Lung delivery represents a fascinating option to limit ubiquitous distribution of systemically, and often chronically, administered drugs used to treat severe pulmonary diseases. Nonetheless, clinical outcomes of inhaled therapies strongly depend on drug ability to deposit along the airways and to overcome barriers imposed by the lungs. In this context, the general aim of our studies is the development of inhalable nanomedicines able to deliver the intact drug in the lungs and to shield its interactions with lung lining fluids while enhancing drug availability at the cell target. This objective has been pursued through the design and production of differently engineered nanoparticulate systems with increasing levels of complexity, driven by technological and biological design rules. Some examples, such as drug nanocrystals, micelles and biodegradable poly(lactide-co-glycolide) (PLGA) nanoparticles, will be discussed highlighting how the most appropriate formulation approach can be selected only taking into account the distinct physico-chemical profile of the drug under investigation (e.g., molecular weight, solubility, stability) and the peculiarities of the lung pathology (e.g., cystic fibrosis, lung cancer). Surface engineering of nanocarriers with either polymers or phospholipids turns out as crucial to face the current challenge of overcoming lung barriers, especially mucus. Last but not least, in vitro/in vivo studies represent a critical step to select the best formulation to candidate for further development.

Inhalation therapy has a long and rich history in the treatment of different respiratory diseases using various natural inhalation remedies such as leaves from plants, vapors from aromatic plants, balsams, and myrrh. Demand for developing tailor-made inhalable drug formulations increased, which, coupled with advances in biology and engineering, have lead to a more optimized therapeutic efficiency. The pulmonary route of administration has gained a great deal of attention since the early 1990s as an alternative to the parenteral route. At the beginning of 19th century, liquid nebulizers had been developed and used as a legitimate inhalable pharmaceutical therapy. Examples of nebulizer drugs that had been developed and investigated at this time were adrenaline, porcine insulin, penicillin and steroids.

The invention of liquid nebulizers paved the way for the development of various types of inhaler devices. In 1956, the pressured metered dose inhaler (pMDI) was introduced and became the main therapy for asthma. Despite advances in drug formulation technology, the majority of the inhalable aerosol therapeutics suffer from limitations such as short half-life, and low bioavailability, resulting in the necessity of increasingly frequent dosing. Consequently, there was an urgent need for an effective inhalation therapy which could overcome these limitations and provide sustained therapeutic effect. To formulate an effective inhalation therapy, the anatomy of the respiratory system, lung deposition
mechanisms and lung defense mechanisms should be fully understood.

The respiratory system is divided into two main parts (Figure 1): the upper respiratory tract consisting of nose, nasal cavity and pharynx and the lower respiratory tract consisting of larynx, trachea, bronchi, alveoli, and lungs. Lungs are responsible for gas exchange throughout the body. Healthy lungs inhale about 1 pint of air about 12-15 times every minute. The lungs are composed of five lobes; right lung contains three lobes, while the left lung contains two lobes. The interior of the lung is comprised of bronchi, alveoli, blood vessels and lymph nodes. The bronchi are divided into bronchioles which branch in the lung, forming passageways for air, and terminate with the alveoli, which is responsible for gas exchange. There are over 300 million alveoli in the lung, and each alveolus is lined with pulmonary capillaries forming a huge network comprising over 280 billion capillaries, which provide a huge surface area of about 70 m² available as a blood gas barrier. The alveolar gas exchange mainly occurred at the interface consisting of alveolar epithelium, endothelium and interstitial cell layers, where the distance between the capillaries and alveolar is very small, about 0.5 μm, and thus facilitating gas exchange via diffusion.

Pulmonary clearance mechanisms

The primary function of the respiratory defense mechanism is to prevent foreign particles from entering the respiratory system and to maintain it healthy and sterile. Similar to foreign particles, when aerosol particles are administrated, the respiratory system eliminates the aerosol particles to avoid their interaction with the lung cells, leading to therapy failure. Clearance mechanism of inhaled particles is dependent on the deposition site within the lungs. For example, particles deposited in the tracheobronchial tree are rapidly eliminated by mucociliary escalator, while particles deposited in the lower alveolar region are cleared by macrophages.

As a result of the strong pulmonary clearance mechanisms and rapid systemic absorption, inhaled drugs exhibit low bioavailability at the lungs. The low drug bioavailability at the lung represents the main obstacle toward formulating inhaled drugs with high therapeutic efficiency and sustained drug release. Since drug bioavailability at the targeted site (lung) is considered the key factor for optimal therapy, as it determines whether a drug causes a complete treatment or a partial treatment with high toxicity, several approaches have been developed to overcome the rapid drug absorption and prolong its half-life. Among different approaches, particulate-based drug delivery systems which rely on using carriers, which encapsulate the inhaled drug, seem to be advantageous for pulmonary delivery over other approaches. The advantages of particulate-based drug delivery include (1) protect the drug from enzymatic degradation, (2) evade pulmonary clearance, (3) slow the drug absorption, (4) deliver the drug to targeted site at the lungs, (5) provide a controlled drug release, (6) reduce dose frequency, (7) maximize the therapeutic efficiency, and (8) minimize adverse side effects.

To achieve such inhalation therapeutic formula, several factors such as aerodynamic diameters, shape and surface properties of carriers should be tailored and optimized. Researchers from multidisciplinary fields such as chemistry, biology, toxicology, and biomaterials science heavily studied and investigated these factors in an attempt to identify the optimal parameters for
developing an effective particulate-based pulmonary drug delivery system

Types of particulate-based pulmonary drug delivery systems

Particulate-based pulmonary drug delivery systems offer great opportunities to formulate local and systemic targeted therapy for various diseases such as respiratory diseases, diabetes, and cancer therapy. Several types of carriers have been used for formulating various particulate-based pulmonary drug delivery systems attempting to optimize drug loading, residence half-life, drug release, toxicity and simultaneously overcome the multiple lung clearance mechanisms, enzymatic degradation, and rapid systemic absorption. Therefore, the selection of drug carriers is of significant importance, but several other factors such as physicochemical properties of the drug, the used inhaled device, targeted site, diseases status, the nature and safety of the carrier should also be considered.

Biography

Francesca Ungaro is Associate Professor of Pharmaceutical Technology at the Dept. of Pharmacy of University of Napoli Federico II. Since her PhD, she has been studying innovative delivery systems for small and biotech drugs, with particular regard to micro- and nano-particles. In the last 10 years, special attention has been focused on engineered carriers for inhalation. In particular, she has been coordinating several national and international projects (1 ongoing) aimed to the development of inhalable formulations for cystic fibrosis treatment. She is author of 63 scientific articles in highly-ranked journals, 1 patent, 4 book chapters, 1 editorial and more than 100 presentations at symposia (h-index =22, total citations >1500).

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