Breath-holding - A Strategy in Enhancing Drug Delivery to the Lungs: A Review

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Abstract. After inhalation of pharmaceutical aerosols, holding of breath prior to exhalation is one of the simpler inhaler techniques when using pressurized metered-dose inhalers and dry powder inhalers. Many benefits are offered by breath holding in enhancing particle deposition, drug efficacy, reducing deposition of particles in the undesired sites and masking of hotspots. Many of the patients are not aware why this procedure is recommended by medical professionals and thus fail to get these benefits. If the breath hold step is successfully addressed, pulmonary drug delivery to the lungs will be more successful. This review addresses computer simulation studies, in particular computational fluid dynamics studies, on the influence of breath-hold in deposition patterns and behaviour of drug particles in the respiratory tract of humans. Along with the studies on breath holding reviewed here, we also briefly discuss the particle phase modelling tools like the discrete element method and discrete phase method.

Keywords: Breath hold; drug deposition; computational fluid dynamics (CFD); Discrete element method (DEM); Discrete phase method (DPM); gravitational sedimentation.

1. Introduction
Drug delivery to the lungs through inhalation is relatively complex due to the resistance mechanisms of the lungs to the inhaled particles and improper usage of inhaler devices [1]. Poor inhaler usage involves lack of coordination between inhalation and actuation of the device, improper positioning of the device, inhalation deprived of required force, failure to completely exhale before inhaling, and lack of post inhalation breath hold pause [1]. Breath-holding means stopping of airflow for few seconds, thus retaining the whole lung capacity after drug inhalation. Breath hold is one of the simplest strategies in inhaler usage recommended by medical professionals in order to enhance the efficiency of drug particle deposition. Breath-hold for few seconds is usually recommended after drug inhalation through pressurized metered-dose inhalers (pMDI) and dry powder inhalers (DPI) before the exhalation phase [2]. Breath holding requires the lowest rate of skill and care amongst various complex drug inhalation procedures.

In most of the experimental and computer simulation studies, the inhalation and exhalation phases are taken into account in research [2,3]. In the analysis of inhalation and exhalation processes, the effects of size, shape, electrostatic charge, and hygroscopicity of drug particles are considered. Other factors influencing drug deposition are airway morphological characteristics, inhalation rate, respiratory volume, inhalation patterns, turbulence, and shear flow impacts. Just a few researchers have suggested...
breath-holding manoeuvre as a method of improving the accumulation of drug aerosols inhaled. Also due to safety and regulatory restrictions, in vivo testing of particle behaviour in real airways of humans along with breath-hold pauses are limited. Imaging studies employing scanning technologies are also insufficient in resolution.

Computational fluid dynamics (CFD) makes use of computational strategies and algorithms to address fluid flow problems and the results can be analysed with in vivo and in vitro data [4]. With the development of high-performance computer software and hardware, CFD is a reliable tool that allows medical researchers to carry out analysis of drug delivery using 3-D models of human respiratory physiology. This review focuses on the contributions of computer simulations in particular CFD, for a better understanding of the impacts of breath-holding strategy in enhancing drug delivery and drug deposition efficiency. This helps in understanding why the medical recommendations advise this strategy after inhaling pharmaceutical aerosols. We also briefly address about different types of geometric models of lung airways used for CFD study. The influence of gravitational sedimentation in settling of particles during the breath hold and the role of breath holding in drug targeting are also addressed. Particle phase modelling tools like the Discrete Element Method (DEM) and Discrete Phase Method (DPM) are also briefly discussed based on the few breath-hold studies investigated here in this review.

2. Geometric Models Of Lung Airways

In 1963 Weibel brought an idealized symmetrical version (extensively called Weibel A model) of the respiratory tract represented through generations beginning from the trachea (0th generation) and ending at alveoli (twenty-third generation) for the research of fluid and particle delivery into the human lungs figure 2 [5]. Weibel version can only give the general trend of fluid and particle flow but cannot give the accurate prediction due to the absence of curvature and asymmetry. The uneven nature of the human lungs is because of presence of two left lobes and three right lobes and variations in size of the daughter airway generations. Based on the lung cast studies conducted by researchers, the geometric dimensions of the asymmetric model of lung airways and lung acinus are available [6]. However, these asymmetric models are also limited due to the fact that it is far from the realistic human lung models and they are not patient-specific representation. Patient-specific noncircular curved geometric version of real human airways can be digitally reconstructed with the help of CT scan and MRI data, which can give an accurate prediction of drug particle transport and deposition [6]. The Weibel, asymmetric and CT based models are represented in figure 1(a), 1(b) and 1(c) respectively.

**Figure 1.** Different geometric models of tracheobronchial tree (a) Weibel based 3-D model of a four generations and triple bifurcation [10]; (b) asymmetric hybrid model by combination of Weibel and Horsefield models [13]; (c) realistic patient specific airway model generated from CT data [11].
3. Deposition During Breath Holding

In order to examine particle deposition during breath holding, Augusto et al. [7] used the CFD technique, and the main drawback of this research was lack of a comparative study of inhalation, exhalation, and breath holding. Inthavong et al. [8] conducted a CFD study of breath holding for two seconds after deep inhalation of aerosols. The results show that there was no increase in particle deposition efficiency until reaching airway generation-6. However, breath-hold is recommendable for locally targeted depositions up to the first few generations due to sedimentation impacts. Later, by adding a breath-hold with the exhalation stage, Augusto et al. [9] updated the previous studies and found substantial increase in particle deposition. The findings suggest that the breath-holding phase should be introduced in real-life scenarios because particles escape through the bifurcations of the airway resulting in lesser deposition efficiency when patients exhale immediately after drug inhalation. The behaviour of particle deposition with and without breath holding and comparison of particle deposition with exhalation was investigated by Kadota et al. [10]. It is clear from their analysis that without breath hold, particles are emitted on exhalation without being deposited in the airways. Later Kadota et al. [11] investigated the particle deposition in the realistic human airway models of asthma patients and healthy individuals with different inhalation patterns without including breath hold. However, the behaviour of particle deposition during terminal velocity was similar to that of a breath holding condition as in his previous study [10].

In the numerical research of Ostrovski et al. [12], breath holding was one of the tactics used in the pulsed aerosol bolus drug targeting integrated with the inhalation technique. Their results indicate that breath-holding manoeuvres are ideally suitable for increasing drug deposition of particles in the upper respiratory airways when the particle size is 5 to 10 μm. The findings of the CFD study of Tao et al. [13] on the 2D pulmonary acinus recommend that gravity only influences the local deposition fraction all through breath-holding and gravitational force is dominant for large particles (1-3 μm), Brownian force for smaller particles (0.01 μm) and medium-sized particles (0.1-0.5 μm) are marginal. This is indicated in figure 3. The research work of Khajeh et al. [14] shows that a breath-hold pause longer than 10s is required for the whole deposition of smaller particles (< 2 μm) inside the alveolar region. Faster deposition of large particles (>5 μm) was observed for shorter breath pause time (<10s). Many researchers observed the phenomenon of accumulation of drug particles dominated by inertia creates hot spots around airway divisions, thus significantly increasing particle accumulation in the locality of

Figure 2. Representation of airway generations (G) [7].
carinal ridges. These regions where the undesirable accumulation of particles takes place are known as hotspots. It is evident from the investigation of Imai et al. [15] that shorter breath-holding is a solution for minimizing unwanted particle accumulation in these upper airway regions. The breath-hold manoeuvre can deliver a uniform dispersal of particles and thus hot spots become insignificant [15].

![Graph showing diffusion, diffusion-sedimentation, and sedimentation-impaction models.](image)

**Figure 3.** Drug particle transport mechanisms corresponding to particle size [16].

### 4. Discussions

The factors related to the CFD simulation such as the type of anatomy (realistic/ideal geometry), flow model (laminar/turbulent), particle tracking method (Lagrangian/Eulerian), number of airway generations and types of mesh are summarized in table 1.

| Flow Model | Author          | Year | Particle Modelling      | Airway Models                              | Airway Generations | Mesh type               |
|------------|-----------------|------|-------------------------|--------------------------------------------|--------------------|-------------------------|
| Laminar    | Augusto et al.  | 2013 | Lagrangian Tracking     | Symmetric Weibel Model TB tree             | G3-G6              | Hexahedral              |
| LRN k-ω    | Inthavong et al.| 2010 | Lagrangian Tracking     | CT scan TB tree                            | G0-G5              | Tetrahedral              |
| Laminar    | Augusto et al.  | 2016 | Lagrangian Tracking     | Symmetric Weibel Model TB tree             | G3-G6              | Hexahedral              |
| SST k-ω    | Kadota et al.   | 2017 | Lagrangian Tracking     | CT realistic TB tree                       | G0-G7              | Polyhedral              |
| k-ω        | Kadota et al.   | 2019 | Lagrangian Tracking     | CT realistic TB tree                       | G0-G7              | Polyhedral              |
| Laminar    | Ostrovski et al.| 2018 | Lagrangian Tracking     | Asymmetrical Hybrid Model (Weibel + Horsfield) TB tree | G0-G6              | Tetrahedral + prism layer |
| Laminar    | Tao et al.      | 2018 | Lagrangian Tracking     | 2D Pulmonary Acinar Model + TB tree        | G0-G8              | Not given               |
| Laminar    | Khajeh et al.   | 2014 | Lagrangian Tracking     | Simplified Acinar Model                    | D2-D4              | Tetrahedral              |
4.1 Flow Model
The complex oral cavity extending to the larynx of the respiratory airways figure 2 is ignored in most CFD studies thus airflow and particle simulation from the trachea figure 1 is initiated so the flow becomes laminar. Based on the experimental results, it is found that the flow in the generations G3-G6 is laminar [7]. So, Augusto et al. [7, 9] particularly selected G3-G6 to avoid the turbulence effects, and also Reynolds number (Re) calculated in these four generations found to be in the range 173-669 confirming laminar flow. For low Re and low inlet flow rate, a laminar flow model was used in the studies of Ostrovski et al. [12] and Tao et al. [13]. Transitional flow and turbulent intensity are due to the laryngeal jet formed by the constriction as a result of the soft palate and glottis on the oral area and throat area respectively and additionally because of the flow instabilities on the carinal ridges which affect drug-aerosol transport and deposition [8, 17]. For the correct prediction of particle deposition in the upper airways, the choice of turbulence model is essential. The minimum turbulent dispersion of particles due to the assumption of absence of the laryngeal jet, Inthanvong et al. [8] preferred LRN k-w model over other turbulence models. The use of the SST k-ω model [10] for the investigation of turbulent flow in realistic human airways provides better results than the k-ω model [11]. This is because of the possibility to use k-ω formulations in the proximity of the wall and k-ε formulations away from the wall [10]. For its good behaviour in adverse pressure gradients and flow separation, the SST k-ω model is advantageous than k-ω model. Although the computational cost is higher, for the accurate prediction of micron particle deposition under unsteady conditions, to solve eddies with large-scale energy and the ability to provide instantaneous velocity fluctuations, LES and DNS models can be used in the future to investigate the particle deposition under breath-hold conditions.

4.2 Investigation of Particle Dynamics
Aerosol system is a two-phase scheme comprising of a fluid phase (continuous) and a particle phase (dispersed). Lagrangian and Eulerian are the two typical approaches used for dealing with two-phase schemes [18]. Clouds of particle or individual particles are monitored as they pass across the computational domain in the Lagrangian method [19]. The Lagrangian method is also called the approach of a moving frame so that a particle's instant position can be determined as a function of time in relation to its point of entry [19]. The second law of motion of Newton governs the motion of particles in these four generations found to be in the range 173-669 confirming laminar flow. For low Re and low inlet flow rate, a laminar flow model was used in the studies of Ostrovski et al. [12] and Tao et al. [13]. Transitional flow and turbulent intensity are due to the laryngeal jet formed by the constriction as a result of the soft palate and glottis on the oral area and throat area respectively and additionally because of the flow instabilities on the carinal ridges which affect drug-aerosol transport and deposition [8, 17]. For the correct prediction of particle deposition in the upper airways, the choice of turbulence model is essential. The minimum turbulent dispersion of particles due to the assumption of absence of the laryngeal jet, Inthanvong et al. [8] preferred LRN k-w model over other turbulence models. The use of the SST k-ω model [10] for the investigation of turbulent flow in realistic human airways provides better results than the k-ω model [11]. This is because of the possibility to use k-ω formulations in the proximity of the wall and k-ε formulations away from the wall [10]. For its good behaviour in adverse pressure gradients and flow separation, the SST k-ω model is advantageous than k-ω model. Although the computational cost is higher, for the accurate prediction of micron particle deposition under unsteady conditions, to solve eddies with large-scale energy and the ability to provide instantaneous velocity fluctuations, LES and DNS models can be used in the future to investigate the particle deposition under breath-hold conditions.

\[ m_p \frac{du_p}{dt} = F_D + m_p g + F_{BR} + F_a \]  (1)

where \( m_p \) signifies the particle mass, \( u_p \) is the velocity of the particle, \( F_D \) denotes drag force, \( F_{BR} \) represents force due to Brownian motion, \( g \) is the acceleration due to gravity and \( F_a \) are the additional forces to be considered. The influence of gravitational effect in particle deposition during breath hold is dominant for relatively larger particles (>1μm) [20]. Therefore, the force due to Brownian motion term in (1) is ignored. This term is only necessary for submicron and nano particles, where the diffusion behaviour predominates [10, 11]. For the sake of simplicity, additional forces like electrostatic, thermophoresis and terms depending on the density ratio like the forces due to buoyancy, pressure, Basset force, Saffman lift force, and virtual mass effect may be ignored [8, 18]. Eulerian approach is common when the concentration of particles is large and the mean diameter is small [19]. Therefore, the Eulerian approach is generally not used for the investigation of particle tracking in breath hold condition [18].

4.2.1 DPM and DEM Approach of Particle Tracking. DPM method is most suitable for monodispersed spherical particles and also when the volume percentage of the particle phase is very small [9]. Therefore, the one-way coupling is taken into consideration and the fluid forces only influence the trajectories of the particles in this method, while the particle phase does not affect the fluid phase [9].
While the CFD-DEM is a useful tool for the construction of irregularly shaped particles simulating strongly coupled gas-solid flow [21] and also when the non-spherical particles are injected along with the monodispersed spherical particles like that of the aerosol bolus study of Ostrovski et al [12]. In general, both the CFD-DPM and DEM methods are suitable for successfully simulating drug particle delivery and deposition in humans' respiratory tracts. However, the CFD-DPM method is mostly preferred in the studies investigated here due to the fact of consideration of the uniform size of drug particles for the sake of simplicity. As compared to the lower respiratory tract such as the alveolar zone, the upper respiratory tract wall movement during respiration is very slight. Therefore, it is recommended the usage of user-defined functions to simulate the movement of the airway walls and the deposition of particles in the alveolar regions during respiratory cycles [14].

4.3 Airway Models
Due to the exclusion of the effects of the oral region, larynx and further lower branches like alveolar regions, the airway models [7-12] was limited. Due to the injection of particles from the trachea rather than introduction from the mouth, as in actual physical scenarios, relative deposition fractions were measured as an alternative to the real amount of particles reaching the targeted sites. Therefore, it is necessary to consider the whole airway model rather than considering segmental models figure 1. Most of the investigations [7,9,12] use Weibel model because of the availability of dimensions, low computational cost and easiness in generating 3-D models. However, the estimation of particle deposition during breath holding in the Weibel model are far away from the actual prediction given by the realistic CT based models [22]. This is due the lack of curvature and asymmetry [22]. So, it always advisable to use the CT based models for getting accurate prediction of particle deposition [22]. However, using algorithms artificially generated models that resemble the realistic complicated human lung structures are available. One of the finest examples is the KG models of 3 D airway tree, 4D pulmonary acinus, 4D alveolar system, and 4D lung shape developed by Kitaoka et al. [23]. The simulation results are close to those of patient-specific airway models are clear from the analysis of Kim et al. [24] using KG models. The use of the KG model is suggested as a potential area of future study since this model is computer-efficient than CT based patient-specific airway models.

4.4 Drug Deposition by Sedimentation
Sedimentation due to gravity is the main mechanism behind the transport of drug particles during the breath-hold scenario. This is more prevalent in regions of small dimensions and low-velocity areas like smaller respiratory tracts and alveolar regions figure 4. Diffusion and sedimentation dominate for the transport of the small sized particles 0.1-1μm. For large size particles (1-10μm), impaction and sedimentation are the prominent mechanism of drug transport figure 3 [20]. The significant factors that have an effect on the amount of particle deposition due to sedimentation are particle size and residence time [18]. Sedimentation becomes more pronounced as the particle size increases. To express the significance of gravitational sedimentation in the deposition of the aerosol, a characteristic length known as the settling distance is used. Settling distance is represented by the equation

\[ s_t = \frac{V_t}{t} \]  

where \( t \) is the residence time, \( V_t \) is terminal velocity given by \( V_t = g \tau \), \( g \) signifies acceleration due to gravity and \( \tau \) denotes the relaxation time [18]. The aerosol deposition and drug retention within the targeted sites are also influenced by the inhalation rate. With the rise in inhalation rate, the particle residence time decreases, resulting in the reduction of the impact of sedimentation [18].
5. Conclusions
Computer simulation studies using CFD have been discussed here with a focus on the impact of breath holding on increasing particle deposition and reason behind the recommendation of this strategy after inhaling pharmaceutical aerosols in clinical trials. It is clear that progress in delivery of respiratory medicine through inhalation needs to be accompanied by breath hold manoeuvre. Breath holding has got many advantages like it increases the efficiency of particle deposition in targeted site especially in intra thoracic regions (lower bronchi, alveolar regions etc.), rises the dose carried to the targeted sites which in turn rises the drug efficacy, avoids undesirable accumulation of particle in the upper airway generations. As compared to non-breath-holding conditions, they provide uniform distribution of particles and masking of hot spots thus preventing undesirable deposition of particles around airway bifurcations. Based on the breath-hold studies investigated, it is seen that the particle tracking tools like the DEM and DPM approaches are suitable for multiphase flow prediction in the human airways. However, DPM approach is commonly preferred by the researchers for the particle tracking. Laminar flow model is mostly suitable for low Reynolds number, low inlet flow rate and for generations G3-G6. Even though, the SST k-ω model is advantageous than k-ω model and LRN k-ω based on the studies investigated in this review, LES and DNS models can be used in the future to investigate the particle deposition under breath-hold conditions. Even though medical professionals recommend a breath hold of 5-10s, a future direction is to find the optimum time for breath-hold, which increases the total drug deposition efficiency of the lungs. The use of the KG model is suggested as a potential area of future study since this model is computer-efficient than CT based patient-specific airway models and Weibel model.

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