire interval as follows:

$$0 \leq d_i \leq 1 \tag{8}$$

If answer ( $y_i$ ) is the goal of optimization then  $d_i = 1$  and if the answer is acceptable outside an area then  $d_i = 0$ , as shown schematically in Figure 7. In the present study, the value of  $d_i = 1$  is obtained for the utility limit function and is expressed in the Figure 7, which indicates convergence and access to the optimal value in this research [36].



**Figure 7.** Details of endotracheal tube and definition of geometrical design variables [37]

**3. 1. Response Surface Method (RSM)** In analysis of engineering problems especially experimental and numerical approaches where the output relies on different input variables, carrying out statistical methods can remarkably improve design, modeling, analysis and optimization steps. Response surface method is very promising in saving time and cost of design and analysis of models. It specifies the precision of the fitted model and establishes a mathematical model to the problem. Its advantages include yielding the diagrams of interaction effect of parameters, optimization and ensuring the model accuracy [34]. RSM can relate input parameters to the output through a second order linear regression equation. General form of such equation is presented in Equation (9) [37]:

$$y = \beta_0 + \sum_{i=1}^k \beta_i x_i + \sum_{i=1}^k \beta_{ii} x_i^2 + \sum_i \sum_j \beta_{ij} x_i x_j + \varepsilon \tag{9}$$

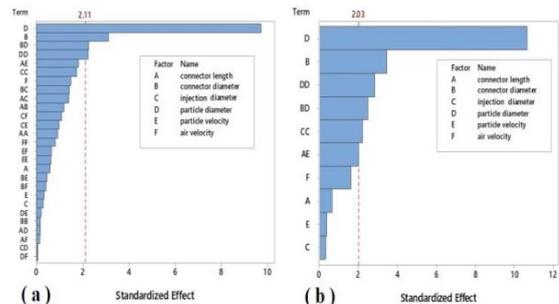
where,  $y$  is the output,  $\beta$  is the regression equation coefficients,  $x_i$  is main input parameter,  $x_i^2$  is the squared of main input parameters,  $x_i x_j$  is the second order interaction effect of input parameters [38]. The proposed model, if established precisely, can successfully predict the output over the entire range of input variables [39].

**3. 2. Input and Output Variables of the Drug Delivery Process**

In this research considering the variation of the six design variables according to Figure 2 and Table 1, in total 45 different sets of design variables are considered for modeling and optimization using composite central design (CCD). To avoid unpredicted errors, simulations are done randomly [40]. Minitab version 18 and Design Expert version 10 software packages are used for data analysis and extracting regression equation. Using RSM, a governing equation is derived with fitting the model to the data points. Then sensitivity analysis and optimization of the model are followed.

**3. 3. Data analysis and Model Establishment**

ANOVA defines the effectiveness of each of regression



**Figure 8.** Details of endotracheal tube and definition of geometrical design variables

parameters which in turn defines the effectiveness of each input variables as well as their interactions [39]. Considering generally accepted reliability of 95% for engineering problems, Pvalue less than 0.5 is considered to ascertain the effectiveness of different parameters [36]. Figure 8 shows the term before and after modification. PRESS which defines the precision of the model fitted to the process is prominent in the field of design of experiment. The lower PRESS value is, more accurately model can predict the outputs. In this model the minimum PRESS coincided with full quadratic regression model. Considering minimal value of 35544.02 for PRESS the second order regression model of process can be defined using Equation (10):

$$\begin{aligned} \eta = & -48.3 + 5.42L + 5.17d_2 - 53.4d_1 / 2 \\ & - 6.62d_p + 0.855V_p - 2.0IV_a \\ & + 13.16(d_1 / 2)^2 + 1.040(d_p)^2 - 0.0447LV_p \\ & - 0.692d_2d_p \end{aligned} \quad (10)$$

Considering the value R-sq=88.85% and appropriate distribution of residuals it can be inferred that proposed model is desirably accurate. R-sq which shows the precision of the fitted model can be computed using Equation (11):

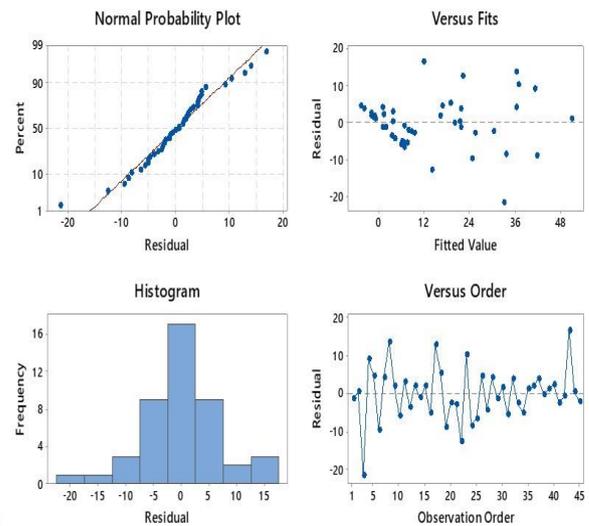
$$R^2 = \frac{SS_R}{SS_T} = 1 - \frac{SS_{Res}}{SS_T}, \quad (11)$$

The closer to unity (100%) is this value, the correspondence of the model to the data point is higher and more accurate prediction is expected [5]. another important factor playing a role in accuracy of the model is the distribution of residuals. The fitted model should pass close to the data points with random distances. This value is defined in R-sq and its distribution is shown in Figure 9. Generally, from both the value of fitted points and the random nature of this fit, presented model is desirable.

#### 4. OPTIMIZATION RESULTS

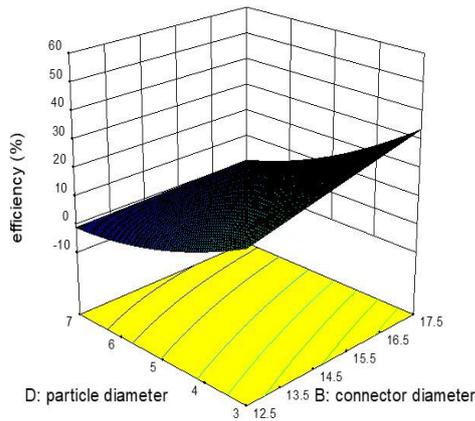
In this section, considering developed model, it is attempted to specify the effectiveness of the input parameters over the efficiency of the drug delivery. Appropriate main effect, interaction and contour plots will be presented.

Surface plot of drug delivery process is illustrated in Figure 10. To analyze the effect of connector diameter, main effect plot in Figure 11(a), interaction plot in Figures 11(e) and 11(f) and contour plot presented in Figure 12. It can be implied that efficiency of the system increases with a raise in connector diameter. The interaction effect of connector diameter and particle size confirms that with simultaneous increase in connector



**Figure 9.** Details of endotracheal tube and definition of geometrical design variables

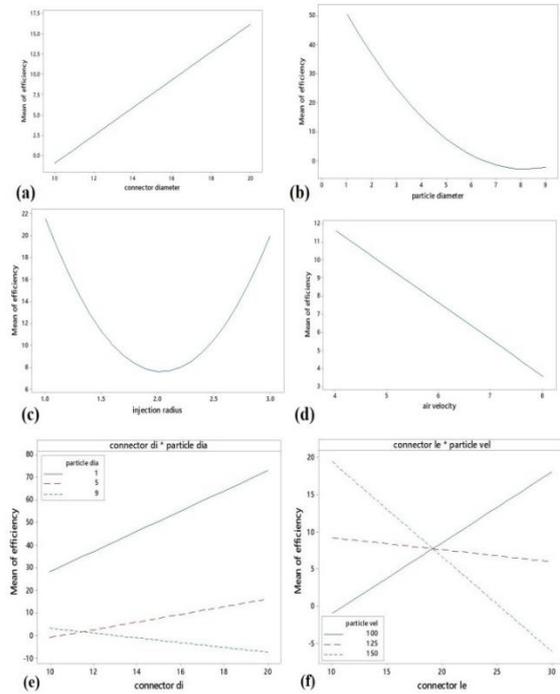
diameter and decrease in particle size the efficiency considerably rises. This can be explained that the more spacious is the path; there is lower chance for particles to collide to each other or to the walls. Having that said, with increase in diameter of the connector the velocity of two-phase flow decreases because it is assumed that air flow rate is constant. With lower velocity it is less probable for particles to collide and therefore blockage would decrease. Additionally, it can be seen from plots in Figures 11 and 12 that reduction in particle size improves the efficiency while increasing particle size noticeably drops the efficiency. This is attributed to the fact that with bigger particles the probability of collision of a particle with other particles or wall increases and blockage would ascend. Considering connector length and particles velocity presented in Figure 13, it can be observed that maximum efficiency coincides with either shortest connector length and highest particle velocity or longest connector length and lowest particle velocity. This inference can be confirmed according to Figure 12. When connector is long, particles spends more time inside the connector and with turbulence in the connector the collision probability and blockage increases. In this condition, if particles are injected with lower velocity the chance of collision decreases and efficiency improves while higher injection velocities increase the collision and boosts blockage. On the other hand, if short connector is used, in an arbitrary time frame lower number of particles exists in the connector and the collision of particles no longer plays an important role in the efficiency of drug delivery. Whereas, with higher speed of particle injection, more particles pass the connector quickly without being blocked in it and therefore, efficiency increases.



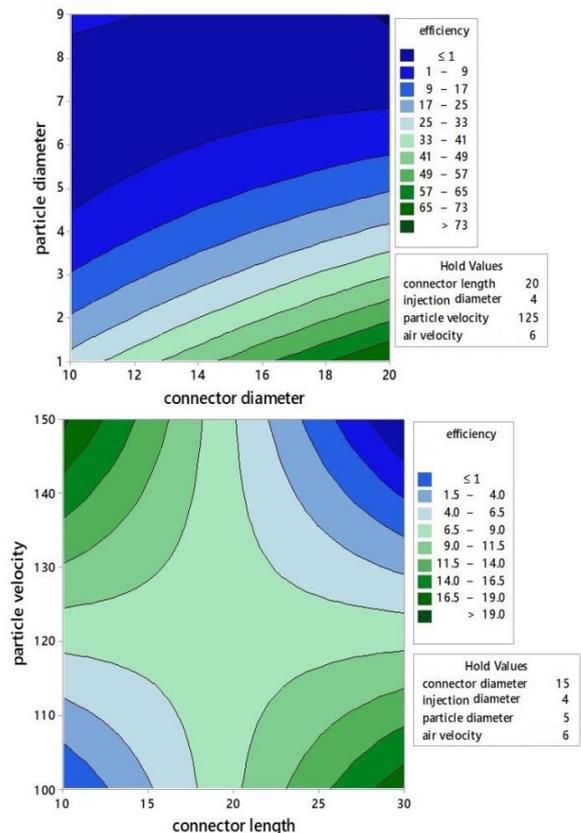
**Figure 10.** Details of endotracheal tube and definition of geometrical design variables

Considering injection diameter, Figure 11(c) reveals that the highest efficiency coincides with lowest injection diameters. With a low cross section-area of injection the concentration of particles towards center rises which decreases the scatter of the particles. However, concentration of particles toward center increases the chance of collision. Due to the short length of the entrance mouth, nonetheless, the collision is not the main reason of blockage. The injection diameter is not among main factors and in the regression model, only, its second order is presented. Nevertheless, according to Figure 11(c), after passing a threshold with a bigger diameter of injection efficiency again increases. According to ANOVA table the effect of air flow rate is negligible on efficiency of drug delivery though Figure 11(d) shows that with a decrease in air flow speed, the efficiency of the system slightly improves. This is attributed to the fact that when particles are taken by the flow their speed gradually matches the speed of the flow. With lower flow speeds the chance of collision and blockage would be lower though this parameter is almost ineffective for the considered system.

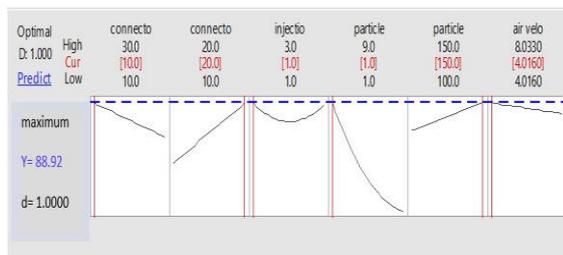
Based on the analysis of drug particles blockage within the Endotracheal tube system, optimization is performed for maximizing the efficiency. Considering the upper level of efficiency in the tests and considering Desirability limit the results of optimization are shown in Figure 13. According to the results maximum efficiency of 89% coincides with minimum connector length (10mm), maximum connector diameter (20 mm), the lowest injection diameter (2mm), the lowest particle diameter (1 mm), the highest particle velocity (150 m/s) and minimum air flow rate (4 m/s). The extracted optimal device can be used in all respiratory patients who need to breathe in unusual and emergency conditions such as anesthesia in corona virus. The extracted optimal geometry can be easily mass-produced by medical equipment manufacturers.



**Figure 11.** Details of endotracheal tube and definition of geometrical design variables



**Figure 12.** Details of endotracheal tube and definition of geometrical design variables



**Figure 13.** Details of endotracheal tube and definition of geometrical design variables

## 5. CONCLUSION

In this paper, applying CFD and RSM, an optimized geometry was introduced for higher efficiency of the drug delivery for patients with emergency respiratory diseases. In CFD modeling, finite volume method and for two-phase flow modeling, Lagrangian method was used. Reynolds averaged Navier–Stokes equations with Reynolds stress turbulence model were solved using SIMPLE pressure correction algorithm within the computational domain. The velocity fluctuations were simulated using the Discrete Random Walk (DRW).

For optimization process, six different parameters including three dimensions of the connector of the tube: connector length, connector diameter and injection diameter, injection velocity of the drug particles, air flow velocity and particle size were investigated. Using Design of Experiments (DOE) and RSM, the output efficiency of the model and second-order regression equation model were derived and accuracy of the model was confirmed. Then the effect of each input parameter on the efficiency is investigated. Dringer algorithm was applied to optimize the process and the best combination of input parameters yielding the highest efficiency is introduced. According to the results maximum efficiency of 89% coincides with minimum connector length (10mm), maximum connector diameter (20 mm), the lowest injection diameter (2mm), the lowest particle diameter (1 mm), the highest particle velocity (150 m/s) and minimum air flow rate (4 m/s). The extracted optimal device can be used in all respiratory patients who need to breathe in unusual and emergency conditions such as anesthesia in corona virus. The extracted optimal geometry can be easily mass-produced by medical equipment manufacturers.

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### Persian Abstract

#### چکیده

مطالعات انجام شده نشان می دهد که بیشتر ذرات اسپری شده به بیماران رویی در حالت اورژانسی، در داخل لوله تراشه و کانکتور متصل به آن انباشت می شوند. در این مقاله به وسیله دینامیک سیالات محاسباتی و سپس استفاده از روش بهینه سازی سطح پاسخ، به معرفی یک هندسه بهینه جهت بهبود عملکرد دارورسانی و افزایش بازده دارورسانی توسط این دستگاه پرداخته شده است. در این مطالعه ۶ پارامتر طراحی جهت تحویل بهینه دارو به بیماران بررسی شده است. این پارامترها عبارتند از: ابعاد کانکتور متصل به لوله تراشه (۳ پارامتر)، سرعت تزریق ذرات، سرعت جریان هوا و اندازه ذرات. جهت مدلسازی عددی از روش حجم محدود و جهت مدلسازی جریان دوفازی از روش لاگرانژی استفاده شده است. در قسمت بهینه سازی با استفاده از روش طراحی آزمایشها و روش سطح پاسخ، بازده خروجی مدل سازی دستگاه و معادله رگرسیون خطی مرتبه دوم حاکم بر مدل استخراج گردیده و از دقت آن اطمینان حاصل شده است. اثر رفتار هریک از پارامترها بر روی بازده مورد بررسی قرار گرفته است. همچنین با استفاده از الگوریتم درینگر، بهینه سازی بر مدل حاکم بر فرآیند صورت گرفته است و مقادیر بهینه هریک از پارامترهای ورودی به منظور دستیابی به بیشترین مقدار تحویل دارو به ریه های بیمار ارائه گردیده است.