PRESSPART

White Paper

Technological Developments Towards Consistent Respiratory Drug Delivery

Devices for delivering drugs to the lungs have evolved considerably over the past few decades. The choice of device may depend on factors such as the patient's age, severity of condition, and ability to operate the device effectively, as these can all affect the therapy's efficacy. Several challenges still remain for manufacturers to ensure that the correct dose of drug is delivered to the appropriate part of the respiratory system with every activation of the device

Respiratory disorders affect hundreds of millions of people worldwide, with an estimated 300 million people suffering from asthma and 210 million with chronic obstructive pulmonary disease (COPD)[1].These diseases are usually treated with inhaled aerosol medications containing pharmacological agents such as β-agonists, anticholinergic agents, and corticosteroids. A variety of drug delivery devices are available; the most commonly used are nebulisers, pressurised metered dose inhalers (MDIs) and dry powder inhalers (DPIs). Each type of device has its own advantages and disadvantages, depending on factors such as the patient's age, severity of condition, situation (eg. hospitalised versus out-patient), and ability to operate the device effectively. All of these are likely to affect the therapy's efficacy, and also have cost-related implications that should be considered.

Nebulisers

The original device for delivering inhaled aerosol drugs was the nebuliser, which was the only available method until 1956 when the pressurised metered dose inhaler (MDI) was introduced. Nebulisers are still used today, primarily for treating patients that are very young, severely ill or lacking sufficient coordination to operate a portable inhaler

Various types of nebuliser are available, one of the most commonly used is the pneumatic jet nebuliser, which is powered by a gas source that aerosolises the drug solution and delivers it to the patient via a mouthpiece or face mask. Advantages of nebulisers include adjustable dosing over time, and their capacity to provide high drug doses to patients who are severely ill. In addition, nebulisers can be used to deliver combination therapies, and, unlike some pressurised MDIs, these devices do not release CFCs or greenhouse gases into the atmosphere.

However, variability in performance between nebulisers from both the same and from different manufacturers has been reported[2,3]. This could occur as a result of evaporative loss within the nebuliser, causing the solution to become increasingly concentrated. In addition, as the solution cools during nebulisation, the output and droplet size can be directly affected.

Nebulisers have other performance disadvantages, including the risk of drug degradation and contamination, and a 'dead zone' of around 0.5-1.0 ml volume where solution can become trapped inside the nebuliser. Moreover, nebulisers are not easily portable and usually require a source of pressurised gas, reducing their usability outside clinical settings. Treatment with nebulisers often requires minutes or even hours of administration, as well as preparation and cleaning of the device before and after use, with relatively high costs per treatment.

There is still a demand for devices with the advantages that nebulisers offer, and a newer class of ultrasonic nebulisers has more recently become available that is small and portable, with faster delivery than jet nebulisers. Breath-actuated devices have also been developed that reduce drug loss during exhalation.

Dry powder inhalers (DPIs)

DPIs deliver the drug in dry powder form, from single- or multiple-dose capsules pre-loaded into the device. These devices are breath-actuated, which reduces the need for patients to exactly coordinate their breathing and device actuation to receive the optimal drug dose. The first DPI was the spinhaler, which was introduced in 1971[4]; DPIs are compact and portable, and provide immediate treatment with rapid relief from symptoms, and no risk of drug contamination. These devices do not require propellants and most newer designs incorporate dose counters. However, DPIs are not suitable for all patients with respiratory diseases because the breath-actuation requires moderate to high inspiratory flow, and having to preload the dose can be a problem for some patients. These devices also result in high pharyngeal deposition and not all medications are available for DPIs.

Metered dose inhalers (MDIs)

When the pressurised MDI was introduced in 1956 it represented the first small, portable device for pulmonary drug delivery. Typically, the MDI consists of a metal canister, which contains the medication as a pressurised aerosol, and a crimped cap that contains the drug metering valve; in-built dose counters are now included on many newer MDIs. The patient inhales the drug through an actuator that encloses the system[5]. Despite the introduction of DPIs in the 1970s, MDIs have remained the inhaler of choice for many patients. Their additional benefits include that the treatment is easy to self administer with no requirement for drug preparation, they are more suitable for patients with lower inspiratory flow, and dose-dose reproducibility is relatively high.

However, some issues remain with these devices that impact on their reliability in delivering the correct dosage. The main disadvantage with MDIs is that the patient must use proper inhaler technique to coordinate their breathing and device actuation, in order to ensure the correct dose is delivered to the lungs. Poor coordination and technique is reportedly common among patients[6,7] and can result in the patient receiving lower doses of the drug. It can also cause oral deposition and reduced drug distribution and efficacy at the target tissues. Proper inhaler technique requires suitable patient training from healthcare workers, as well as proper training of the healthcare workers themselves on proper device use[6,7]. In the late 1970s, open-tube spacer devices were developed[6] that allowed the aerosol to be contained in a chamber and released on demand. However, this reduced the portability of the MDI and also increased costs. More recently, breath-actuated MDIs have been designed[7] that release the drug on demand, so avoiding the need for coordinated breathing.

There can be issues of inaccurate delivery with MDIs, caused either by drug deposit on the device components, oral deposit, blockage or instability of the device. Several technological advances have taken place in recent years to address these issues.

Drug deposition on components

MDIs require gas propellants and these were traditionally CFC-based until the 1987 Montreal Protocol[8] phased out the use of CFC gases in MDIs. Hydrofluoralkane (HFA) gas propellants are now used instead, but the molecular properties of an HFA-MDI's active pharmaceutical ingredient can cause it to interact with the canister. If the drug formulation is in suspension, the interaction can result in drug deposition on the canister wall or exposed surfaces of the valve components. Interactions with solutions more commonly cause degradation, which results in increased impurity levels. In both cases the interaction leads to a reduction in the drug content in the formulation, meaning the patient receives less than the prescribed dose.

Deposition and degradation can be reduced by using an appropriate coating on the canister and valve components to protect the contents. Coating can improve the stability of the formulation as well as product performance, and helps to extend the product's shelf life. A range of coatings is available, though the compatibility of available coatings is far greater for canisters that are manufactured by deep-drawing than canisters manufactured by impact extrusion. Deep-drawing is suitable for a variety of metal substrates, while canisters that are manufactured by impact extrusion may only be created from aluminium. For solution formulations, internal coating or anodisation of the canister can be used to change the surface characteristics of the canister and ultimately act as a protective barrier. Low surface energy coatings can be used with suspension formulations to reduce drug deposition.

Device blockage

The MDI's pressurised aerosol mechanism is dependent on highly accurate design of the MDI's stem block and components to avoid the risk of propellant leakage or actuator failure. The stem block geometry, spray hole diameter and spray hole length are designed to ensure reliable delivery of the desired spray particle characteristics, with reduced drug deposition around the mouthpiece. It is possible to customise actuators that are produced by injection moulding for optimal function to within tightly controlled tolerances.

Device stability
Great stringency is required during canister manufacturing to ensure accurate filling weights and avoid leakage. HFA-MDIs are subject to much greater pressure than those containing CFC propellants, requiring tighter tolerances during the canister manufacturing process. Traditional processes, such as impact extrusion, have much greater variation than deep-drawing, which is a high precision process with multiple control opportunities that result in tighter tolerances in the weight and dimensions of the finished products. It is safer to use canisters manufactured through deep-drawing for HFA-MDIs, because impact-extruded cans are subject to weakness under pressure. In particular, the neck of impact extruded canisters has to be formed as a secondary process, and can become unrolled at the higher temperatures and pressures used during later MDI manufacturing steps. This is a major deficiency when manufacturing HFA-MDIs, because the pressure increases considerably more with temperature. The deep-drawing process uses a cut edge design that eliminates the rolled neck and associated risks, as well as forming a more effective seal with the inhaler's valve gasket.

Conclusions

Several types of drug delivery device are available for inhaled medications to treat respiratory disorders, each with advantages and disadvantages. MDIs are popular with patients and healthcare professionals but issues have remained with their performance and reliability. Several technological developments over recent years have helped to improve the reliability and performance of these devices. In particular, the introduction of HFA propellants has driven innovative manufacturing and designs, such as the development of new surface coatings, that are broadening the choice of treatments as well as providing safer and more dependable inhalers.