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CFD simulation of porous microsphere particles in the airways of pulmonary fibrosis

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\begin{abstract}
Background and objective: Pulmonary fibrosis (PF) is a chronic progressive disease with an extremely high mortality rate and is a complication of COVID-19. Inhalable microspheres have been increasingly used in the treatment of lung diseases such as PF in recent years. Compared to the direct inhalation of drugs, a larger particle size is required to ensure the sustained release of microspheres. However, the clinical symptoms of PF may lead to the easier deposition of microspheres in the upper respiratory tract. Therefore, it is necessary to understand the effects of PF on the deposition of microspheres in the respiratory tract.

Methods: In this study, airway models with different degrees of PF in humans and mice were established, and the transport and deposition of microspheres in the airway were simulated using computational fluid dynamics.

Results: The simulation results showed that PF increases microsphere deposition in the upper respiratory tract and decreases bronchial deposition in both humans and mice. Porous microspheres with low density can ensure deposition in the lower respiratory tract and larger particle size. In healthy and PF humans, porous microspheres of 10 μm with densities of 700 and 400 kg/m\textsuperscript{3} were deposited most in the bronchi. Unlike in humans, microspheres larger than 4 μm are completely deposited in the upper respiratory tract of mice owing to their high inhalation velocity. For healthy and PF mice, microspheres of 6 μm with densities of and 100 kg/m\textsuperscript{3} are recommended.

Conclusions: The results showed that with the exacerbation of PF, it is more difficult for microsphere particles to deposit in the subsequent airway. In addition, there were significant differences in the deposition patterns among the different species. Therefore, it is necessary to process specific microspheres from different individuals. Our study can guide the processing of microspheres and achieve differentiated drug delivery in different subjects to maximize therapeutic effects.

\end{abstract}

1. Introduction

Pulmonary fibrosis (PF) is a chronic, progressive, and fibrotic interstitial lung disease that mostly occurs in middle-aged and elderly individuals and has a high mortality rate [1,2]. Further, PF is a complication of COVID-19 [3]. In patients with PF, the patient's normal alveolar tissue is damaged and replaced by scar tissue, thereby losing its original function. Traction bronchiectasis is one of the imaging manifestations of PF. Interstitial contraction can pull on the airway wall, causing the airway to dilate [4–6]. In addition, PF is characterized by a gradual decline in lung function, leading to breathing difficulties [7].

In recent years, inhalable microspheres have been increasingly used for the treatment of lung diseases [8,9]. Compared with traditional oral drugs and direct inhalation drugs, inhaled microspheres possess the following advantages: First, when the microspheres enter the body, the polymer slowly dissolves in the physiological environment, and the encapsulated drug diffuses in the body according to the degradation of the microspheres, releasing the drug slowly at a certain rate, maintaining a stable blood concen-
tration at the lesion site, realizing long-term sustained release, reducing the frequency of drug administration, and improving compliance [10,11]. Second, side effects such as liver damage can be reduced by avoiding first-pass effects [12]. These inhaled microspheres must be deposited in the lungs to realize their intended therapeutic effects. However, PF may make it difficult to transport microspheres into the lungs.

Computational fluid dynamics (CFD) has recently been widely used to study the transportation and deposition of inhaled particles in the respiratory tract [13,14]. CFD provides an effective method for studying respiratory tract deposition. It can easily change most of the related parameters, such as the airflow geometric characteristics, airflow characteristics, drug properties, and other conditions. It also can easily make competition results and provide details of different simulation. To realize the continuous release of drugs, microspheres need to avoid being engulfed by macrophages after deposition [15]. It has been shown that microspheres of diameter 1–6 μm are easily phagocytosed by macrophages [16]. These microspheres, which are swallowed by macrophages, are no longer able to release drugs and lose their original therapeutic effect. The phagocytosis rate of macrophages is highly correlated with the size of the microspheres. Microspheres of diameter 1 μm are most likely to be phagocytosed by macrophages, whereas those with a diameter greater than 10 μm are required to avoid phagocytosis by macrophages [17]. However, most of the current inhaled preparations have a particle size of 1–5 μm [18], which means that a large number of microspheres will be phagocytosed by macrophages, greatly limiting the efficacy of the microsphere inhalation. In contrast, the low mass density of porous microspheres contributes to deep lung deposition owing to their porous structure, thereby avoiding phagocytic clearance [19]. In addition, most airway models are based on healthy humans, and only a few studies have specifically established pathological airway models for studying particle deposition. Compared with healthy airways, a special airway structure or breathing pattern may lead to changes in deposition results. Farkas et al. studied the airway deposition of drugs in patients with chronic obstructive pulmonary disease (COPD), and the lung drug deposition scores of patients with severe COPD were nearly twice lower than those of healthy patients [20]. Choi et al. showed that severe asthma results in increased drug deposition in the upper lobes of the lungs [21]. Rajaraman et al. investigated the deposition of NaCl particles in the narrow airways of patients with asthma. The narrow airway structure in patients with asthma exacerbates the hygroscopic growth of NaCl particles, leading to an increase in particles deposited in the respiratory tract [22]. These studies suggest that lung disease can significantly affect the deposition patterns of inhaled particles. Therefore, it is necessary to establish a specific respiratory tract model for PF to study particle deposition. In addition, when testing new drugs, mice—the most common animal model—are employed as substitutes for humans. Currently, most research institutes use the human respiratory tract model, and there is a lack of studies on relevant laboratory animals. Therefore, we established a mouse PF airway model to study the deposition of microsphere particles in the mouse airway.

The purpose of this study was to investigate the deposition of microspheres of different densities and sizes in the respiratory tracts of humans and mice. Airway models of healthy, moderate, and severe PF in humans and mice were established. The transport and deposition of the ordinary and porous microspheres were calculated using CFD and Lagrange multiphase model simulations. The results of the simulation will guide drug processing of microspheres to achieve differentiated drug delivery for PF in humans and mice. Through the analysis of the simulation results, the microsphere density that is needed to ensure low deposition in the upper respiratory tract and avoid phagocytosis was obtained, so as to ensure the sustained release effect of microspheres.

2. Methods and materials

2.1. 3D airway model and mesh generation

First, the respiratory tract models of mice and humans were established. The nasal cavity and upper airway models of the mice were derived from CT images. The mice were anesthetized, and CT scans were performed. The CT data obtained were recorded in a Digital Imaging and Communication (DICOM) file. The 3D reconstruction of the images was obtained from micro-CT (PerkinElmer Quantum GX2, Japan, scan thickness 18 μm, scan voltage 70 kV, current 100 μA) scans using medical graphics processing (Materialise’s Interactive Medical Image Complete System (MIMICS), Belgium). The images were imported into a standard Tessellation Language (STL) file. The resulting STL file was then imported into Geomagic (Geomagic Studio, Geomagic, USA) to smooth the surface and interface. For the bronchial portion of the mouse airway, we developed a three-dimensional (3D) model of the upper bronchial tube, containing the main trachea to the third generation of the airway. The mouse bronchial airway model was developed based on the size of a typical mouse lung model reported by Oldham and Robinson [23]. Bronchiectasis, caused by interstitial contraction of the lungs, can occur in many forms. We do not consider “beaded” or “grape-like” bronchiectasis here, but consider the condition of uniform increase in bronchial diameter. As shown in Fig. 1(a), bronchiectasis with varying degrees of PF was characterized by an increase in the diameter of the second and third bronchi. In this study, we considered 20% and 40% increases in airway diameter to represent moderate and severe PF, respectively. The dimensions of the bronchial trees are listed in Table 1. The resulting upper airway and bronchial tree models were spliced and further smoothed in Geomagic.

The human airway model was divided into two parts, as shown in Fig. 1(b). The Mitsakou model was used to model the upper respiratory tract [24]. Mitsakou et al. developed a non-CFD-based model to calculate particle deposition in the oropharyngeal region. The model was a simplified geometric model consisting of the oral cavity, pharynx, and larynx. The Weibel model was adopted for the bronchial tree part [25]. Weibel et al. proposed an ideal airway model that approximates the airway as a symmetrical tree-shaped network composed of bronchial tubes of a reduced size. The Weibel airway model has been widely used owing to its simple structure. Similar to the mouse airway model, different degrees of bronchiectasis were characterized by increasing diameters of the second and third airways. It was then spliced and merged with Geomagic. The dimensions of the human airway model are listed in Table 1.

The airway model was then imported into ANSYS-Workbench. The mesh partition module was used to divide the geometry into unstructured tetrahedral grids. In order to generate a suitable grid, the grid independence verification is carried out to optimize the computation cost and time. The model was considered to be grid independent when the change in the total particle deposition result was less than 2%. After grid-independence studies, the final mouse grid contained 6.3 million elements, while the human model contained 5.2 million. After that, the generated grids were read using ANSYS FLUENT 15.0 for numerical simulation.

2.2. Governing equations of continuous phase and discrete phase

2.2.1. Continuous phase equation

Because of the complex geometry of human and mouse respiratory systems, it is necessary to select appropriate numerical meth-
Fig. 1. Airway models in mice and humans. (a) Mice airway model, consisting mainly of the upper respiratory tract (nasopharynx), main airway and bronchus. (b) Human airway model, mainly including upper respiratory tract (oral cavity, pharynx, larynx), main airway, bronchus. A, B, and C, respectively, represent bronchial models with different degrees of bronchiectasis.

| Generations (G) | Healthy mice | Moderate PF mice | Severe PF mice | Healthy human | Moderate PF human | Severe PF human |
|-----------------|--------------|------------------|----------------|---------------|------------------|-----------------|
|                 | L (mm) | D (mm) | L (mm) | D (mm) | L (mm) | D (mm) | L (mm) | D (mm) | L (mm) | D (mm) | L (mm) | D (mm) |
| 1               | 4.6    | 1.03   | 4.6    | 1.03   | 4.6    | 1.03   | 47.6   | 12.2   | 47.6   | 12.2   | 47.6   | 12.2   |
| 2               | 1.91   | 0.95   | 1.91   | 1.14   | 1.91   | 1.33   | 19     | 8.3    | 19     | 9.8    | 19     | 11.6   |
| 3               | 0.69   | 0.72   | 0.69   | 0.86   | 0.69   | 1      | 7.6    | 5.6    | 7.6    | 6.7    | 7.6    | 7.8    |

Table 1
Airway parameters of mice and humans with different degrees of PF, including L (length) and D (Diameter).
ods to simulate the airflow structure. The airflow of human and mouse respiratory tracts is in transition between laminar flow and turbulent flow; thus, the low Reynolds number (LRN) K–ω model is adopted [26]. Compared with the standard K–ω model, the definition of turbulent viscosity is modified in the LRN method to suppress the turbulent eddy viscosity at sufficiently low Reynolds numbers. Therefore, the LRN K–ω model is more suitable for the current problem [27]. The governing equations include the mass conservation equation and momentum conservation equation, and two transport equations of turbulent kinetic energy (K) and specific dissipation rate (ω).

Continuity equation:

$$\frac{\partial \rho}{\partial t} + \frac{\partial (\rho u_i)}{\partial x_i} = 0$$  

Momentum equation:

$$\rho \frac{\partial u_i}{\partial t} + \rho u_j \frac{\partial u_i}{\partial x_j} = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j} \left[ \mu \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) \right]$$  

Turbulent kinetic energy (K) equation:

$$\rho \frac{\partial K}{\partial t} + \rho u_i \frac{\partial K}{\partial x_i} = -\frac{\partial}{\partial x_j} \left[ \mu \frac{\partial K}{\partial x_j} \right] + \tau_{ij} \frac{\partial^2 K}{\partial x_i \partial x_j} - \rho \beta f_p \omega K$$  

Specific dissipation rate (ω) equation:

$$\rho \frac{\partial \omega}{\partial t} + \rho u_i \frac{\partial \omega}{\partial x_i} = -\frac{\partial}{\partial x_j} \left[ \frac{\omega}{K} \frac{\partial K}{\partial x_j} \right] + \alpha \omega \frac{\partial \omega}{\partial x_j} \frac{\partial^2 \omega}{\partial x_j^2}$$  

In the above equation, ρ, p, u, µ, µt, and τij are the time average velocity, time average pressure, fluid density, dynamic viscosity, turbulent viscosity, and shear stress tensor, respectively.

2.2.2. Discrete phase equation

The Lagrange method was used to model the transport of microspheres and simulate their deposition. The trajectory of a particle was calculated using the equilibrium equation of the force acting on it. The force balance equation can generally be written as

$$\frac{d u_p^i}{d t} = F_D (u_p^i - u_i^p) + \frac{g (\rho_p - \rho)}{\rho_p} + S_i$$  

where F_D represents drag force per unit particle mass and is defined as

$$F_D = \frac{18 \mu_L C_D \rho}{24}$$  

where C_D is the drag coefficient, which can be obtained using the following equation:

$$C_D = a_1 + a_2 \frac{Re}{Re} + a_3 \frac{Re}{Re}$$  

where a_i is a constant for the smooth spherical particles. In addition, the Reynolds number is derived from the following equation:

$$Re = \frac{\beta d_p |u_p^i - u_i^p|}{\mu}$$  

In the above equation, the properties of air and particles, such as air velocity, particle velocity, air molecular viscosity, air density, particle density, and particle diameter, are expressed by u_i^p, u_p^i, µ, ρ_k, ρ_p, and d_p respectively. In Eq. (4), S_i represents an extra force, such as the Saffman’s lift force, thermophoretic force, Brownian motion, and virtual mass force. Among them, the Brownian motion and Saffman’s lift force should only be considered for nanoparticles. Thermophoretic force is caused by the unequal moment exchange between the particles and the fluid due to temperature gradient. The influence of temperature on deposition was not considered in this study, so the thermophoresis force was ignored. The virtual mass force is considered only when the fluid density is greater than the particle density, so we ignore the virtual mass force [28,29].

Deposition fraction (DF) is a parameter used to determine the fraction of total inhaled particles deposited in a particular region of the model and can be calculated as follows:

$$DF = \frac{\text{mass of deposited microsphere particles in region}}{\text{total mass of inhaled microsphere particles}}$$  

2.3. Boundary conditions and numerical methods

The flow phases under steady-state, incompressible, and Newtonian conditions were considered in the simulation, and a mass flow inlet was used as the inlet boundary condition. Despite the transient nature of the respiration process and subsequent particle transport, it has been demonstrated that the flow field under steady-state conditions agrees well with the transient flow field, except during the deceleration and flow reversal phases [30]. Therefore, a steady-state hypothesis is used in the simulation. Patients with PF may experience dyspnea due to a decline in lung function. Studies have shown that such dyspnea causes a significant increase in the tidal volume of patients, while there is no significant difference in the time of inhalation and exhalation [7]. As shown in Table 2, different inhalation flow rates were used to characterize the degree of PF. Inhalation flow rates in humans were measured after subjects were at full rest [7], and in mice were measured using unrestrained whole-body plethysmography [31]. Moderate and severe PF were considered in this study to cause tidal volume increases of 25% and 50%, respectively. The airway wall was set as a rigid body without slipping, and the velocity on the wall was set to zero. The outlet type was a pressure outlet, and the pressure was set to 0.

To obtain the exact solution, all transport equations were discretized using the second-order upwind scheme. The SIMPLE algorithm was chosen to solve the steady-state control equation of the pressure–velocity coupling. When the residual value of the steady-state flow equation reaches 10^{-6}, the solution is considered to converge and the iterative process stops. However, in most cases, the residuals tend to be stable at 10^{-5} or 10^{-4} and the solutions are considered to converge.

After the steady-state flow equation converged, the fluid-particle flow was analyzed using discrete phase modeling (DPM). Because the particle flow is very thin compared with the continuous phase, the interaction between particles is not considered, and unidirectional coupling between air and the particle flow field is observed. A series of particles with different sizes and densities were defined to represent porous microspheres of different sizes and porosities. The particle size of microspheres ranges from 1 μm to 15 μm. Microspheres smaller than 1 μm are easy to be exhaled due to lack of strong deposition mechanism, while microspheres larger than 15 μm may be deposited in the upper respiratory tract due to large particle size. In addition, microspheres larger than 10 μm are hardly phagocytosed by macrophages. The density of porous microspheres ranges from 1200 kg/m^3 to 50 kg/m^3. The microspheres with different porosity can be formed by adding different porogen [32]. The airway wall and exit were set as capture and escape conditions, respectively. Because of the presence of mucous membranes in the airway, any particle collision with the airway wall is captured by the airway wall, leading to deposition, and the particles do not rebound.
Table 2
Respiratory patterns of mice and humans with different degrees of PF.

| Species | Condition | Mice | Human |
|---------|-----------|------|-------|
|         | Healthy   | Moderate PF | Severe PF | Healthy | Moderate PF | Severe PF |
| Mass flowrate (L/min) | 0.073 | 0.096 | 0.117 | 23.6 | 32.4 | 37.6 |
| Tidal volume (ml) | 0.11 | 0.137 | 0.166 | 630 | 810 | 940 |
| Inspiration time (s) | 0.09 | 0.085 | 0.085 | 1.6 | 1.5 | 1.5 |

Fig. 2. Deposition fraction of microsphere particles in respiratory tract of human with different degrees of PF. (a) upper respiratory tract, (b) main airway and G1 bronchus, (c) G2 and G3 bronchus.

3. Results

3.1. Deposition of microspheres in human airways

3.1.1. Effects of PF on human airway deposition

Fig. 2 shows the deposition fraction of microsphere particles of different sizes in human airways with different degrees of PF. The deposition of microspheres of the same size in the upper respiratory tract significantly increased owing to PF. For healthy humans, microspheres larger than 15 μm are all deposited in the upper respiratory tract, resulting in zero deposition in the bronchus. In patients with PF, drugs with microspheres larger than 11 μm are almost entirely deposited in the upper respiratory tract. This is because of an increase in the tidal volume and airflow velocity in the upper respiratory tract. As shown in Fig. 3, the increase in tidal volume caused a significant increase in the flow rate of the upper...
respiratory tract, most notably in the larynx. The increase in tidal volume resulted in a nearly 60% increase in the throat velocity.

For the main airway and G1 bronchus without bronchodilation, when the particle size of the microspheres was less than 7 μm, the increase in tidal volume promoted the deposition of microspheres, resulting in more particles being deposited in the bronchus. However, when the particle size of the microspheres was larger than 7 μm, the number of microspheres deposited in the main airway and G1 bronchus was reduced because of the deposition of a large number of microspheres in the upper respiratory tract.

Finally, for the G2-G3 bronchial region with bronchiectasis, an increase in airway diameter led to a decrease in the deposition of microsphere particles of all sizes, and this trend became more obvious with an increase in microsphere size. For microsphere particles of 1 μm, the deposition fraction of healthy humans and severe PF humans was 8.18% and 5.3%, respectively, which is a reduction of 35%. For microsphere particles of 10 μm, the deposition fraction reduced from 5.21% to 1.34%, which is a reduction of 74%. This is because bronchiectasis slows the flow of air, making it more difficult for the particles to settle on the bronchial wall. Fig. 3 shows the flow field in the human bronchi with different degrees of PF. In humans with PF, bronchiectasis reduces the local flow velocity at dilution, while tidal volume increases the flow velocity in non-dilated airways. For the microsphere particles with small particle sizes, increasing tidal volume did not cause too many microsphere particles to deposit in the upper respiratory tract, but was conducive to their deposition on the dilated bronchial wall. However, with the increase in microsphere size, the increase in tidal volume leads to excessive microsphere particle deposition in the upper respiratory tract, reducing bronchial wall deposition.

3.1.2. Deposition of porous microspheres in human airways

Microspheres must be larger than 10 μm to ensure that they are not engulfed by macrophages. However, it is difficult for ordinary microsphere particles larger than 10 μm to cross the upper respiratory tract and deposit in the subsequent airway. Therefore, we simulated porous microspheres of different densities with the expectation that by using porous microspheres, the microspheres could pass through the upper respiratory tract and have sufficiently large particle sizes. As shown in Fig. 4, the use of porous microspheres significantly increased the fraction of microspheres deposited in the upper respiratory tract. In healthy humans, microsphere deposition in the entire bronchial region reaches its maximum when the density reaches 700 kg/m³. Humans with PF may need low-density microspheres because of their increased tidal volume. For humans with moderate and severe PF, porous microsphere particle densities as low as 500 and 400 kg/m³ are required. Subsequently, with a further decrease in the microsphere density, the deposition fraction decreases. This is because of the lower density of porous microspheres being subjected to weaker inertial impact. When the main reason for the reduction in bronchial deposition is no longer the high deposition in the upper respiratory tract, the weaker inertial impact will reduce the probability of microsphere trapping on the bronchial wall.

3.2. Deposition of microspheres in mice airways

3.2.1. Effect of PF on airway deposition in mice

As a common experimental animal, mice are widely used in drug development. The safe and efficient delivery of microspheres into the airways of mice is of great significance for drug development. Therefore, we simulated microsphere particles in the airways of mice.

The deposition pattern in mice is quite different from that in humans. The high velocity combined with the small airway geometry in the mouse model produces highly sensitive behavior for incremental changes in the particle size. Fig. 5 shows the deposition fraction in the mice with different degrees of PF. For healthy
mice, the deposition fraction of microspheres smaller than 1 μm in the nasopharyngeal airway was only approximately 14.29%; however, when the particle size increased from 1 to 4 μm, the deposition fraction of the nasopharyngeal airway rapidly increased from 14.29% to 94.07%. This phenomenon is also enhanced by an increase in tidal volume, resulting in a greater tendency for inhaled microsphere particles to be deposited in the nasopharyngeal airway. For mice with moderate and severe PF, the deposition fraction of microspheres of 1 μm in the nasopharyngeal airway was 15.59% and 17.96%, respectively, while that of microspheres of 4 μm was in

Fig. 4. Deposition fraction of 10 μm microspheres with different densities in the (a) upper respiratory tract region and (b) bronchial region.
the nasopharyngeal airway. Fig. 6 shows the flow field of the airway in mice; for healthy mice, the maximum laryngeal flow rate can reach 14 m/s, which is much higher than that in humans.

Similar to human airways, bronchiectasis in mice also causes a decrease in the flow rate. For microsphere particles of 1 μm, the bronchial deposition fraction was 2.01% in healthy mice and 1.34% in mice with PF. However, unlike the human airway deposition pattern, with an increase in particle size, the deposition fraction of the mouse bronchi rapidly decreases to 0 owing to the high respiratory velocity of the mice. When the microspheres were administered to mice, the particle size of the microspheres was required to be less than 3 μm to ensure that they entered the subsequent airway. However, smaller microspheres indicate a higher phagocytic rate, and microspheres of 1–3 μm are most likely to be phagocytic, which will greatly reduce the sustained release effect of microspheres.

3.2.2. Deposition of porous microspheres in mice airways

Similarly, we simulated the deposition of porous microspheres in mouse airways. Due to the high inhalation flow rate of mice, a lower density of porous microspheres is required when administering drugs to mice compared to that in humans. Fig. 7 shows the deposition fraction of porous microspheres with different densities in the mouse airway. For microsphere particles of 10 μm, the density of microspheres should be less than 200 kg/m³ to ensure that the particles can pass through the nasopharyngeal airway, and a density of porous microsphere particles as low as 75 kg/m³ is required to reach the maximum deposition fraction. Mice with PF required lower microsphere density. Porous microspheres with a density of 75 kg/m³ may be difficult to process because of their low density. Therefore, we simulated the deposition of porous microspheres with a diameter of 6 μm. For the porous microspheres of 6 μm, the microsphere density only needed to be less than 600 kg/m³ to allow microspheres to cross the nasopharyngeal airway, while the deposition fraction of microspheres in the bronchus of healthy mice reached its maximum at a density of 200 kg/m³. For mice with moderate and severe PF, the density of the porous microspheres should be 150 kg/m³ and 100 kg/m³ to achieve the maximum bronchial deposition fraction.

4. Discussion

In this study, we established airway models of humans and mice with different degrees of PF, and simulated the deposition of porous microspheres with different densities in different airway models. Our study has two main objectives. The first was to quantify the effects of PF on airway deposition in mice and humans to achieve differentiated drug administration for individuals with PF and improve drug delivery. Second, the relationship between microsphere size, microsphere density, and bronchial particle size was explored by studying the deposition of porous microspheres of different densities. By using porous microspheres with lower density, the particle size should be as large as possible on the premise of lower deposition of the upper respiratory tract to avoid the microsphere particles being swallowed by macrophages and ensure the continuous release of microspheres.

Several studies have examined airway deposits in patients with asthma and obstructive lung disease [20–22]. However, the main symptom of these diseases is narrowing of the airway diameter, which differs from PF. PF has two main symptoms. First, tidal volume increases in patients with PF due to loss of lung function. Normal alveolar tissue is damaged and replaced by scar tissue, which loses its original function. In order to get enough oxygen, the patient has to breathe harder to compensate for the lost lung function, resulting in an increase in tidal volume. Second, the presence of scar tissue will cause interstitial contraction of the lung, which can pull the airway wall laterally, leading to traction bronchiectasis. In both humans and mice, PF resulted in more deposition in the upper respiratory tract and less bronchial deposition. This is because an increase in tidal volume increases the flow rate of the upper airway, whereas bronchiectasis decreases the flow rate of the bronchi. For micron-sized particles, inertial impact is the main mechanism of tracheobronchial deposition. High tide volume and bronchiectasis enhance the inertial impact of the upper respiratory tract and weaken the inertial impact of the bronchi, making it easier for microsphere particles to deposit in the upper respiratory tract and more difficult to deposit in the bronchus. The deposition in the upper respiratory tract can be reduced by reducing the particle size of the microspheres. However, the particle size of the microspheres must be larger than 10 μm to avoid being engulfed by
macrophages; further, the smaller the particle size, the easier it is to be captured by macrophages, which greatly reduces the therapeutic effect.

Previous studies on the deposition of inhaled particles in the respiratory tract have mostly involved the direct inhalation of drug particles [29,33,34]. These drugs do not require slow release as microspheres do, so there is no size requirement. The porous structure of the porous microspheres enables them to have a lower density, which can ensure that the microspheres have a larger size and lower mass. According to our simulation results, for healthy humans, porous microspheres with a density of 700 kg/m$^3$ can ensure high lung deposition of microspheres of 10 μm, whereas for humans with severe PF, the density of porous microspheres needs to be reduced to 400 kg/m$^3$.

Mice normally breathe through their nose, which means they cannot inhale microsphere particles through their mouths as humans do. The complex geometry of the mouse nasal cavity greatly increases the possibility of microsphere deposition in the nasal cavity. In addition, the high metabolic rate of mice leads to a high respiratory rate, which results in the deposition of microspheres larger than 4 μm in the nasopharyngeal airway. This is consistent with previous CFD simulation results of inhalation of particles in mice. In simulations by Kolanjiyil et al., particles larger than 5 μm could not enter the subsequent airways of the mouse [35]. In Yidan Shang’s simulation, particles larger than 3 μm were deposited in the nasopharyngeal airway [36]. The reason for this difference is the different methods of inhaling particles used in the two studies. In addition, our simulation results are consistent with those of previous animal experiments. Kuehl et al. and Oldham et al. studied the relationship between inhaled particle deposition and particle size in B6C3F1 mice and BALB/C mice, respectively, through animal experiments, and both studies showed that the lung deposition of 5 μm particles in mice was almost zero [37,38].

Therefore, a lower density of porous microspheres is required for administration to mice. If porous microspheres with a diameter of 10 μm are used, the density of porous microspheres should be less than 75 kg/m$^3$. Considering the processing of microspheres, we recommend the use of porous microspheres with a diameter of 6 μm and density of 200 kg/m$^3$ for administration to mice. For mice with PF, the density was reduced to 100 kg/m$^3$. These results can be used to guide the processing of microspheres and achieve differentiated drug delivery for different individuals.

In this study, CFD simulation was used to study the deposition of microspheres in the respiratory tract. However, there are still limitations in this study. Firstly, we assume that the airway model is an immovable rigid body, but in fact, the airway will deform during respiration. Secondly, the description of porous microspheres in this paper is achieved only by reducing the density of the microspheres, and the effect of the porous structure of porous particles on the transport and deposition of the microspheres is ignored. Finally, our simulation results still need more experimental analysis. The airway model can be manufactured by 3D printing for subsequent in vitro experiments. In addition, animal experiments can be performed to verify the simulation results by injecting microspheres to mice.

5. Conclusion

This study simulated the deposition of microsphere particles in the airways of humans and mice with different degrees of PF. To simulate the deposition of porous microspheres with different densities, we established airway models of human and mouse fibrosis at different degrees. The following conclusions can be drawn from the analysis of the simulation results:

(1) PF has a significant influence on microsphere deposition in both mice and humans. The high tide volume and bronchiectasis caused by PF make it easier for the inhaled microsphere particles to deposit in the upper respiratory tract rather than in the bronchus. This greatly reduces the chance of microsphere particles becoming lodged in the lungs.

(2) There is a significant difference between the deposition patterns of mice and humans. Microspheres larger than 15 μm
have difficulty crossing the human upper respiratory tract. Owing to the high flow rate of inhalation in mice, all particles larger than 4 μm would be deposited in the upper respiratory tract. Therefore, for mice, microspheres with smaller particle sizes and lower particle densities should be used to ensure subsequent airway deposition.

(3) Porous microspheres can significantly improve the bronchial deposition of larger microspheres. Our results suggest that porous microspheres of 10 μm with densities of 700 and 400 kg/m³ are recommended when administering drug to healthy and PF humans. For healthy and PF mice, porous microspheres of 6 μm with densities of 200 and 100 kg/m³ are recommended.

The effect of the clinical symptoms of pulmonary fibrosis on the deposition of inhaled microspheres can be guided by CFD analysis. Through CFD simulation, we targeted to study the deposition of microspheres in diseased airways with pulmonary fibrosis. What’s more, we studied deposition in mouse airways, which has important implications for drug delivery experiments in animals. Through analysis of the simulation results, the size and density of the customized microspheres were designed for patients with pulmonary fibrosis. These studies could help us treat pulmonary fibrosis and fight against the COVID-19 pandemic. Our study fills the gap in the study of pulmonary deposition in individuals with pulmonary fibrosis and laboratory animals, and inspires us to use CFD to study the effects of other diseases on respiratory deposition.

Declarations

This study does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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