A Novel Approach to Inhalation Therapy

The adaptation of e-cigarettes as drug delivery devices holds great potential for inhalation therapy. So, can we apply the advances made in nicotine delivery to other active substances?

Inhalation therapy is used to treat patients with both acute and chronic respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and more.

Respiratory disease is a huge global issue – an estimated 328 million people suffer from COPD globally, with many cases undiagnosed.[1] WHO reports COPD as the third leading cause of death worldwide; 3.23 million in 2019, which was 6% of total deaths globally. According to WHO, asthma affected an estimated 262 million people globally in 2019 and caused 455,500 deaths.

Both of these conditions are primarily treated with inhalation therapy. For the treatment of asthma, patients typically inhale bronchodilators and antiinfl ammatory agents. Whereas with COPD, treatment generally is via the inhalation of bronchodilators, steroids, and antibiotics.

Overall, inhalation therapy brings several benefits over tablets and capsules. There is the obvious advantage of target organ delivery for afflictions of the throat, lung, and oesophagus. However, inhalation therapy can also have distinct advantages for other conditions, although not delivered directly to the target organ. The delivery of therapies into the alveolar spaces of the lung results in rapid absorption to oxygenated blood.

This allows the active substance to reach the target organ quickly and relatively intact. In comparison, intravenous injections rely on the delivery of the substance into de-oxygenated blood, which first requires passage around the body: through the heart, lungs, and then to the target organ. This relative delay can result in significant metabolism of the active substance before it reaches the target organ. Through inhalation, efficacy can be achieved with a lower dose, potentially reducing the risk of side effects and adverse events.

The deposition of the active substance is essential in achieving efficacy. The correct administration of an inhaled drug to the patient depends on several factors related to the drug's formulation, device design, and patient use. For the treatment of lung disease, aerosol droplets must be of a size where they are not deposited on the back of the throat or in the bifurcations of the bronchi. This ensures that as much of the active substance is delivered to the alveoli as possible. In contrast, to treat a disease related to the throat or oesophagus, the particle size should be larger, to ensure deposition in the upper airway limiting the dose delivered to the lung.

Current Inhalation Technology

Inhalation therapy is traditionally performed by four types of devices: pressurised metered dose inhalers (pMDI), soft mist inhalers (SMI), dry powder inhalers (DPI), and nebulisers.

Many different inhaler devices and medications are available to treat asthma and COPD, with over 230 drug delivery system combinations available. Despite this, disease controls in clinical practice are often unsatisfactory, where a key determining factor is the match or mismatch of an inhalation device with the needs of an individual patient.[2] The choice of inhaler device is essential, and can significantly impact the effectiveness of the treatment.

Different groups of devices bring specific advantages and disadvantages. For example, nebulisers, which turn liquid medicines into mist, are easier to inhale. They are therefore commonly used in situations where delivery with a classic inhaler might be difficult, such as to administer salbutamol to patients who are struggling to breathe during an asthma attack, or to frail or older patients unable to inhale deeply.

One historic downside of nebulisers is that they are typically large, desk-based systems, and therefore less suitable for home use. There is a need for new innovations in inhalation therapy to address the disadvantages of current technologies. Naturally, it is easier to adapt the inhalation device to improve the performance of generic drugs than to develop a new drug.

There has consequently been substantial evolution in inhaled medicine dispensers, and there are numerous technical innovations in development – for example, handheld nebuliser technology.[3] Researchers have suggested three main areas in which we can expect innovation: device engineering and design, chemistry and formulations, and digital technology.[4]

New Therapeutic Options

Novel methods of inhalation therapy may help expand the number of medicines delivered by aerosol to treat a broader range of conditions. For example, sildenafil (Viagra®), was designed as an antihypertensive, but the high doses required for the drug to be efficacious when administering it systemically via tablet caused such notable side effects that the drug is instead prescribed to treat erectile dysfunction. Researchers are investigating the possibility of sildenafil delivery to treat hypertension using inhalation therapy at a lower dose than is given orally.[5]

Take corticosteroids as another example. Inhaled beclomethasone is routinely prescribed as a mainstream treatment for asthma and COPD, with very little to no side effects. For patients suffering exacerbations, the most common course of action is to prescribe the closely-related prednisolone as tablets. These are typically administered for around four weeks.

However, the side effects can be severe and include risk of infection, increased appetite, higher blood pressure, and mood swings. In addition, therapy must be slowly phased out to avoid side effects or withdrawal symptoms at the end of the treatment. This example clearly shows the potential of lower-dose inhalation to reduce systemic adverse events.

Learning from Nicotine

So where can pharmaceutical companies look for inspiration when developing novel inhalation therapies? One, perhaps surprising, answer, is to the nicotine industry. One of the reasons smoking is so addictive is that it is one of the most effective and efficient methods of delivering a drug to the lung.

Recent research from the industry has identified that one of the reasons smoking provides such efficient and quick drug delivery is the way that the nicotine coalesces with water molecules. This inspired research into whether the pharma industry could develop an aerosol where the drug binds to water in a similar way, to improve the efficiency of drug delivery of other active substances.

Boehringer Ingelheim have previously developed the soft-mist inhaler, and bronchodilator tiotropium bromide. This combination was a huge breakthrough for the treatment of asthma and COPD, and has been a major success. It started a revolution in inhalation therapy: the first time an active substance was delivered through inhaled water droplets. The question now is, how can we emulate this with other drugs?

We've already established that cigarettes are a hugely effective drug delivery mechanism, in the case of nicotine. Interestingly, e-cigarettes are not far behind. This poses an interesting question: instead of nicotine being delivered through e-cigarettes, could we administer other active molecules? Using similar technology would be a cheap, cost-effective, and potentially very efficacious way of getting active substances to the lung. It may also be easier for patients to administer than current inhaler technology. For example, inhaler use depends on very close coordination between the trigger and inhalation, and a deep breath is required.

While there is a prescription route available for e-cigarettes via the MAA in the UK, this is currently for using e-cigarettes during smoking cessation. However, there is no reason for pharma businesses to turn away from trying to deliver other active substances using technologies similar to that used within an e-cigarette.

Non-heated Technologies

Non-heated vaping technology based on ultrasonics, piezo-ceramic mesh, and micro-nozzles, similar to that used in medical nebulisers, is a growing area. These technologies atomise liquid, rather than vaporising it, using mechanical action to create a fine mist or spray, thus removing the need for conventional heater coil technology. Atomisation technologies allow a more controlled dosage, and an improved ability to manipulate and control particle size to optimise where the drug will be deposited. Non-heated technologies are more repeatable and consistent, and may also reduce the risk of irritation or harmful emissions formed through thermal degradation of the liquid.

E-cigarette technology based on piezo technology might be best suited to inhalation therapy due to the ability to fine-tune the mesh, vibration frequency, or other parameters within the device, depending on the liquid formulation.

The evolution of e-cigarette technology is happening rapidly, and device consistency and DDU are unlikely to remain a concern for many years. The second step is then to control how much drug is administered overall.

Improving Patient Compliance with Smart Technology

As with inhalers, treatment efficiency depends on how effectively the patient adheres to the prescribed regimen. Many patients prescribed medication twice daily will not reliably take the prescribed dose. An observational study into COPD patients found that almost half of patients made at least one error, with 50% of these errors relating to the technique, and 19% related to both device and technique.[6] Though the risks of improper administration of a Ventolin inhaler might be low, it is significantly increased for patients using corticosteroid inhalers.

To prevent patients from continuously puffing on a medicated e-cigarette, manufacturers can build firmware into devices that control the amount of drug administered. Incorporating Bluetooth into an e-cigarette means the user can connect their device to an app that monitors relevant data. For example, how much power has been supplied, length of inhalation, frequency of puff, and number of inhalations per day. As well as improving how drug administering is monitored and controlled, the patient and physician can gain insight from this information. Unlike with an inhaler, where ten puffs a day might be prescribed, with an e-cigarette, it may be time-based – 60 seconds per day, for example. Using smart devices as part of a therapy regimen, with either an inhaler or e-cigarette technology, can overcome the issue of patient compliance in a way that no current therapy can. Clinicians could see from device data whether the patient is forgetting their medication, or taking the drug as prescribed and it not working.

Taking The Leap

There is still research to be done in drug formulation and suspension. The design and synthesis of inhaled drugs is challenging, as many factors must be considered. Such factors include the target, mode of action, length of action, and how to achieve it (pharmacokinetics vs receptor or enzyme binding kinetics, limited solubility vs soluble compounds), the desired onset of action, and synthetic risk.[7] Wherever possible, the development of the device and the drug should be performed in parallel.

The nicotine industry is innovating rapidly, with the development of novel e-cigarette technology and the creation of smart devices. Previous pharmaceutical breakthroughs have been inspired by research performed in the nicotine industry. What we need now is a major pharmaceutical player to commit to bringing this technology to market. The hardware and software already exist, and so there is the potential for breakthrough products in the next five years. This will be welcome news to the hundreds of millions of patients worldwide suffering from respiratory disease, and the clinicians and healthcare providers who treat them.

REFERENCES

1. Quaderi SA et al, The unmet global burden of COPD, Global Health, Epidemiology and Genomics, 2018.
2. Cataldo D et al, How to Choose the Right Inhaler Using a Patient-Centric Approach? Advances in Therapy, 2022
3. Cazzola M et al, Advances in pulmonary drug delivery devices for the treatment of chronic obstructive pulmonary disease, Expert Opin Drug Deliv, 2020
4. Biddiscombe MF et al, Is there room for further innovation in inhaled therapy for airways disease? Breathe, 2018
5. Rashid J et al, Inhaled sildenafi l as an alternative to oral sildenafil in the treatment of pulmonary arterial hypertension (PAH), J Control Release, 2018
6. Lindh A et al, Errors in inhaler use related to devices and to inhalation technique among patients with chronic obstructive pulmonary disease in primary health care, Nursing Open, 2019
7. Pasqua E et al, Developing inhaled drugs for respiratory diseases: a medicinal chemistry perspective. Dru Discov. Today. 2021

Paul Hardman

Paul Hardman has 10 years of experience in developing inhaled pharmaceuticals, across API particle engineering, formulation development and scale-up, and device design including interaction with the formulation to enable products to target either systemic absorption or local effect in the lung Passionate about product quality and understanding a product chemistry, from product design to its intended function, how the chemistry changes over time, and assessing any special features Leading the European Committee for Standardisation working group on extractable and leachable compounds in vaping products Currently leading studies related to product chemistry across a wide range of consumer and medicinal products at Broughton.

Email: phardman@broughton-group.com