High-precision pulmonary medicine

Assistant Professor Heidi M Mansour applies nanotechnological engineering, aerosol science, lung biophysics and biomedical approaches to the development of aerosol systems to treat complex lung conditions.

Can you provide a brief introduction to the core activities of your laboratory?

I lead an active research programme on targeted inhalation aerosol delivery of advanced pulmonary medicine for various lung diseases. This involves the design, development and in vitro/in vivo performance testing of multifunctional dry powder inhalation aerosols. The programme requires knowledge of nanotechnology and nanomedicine, particle engineering design, biocompatible biodegradable polymers and lung surfactant biophysics, as well as the translation of innovative respiratory medicine for clinical application.

Over the years, I have trained many postdoctoral scholars, visiting professors, MD/PhD physician scientists National Institutes of Health (NIH) fellows and doctorate-level graduate students in my lab. Many are now assistant professors at research universities in the US, South Korea and China, or senior scientists in the US pharmaceutical industry.

What first encouraged you to become involved in the development of innovative pulmonary drug delivery?

I first became involved in pulmonary research when studying lung surfactant biophysics/surface chemistry and lung surfactant replacement medicine as a pharmacy student at the University of Wisconsin-Madison. At the time, I was conducting independent research on these topics, after which I continued as a graduate student at the University. My contributions to the area of lung surfactants provided me with the opportunity to research inhalation aerosols at the University of North Carolina at Chapel Hill.

Why is drug delivery to the lungs advantageous over other routes of administration?

First, it is the preferred route for the treatment of many pulmonary diseases. It is also readily accepted by patients. Consequently, this is a growing pharmaceutical market sector.

Second, drug delivery to the lungs is an efficient route to reach the systemic circulation in the treatment of other diseases. Currently, there are two pharmaceutical inhalation aerosol products on the market for the treatment of non-pulmonary diseases utilising nanotechnology and nanoaerosols.

Are there any unique regulations involved with inhaled products? Do they inhibit your research in any way?

Inhalation aerosol pharmaceutical products are regarded by regulatory agencies as ‘drug-device combination products’. They are delivered to the ‘organ of life’, hence there are special considerations, specifications, restrictions and regulations in place for inhaled products that we must observe.

To what extent is the relationship between dry powder inhaler (DPI) formulation and the inhalation device critical to performance of the drug?

DPIs are designed to be compact, easy to use and to exhibit superior physicochemical stability properties. Since inhalation aerosol pharmaceutical products are regarded by regulatory agencies as ‘drug-device combination products’, device design and compatibility with the formulation are both key considerations. Therefore, as aerosol generation requires the use of an aerosol device, the relationship between the DPI formulation and DPI device is critical.

What are some frequently used techniques you utilise in engineering nanoparticulate powders as DPIs?

One popular technique is surface modification to improve nanoparticle characteristics as a delivery vehicle and render them readily inhalable, which can be challenging when combining them together. Another is the incorporation of biodegradable, biocompatible nanocarriers such as PEGylated proliposomes for ‘stealth’ and controlled drug release properties. Other techniques include making highly porous dry particles for potent drugs and vaccines, as well as encapsulating the nanoparticles within microparticles to prevent aggregation and making effervescent particles to improve dispersion.

Looking ahead, what are your plans?

We have been optimising our DPI formulation so that scale-up will be economically and practically feasible. We have also been working on enhancing our device design. We are planning to continue advancing multifunctional DPIs that utilise nanotechnology for the treatment of complex pulmonary diseases.
Researchers at the **University of Arizona**, USA, are designing and developing advanced multifunctional dry powder inhalation aerosols for the successful treatment of several pulmonary diseases with unmet medical needs.

**FAMOUS FOR WRITING** *de Materia Medica*, a comprehensive inventory of the medicinal properties of plants, the 1st Century Greek physician Pedanius Dioscorides is also credited as the first to have prescribed inhaled fumigation as a medical treatment. Fast-forwarding to the early modern period, pungent aromas and fumes were widely used as a means of warding off certain illnesses, while further down the line in the 19th Century, Datura fumigation was used to treat asthma.

Despite this long history, device technology to better support inhalation as a first-line treatment method in patients only began to develop in the 20th Century. Today, with significant advances in aerosol technology, inhalation is now a standard method of administering many types of drugs as single-drug and dual-drug therapies, including antibiotics, anti-inflammatoryatories and enzymes. It is also used to deliver other types of therapeutics to treat pulmonary conditions such as asthma, chronic obstructive pulmonary disease, cystic fibrosis and lung infections. Pulmonary inhalation aerosol products have even been approved for the delivery of insulin to treat type 1 and 2 diabetes and an inhaled antipsychotic drug for central nervous system treatment of bipolar schizophrenia.

**ADVANCED AEROSOL MEDICINE**

Delivering drugs into the lungs via inhalation has many advantages and is attractive to patients. It is simple, direct, results in fewer side effects and being non-invasive, allows self-administration. Because it confers high bioavailability, precise drug targeting and low drug degradation rates, this method requires only small drug concentrations to be effective. In addition, the lung’s large surface area – alongside the high permeability of the alveoli layer – means that absorption is almost instantaneous, leading to the rapid onset of drug action.

Targeted delivery of drugs to the lungs via inhaled aerosols as solid-state dry powders is an exciting new area of research with great potential. Dry powders offer many unique advantages, including high physical and chemical stability, improved chemical compatibility and the fact that they do not require preservatives. In addition, relatively high drug concentrations can be administered in each application. However, dry powder medications have several physical and physiological barriers that need to be overcome, such as the multiple bifurcation of the respiratory tract and the innate responses of the immune system. For Assistant Professor Heidi M Mansour, based in the College of Pharmacy at the University of Arizona in Tucson, the key to tackling these obstacles lies in nanoparticle engineering.

In a comprehensive and systematic manner using a quality-by-design approach to experiments, Mansour utilises nanoparticle engineering to tailor nanoparticles, nanocomposites and microparticles with specific solid-state particle properties. “These properties include aerodynamic size, density, size distribution, surface structure and particle shapes that are compatible with inhaled dry powder aerosol administration,” she notes. She also creates multifunctional inhaled solid-state particles that are biocompatible and biodegradable and take the form of lung surfactant-mimic nanocarriers of therapeutic drugs with controlled release properties and high aerosol dispersion performance. “Aerosol dispersion performance is an important consideration in this work as it is central to the delivery of the drug to the desired select regions within the lungs in high local deposition concentrations,” she states.

According to Mansour, inhaled particles can be deposited in specific areas of the respiratory tract through impaction, sedimentation and diffusion. “Key factors that influence the effectiveness of drug deposition in the lungs after aerosolisation include aerodynamic properties, particle properties, solid-state properties and the biophysical structural characteristics of the respiratory tract,” Mansour shares. Thus she is designing and integrating aerosol drug formulations and compatible devices to provide precise and sustainable pulmonary drug delivery of nanoparticles and nanocomposites to the mid- and deep-lung regions.

**IMPROVING AEROSOL DEVICES**

Mansour and her lab’s aim to optimise pulmonary drug delivery has led them to design and test a number of dry powder inhalers (DPIs). DPIs can be passive or active.

Incorporating biomedical nanotechnology in the solid state has enabled Mansour and her team to successfully design and tailor multifunctional DPIs for a number of complex pulmonary diseases that have been historically challenging to treat effectively.
Passive DPI devices are breath-actuated and rely on the patient’s inspiratory flow to provide the energy for supply, whereas active DPIs function independently of a patient’s inspiratory flow rate. Most successfully marketed DPI products utilise breath-actuated devices. Hence, the Mansour lab has been creating and tailoring highly dispersible aerosol powders that are compatible with currently approved breath-actuated DPI devices to facilitate translational medicine.

In order to successfully design DPIs, Mansour also focuses on the inherent complexities of lung architecture, including structure, disease pathophysiology, biofilms and surfactant biophysics. Specific attributes of healthy and unhealthy states are also considered. For example, infection and disease change the nature of the pulmonary airways, via the formation of bacterial biofilms, inflammation or an increase in mucus volume/viscosity, which in turn have an impact on local therapeutic effects. Mansour and her team therefore use particle engineering strategies to address such complications. For instance, they create nanoparticles that exhibit a biphasic release profile and maintain a sufficient drug dose to inhibit biofilm growth, or PEGylated liposomal formulations which are effective at penetrating mucus and/or resisting phagocytic clearance by the immune response and the lungs.

SAFE AND SOUND
Mansour’s laboratory prioritises the creation and optimisation of safe formulations for inhalation, thus taking the potential toxicity of the nanoparticles, polymers and other excipients used in the development of inhalable dry powder seriously. As a result, the researchers conduct extensive testing comprehensively and systematically, both in vitro and in vivo, to explore the performance of formulation/device systems and to verify their safety.

Ultimately, DPIs offer a number of key advantages, such as versatile device design options, enhanced site-specific local targeting, long-term stability, modifiable pharmacokinetics, an extended drug release profile and lack of need for a liquid propellant. It could also be argued that they are superior to other inhalation therapy devices that require liquid formulations, in that they can effectively deliver newer drugs that are poorly water soluble, as well as protein- and peptide-based drugs that typically have complex stability considerations.

Incorporating biomedical nanotechnology in the solid state has enabled Mansour and her team to successfully design and tailor multifunctional DPIs for a number of complex pulmonary diseases that have been historically challenging to treat effectively. In the future, Mansour and her team aim to continue propelling this exciting research area forwards through their continued scientific and biomedical research advancements.