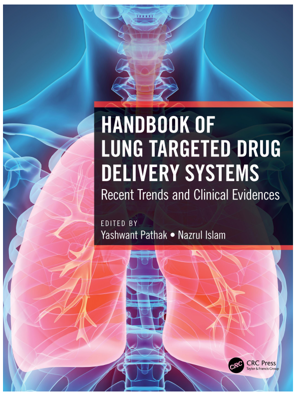

Handbook of Lung Targeted Drug Delivery Systems
Recent Trends and Clinical Evidences

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Modeling for Biopharmaceutical Performance in Lung Drug Discovery

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Modeling for Biopharmaceutical Performance in Lung Drug Discovery

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41.1 Introduction

With the rise in pharmaceutical medicine production, the pulmonary system is starting to be the route of choice for distributing a range of drugs throughout the body. Benefits of lung drug delivery includes a faster onset, avoidance of degradation in the GI tract, more convenience, less intrusiveness, and relative comfort. In the past, use of inhaled biopharmaceuticals was inhibited by high costs, drug requirements, and stability problems; however, technological advances are actively addressing these problems.

Currently, there are more than 40 different types of inhaled pharmaceuticals in the public domain that are used to combat many diseases: asthma, diabetes, cystic fibrosis, cancer, hypertension, influenza, sarcoma, osteoporosis, growth deficiency, tuberculosis, hepatitis, etc. Overall, inhaled biopharmaceuticals are on a rising trajectory and are expected to become more common as time passes.

41.2 Applications of Modeling and Simulation of Biopharmaceutical Performance Drug Delivery

Modeling and simulation play an essential role in drug discovery. It allows researchers to test drug effects and gather information without using human subjects. In lung drug discovery, modeling and simulation play important roles as the lungs are one of the most complex organs in the body. Researchers can use several different methods, such as cellular and molecular models, to conduct rigorous testing of medications.

41.2.1 Modeling for Lung Studies or Lung Treatment

Lung diseases are unique because of the types of environments that vastly affect them. For many years, drugs have been administered through inhalation and nebulization to reach the lungs; using lung models and simulations allows researchers to mirror the effects of these drugs in the lungs. Breathing patterns, disease progression, and genetics all play a role in how medicine reacts in the body. Recently lung modeling has progressed to allow scientists to "accurately reflect the interactions between cells or within tissue interfaces in the macroenvironment of the lung" (1). By using modeling and simulation, drug developers can predict drug effectiveness. It also helps to know how a drug will interact with the lungs when delivered as different delivery systems or dosage forms.

Using models and simulations could also contribute to the decline of animal testing. In 2015 the Wyss Institute at Harvard created the Lung on a Chip. These micro devices that "reconstitute tissue–tissue interfaces critical to organ function may, therefore, expand the capabilities of cell culture models and provide low-cost alternatives to animal and clinical studies…" (2–4). The lung on a chip mimics the air and blood flow; these chips have inspired researchers to develop chips for other organs such as the heart, kidney, and skin, as well. With the creation of these micro devices, researchers are able to accurately test the effects of drugs without testing on animals.

41.2.2 Cellular Models to Study Lung Treatment

Cellular models can imitate healthy and unhealthy tissues in the body. Scientists have developed a new lung model by using embryonic stem cells to discover drugs that will aid with small cell lung cancer research and treatment (5–8). Researchers can use computational fluid dynamic simulations to mimic the structure of the lungs. Computational fluid dynamic simulations are made by using "3D lung airway models that were reconstructed from CT [computed tomography] scans" (9). These models are accurate when studying certain diseases because they can be modeled after the CT scans of patients with the desired disease. The models and simulations based on CT scans work well to understand the complexities in lifelong diseases such as asthma and chronic obstructive pulmonary disease (COPD).

Stem cells have the ability to become any cell in the body, which aids in the process of cellular modeling. "These cells can be expanded and differentiated to produce a potentially limitless supply of the affected cell type, which can then be used as a tool to improve understanding of disease mechanisms and test therapeutic interventions" (10–12). With the ability to become any type of cell and be replicated endlessly, researchers can

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explore the effects of drugs with the diseased cells. Researchers are then able to reproduce the results that they find through computational methods.

41.2.3 Molecular Models for Lung Studies

Molecular modeling and simulation allow researchers to replicate and understand the interactions between molecules with the use of physics. Scientists are able to examine the structures of the molecules and see how they react to the delivery of medications. "Molecular dynamics (MD) is an important computational tool for understanding the physical basis of the structure, the dynamic evolution of the system, and the function of biological macromolecules" (13). MD simulations show meticulously replicated membrane proteins and let researchers see how the proteins work together when introduced to medications.

41.3 The Benefits of Modeling and Simulation

Modeling and simulations of the lungs are a crucial way for scientists to understand the physiology of the organ. By studying simulations, it is possible to understand the effects of certain drugs on the organ.

41.3.1 In Vitro Models for Lung Studies

In vitro models are important in the study of lung drug delivery because of the advantage that exists where the cells are completely isolated from the body's environment. This allows for a more controllable model to test with. They have been a popular model to understand lung cell biology and have given scientists a way to study these tissues for patients.

With past studies of the lungs, it has been seen that much of the information we know about human lungs has been inferred from studies performed on rodents. Although humans and rodents have most of the same cells, differences still exist in the lungs. Human lungs contain basal cells that are located in the trachea and the bronchi, while rodents only have basal cells in the trachea (14). The major differences in both organisms have definitely shone a light on the need for human lung models.

The benefits with in vitro models are that scientists have been able to understand the way that human lungs maintain homeostasis and how the lack of some cellular processes can have detrimental effects on the organ. Using models has also allowed the study of regions in the lungs that are normally too hard to study, such as the alveoli. It has allowed for the discovery of certain therapeutic targets, given scientists a way to test pharmaceutical drugs, and assisted in clinical trials (14). Current models allow for a more controlled cellular environment, which can be compared to studying lung cells in real time.

41.3.2 In Vivo Models for Lung Performance

In vivo models have allowed scientists to see the effects of drugs on lung cells directly in humans. These models are important because studying the cells while they are still in the organism will allow scientists to see the response of the body as a whole.

As mentioned before, many studies done in the lungs have been performed on rodents, which had in vivo environments of the human body (15). This supports the idea again that there is a need for human lung models. While some experiments are successful as in vitro, using the in vivo method allows scientists to create appropriate conclusions about lung cells. A human body environment will allow the lung cells to create real time effects that can be learned from to improve drugs.

Even from these studies, scientists have learned how human lung stem cells divide and renew themselves. This is just one of the benefits of in vivo models. By using these models, scientists have also been able to see remodeling of the extracellular matrix of mouse lungs, which takes part in the development of the lungs. Although not much is known about the lungs due to the lack of human lung models, using rodents as test subjects has given scientists information on which to base their predictions for the effects on humans (14,16,17).

41.3.3 Biopharmaceutical Simulations

Simulations of the lungs assist in designing and developing drug products. Creating simulations has given scientists an easier way to visualize how drugs will affect the environment of the lungs, thus, it has given insight into the best way to deliver drugs into the organ.

Simulations are a very popular method in which it is possible to show a visual of the lungs which has helped in the advancement of insulin delivery, cancer treatments, and nano therapeutics. The ability for scientists to view the effects of drugs on lung cells has created more efficient drug–aerosol drug delivery. This has been crucial for the condition of asthma. By using simulations, inhalers have advanced in targeted delivery methodologies. The medicine moves to the specific sites and has been created to treat those affected sites (18,19).

41.4 Future Usage

Below is a quick outline of future usages of this method, its models, and the challenges that scientists are currently facing.

41.4.1 Lung Cancer Models

Lung cancer is a disease that leads to 30% of all cancer deaths according to research by Min-chul Kwon and Anton Berns (19). This disease is most common with smokers, but also seen in nonsmokers. Annotation of the cancer genes has revealed many common mutations. The advancements of targeted therapy provide scientists with a spark of hope that one day personalized therapy will be used to combat this fatal disease.

On the topic of combating lung cancer, two main models are used to assess the effectiveness of biopharmaceuticals: computerized and mouse models. Computer modeling, or computer process modeling, was first done to diagnose lung cancer and staging the different stages. These models begin with analytical properties that include the Markov chain model and formulas.

The computerized models have both positives and negatives. Currently, computerized models are very time consuming to generate and heavily rely on the environmental factors that are preprogrammed (which does not account for every real-world factor). However, it can provide detailed analysis, graphics, and animations. These models are used to estimate the treatment time for patients and predict the virtual outcome of a drug, before animal testing.

Animal models are very useful in many new drug discovery. The main model for lung drug discovery is with a mouse. Using the mouse as a model is great because they are cost-effective and mimic many similar qualities that human's exhibit. Since the mouse and humans share similar characteristics, this method is useful for studying the response to drug therapy.

41.4.2 Lung Modeling Methods

With limitations in treatments that are controversial in the scientific field, targeted drug delivery methods are gaining popularity. Having drugs that can be delivered through the pulmonary system enables delivery directly to the lung, for both local and system-wide treatments. This is the method that allows for optimization in the number of drugs that the body absorbs. The low efficiency of many drugs in the market is raising a need for a multidisciplinary approach (20,21) which includes many interdisciplinary sciences: polymer science, pharmaceutical technology, biochemistry, and molecular biology. This approach to finding treatments is already in the making. Many drugs have not yet been made for delivery through the lungs but the possibilities include growth hormones and even insulin.

There are two main routes for drugs to be distributed to the body by the lungs — the conducting airways and respiratory region. However, the use of transport through the (upper) airways is limited based on the surface area and the ability of the body to filter out 90% of drug particles. Secondly, the mucus layer that forces the drug out of the body also limits this method of delivery. The current, most common way for similar treatments is through the use of aerosols/inhalation, which provides the best distribution.

Even when working with efficient methods of distribution, there are many techniques to create different sized particles: jet milling, spray drying, spray-freeze drying, supercritical fluid technology, solvent precipitation, solvent evaporation, and particle replication. The first method of creating these nanoparticles is by specially jet milling a drug under nitrogen gas. Spray drying and spray freezing (discovered around 1980) are similar techniques that involve a solution at room temperature being atomized and dried. The freeze-drying method is a restricted and expensive process that adds an extra step by spraying the drug through liquid nitrogen, this improves the performance of the drug and creates close to a 100% yield. When a drug involves proteins and peptides, scientists use the supercritical fluid technology to create controlled sizes of particles by suspending the solution in carbon dioxide. Lastly, Dr. Joseph DeSimone and his team created particle replication (PRINT). The method allows for making uniform-sized, organic microparticles. Being able to control the particle sizes of various solutions will enable a more efficient drug targeting.

41.4.3 Growing Trend

As of 2018, the inhalable drug market, which has a span of five continents, was estimated to be worth about US$25 billion dollars. Due to their convenience, non-invasiveness, efficiency, and minimal toxicities, a projection from Grandview Research predicted a steady increase in market growth (of aerosols, dry powder formulations, and sprays) until 2026, in which the market will almost double in size. The projection also indicated that dry powder formulation is the most popular choice out of the three substances. Now there are more than 220 projects and companies are focusing on developing inhalable drugs and enhanced versions of already existing molecules.

As the discovery of new drugs continues, there are many challenges that must be overcome, such as complying with governmental standards, developing the appropriate physical structures, and developing suitable models. When testing a drug, it is impossible to predict the outcome with so many variables existing; therefore, scientists usually start by using animals to create models to slowly gain an understanding of how a drug reacts. This method is useful, but cannot be fully used to predict the reaction when it is given to humans.

41.5 Conclusion

The lung is a very complex organ and relies heavily on the organs that surround it. Knowing this, it can be hard to research and test the lung in a way that will only affect the lung cells themselves. There have been various ways to model and create simulations of the lungs to test different drugs' effects on the cells. The results of these experiments have helped improve target drug delivery. Scientists have been able to create drugs that treat specific sites in the lungs for conditions such as asthma, diabetes, cystic fibrosis, cancer, etc.

However, although lung drug delivery research has improved with the use of models and simulations, there is still an information gap in that models and simulations cannot directly show the effects on the cells that scientists are less familiar with. For example, some models have yet to be performed on humans, which limits our knowledge of some diseases. Thus, scientists are left to predict outcomes of drug delivery, rather than having the results of an experiment on human lung cells.

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