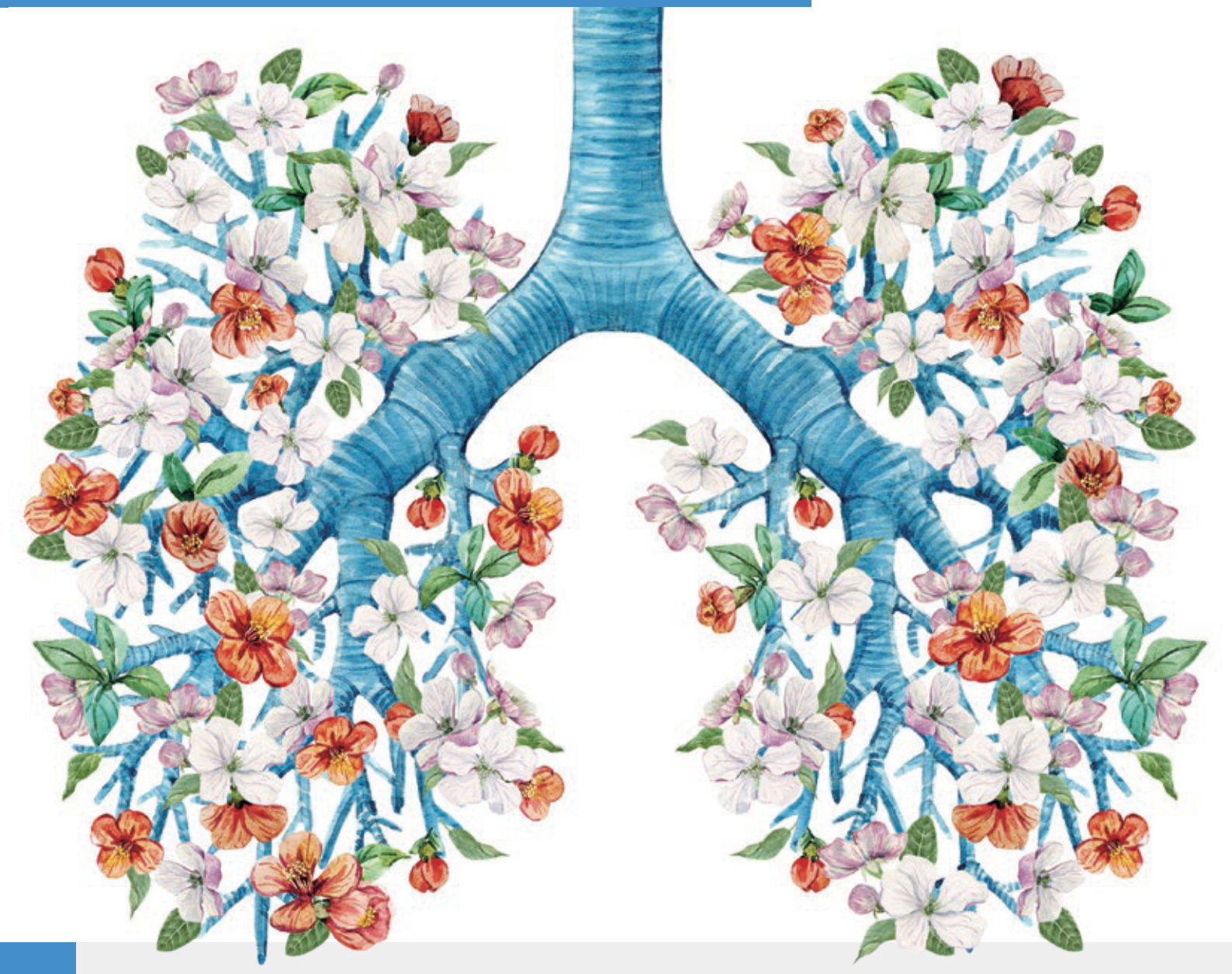
PULMONARY & NASAL DELIVERY

ON drugDELIVERY



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DO SOFT MIST INHALERS HOLD THE KEY TO FASTER INHALATION DRUG DEVELOPMENT?

Here, Wilbur de Kruijf, General Manager and Chief Technology Officer, and Bernhard Müllinger, General Manager and Chief Operations Officer, both at Resyca, a joint-venture between Recipharm and Medspray, discuss the the market requirements for new inhalation options and the benefits of soft mist inhalers.

The rise of the biopharmaceutical segment has increased the value of the inhalation sector, with more and more drug developers exploring inhalation as an alternative delivery mechanism to the parenteral approach traditionally used for biologics.

While inhalation is an ideal delivery pathway for a wide range of drugs, pharmaceutical companies face a range of challenges when developing effective inhalation drug products. In fact, the cost and complexity of developing and customising inhalation devices and formulations are often too high for biologics or drug products requiring large dosages.

Soft mist inhaler (SMI) technology has evolved in recent years alongside traditional inhalation device technologies with a range of different technical capabilities. Does SMI technology offer the opportunity to address this issue and support the expansion of the inhalation segment?

THE MARKET NEED FOR NEW INHALATION OPTIONS

Managing respiratory illnesses has reached an annual cost of US$81.9 billion (£61.8 billion) in the US[1] and $110 billion in the EU.[2] Respiratory diseases are the third leading cause of death in EU countries, accounting for 8% of all deaths in 2017 alone.[3]

With this burden on the healthcare system set to continue, biopharma companies are under continued pressure to respond to the increase in global diagnoses of acute respiratory conditions.

Biopharma companies are also becoming aware of the potential of inhalation as a delivery route for more short-term treatments. Inhaled antibiotics have been developed for treatment of acute bacterial infections in patients with cystic fibrosis (CF), non-CF bronchiectasis and ventilator-associated pneumonia.[4] Studies have also been conducted that examined inhaled therapies for the treatment of cardiovascular diseases, such as paroxysmal atrial fibrillation, and diseases affecting the brain, including acute repetitive seizures.[5]

> "Innovations in orally inhaled delivery devices are essential to meet these rising demands while ensuring that delivery is efficient, effective and patient-friendly."

Direct delivery to target sites within the respiratory system, rapid onset of action and a reduced risk of systemic side effects are significant advantages of inhalation compared with oral therapies.[6] With such advantages in mind, it is no surprise that inhalation is being considered for a wider array of drug formulations.

Advances in drug development are resulting in inhaled therapies that are longer-acting, require smaller doses or are intended to treat non-chronic conditions.[7] Consequently, devices designed for short-term use to deliver these drugs are becoming increasingly sought after.

Innovations in orally inhaled delivery devices are essential to meet these rising demands while ensuring that delivery is efficient, effective and patient-friendly. Throughout development of these new products, it is essential that developers remain aware of the sustainability, cost and complexity involved in manufacturing devices.

UNDERSTANDING SOFT MIST INHALERS

Drug delivery device innovations have led to the development of SMIs, a liquid-based inhaler capable of producing a

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"For paediatric and geriatric patients, who may have difficulties with inhalation technique, SMIs may simplify treatment administration, thereby improving deposition in the lung."

slow-moving aerosol cloud. These devices provide convenient, optimal drug delivery to the lungs while reducing the need for patient co-ordination and inspiratory effort. SMIs are designed to be hand-held devices, further offering ease of use for patients. In contrast to conventional liquid delivery systems, such as nebulisers, SMIs allow integration of the drug product's container closure system into the SMI. This allows distribution of the device in combination with the drug product and locks the two together (creating a closed system). As a result, their use has recently been approved in treatments for a variety of respiratory diseases.[8] They also have great potential to be used to administer treatments that require shorter-term care.

How SMIs Work

Drugs in SMI devices are formulated in liquid formulations, as opposed to a powder (as in dry powder inhalers), and stored within a drug cartridge or syringe. This offers advantages for APIs that are readily available in liquid formulations. By formulating in solution, for example, problems with moisture adsorption and subsequent agglomeration can be avoided. Jet-milled powder used in some inhalers is extremely cohesive and prone to strong agglomeration due to the electrostatic charge and increase in surface energy.[9]

As opposed to other technologies that use propellants, such as inspiration or electrical energy, aerosol formation in SMIs is powered by mechanical energy, such as that from a compressed spring or other simple robust mechanical system. Patients trigger the release of the drug (e.g. by pushing a button) whereupon the mechanical energy is used to transfer a predefined metered volume of the drug from the cartridge. This ensures that the dose delivered with each actuation remains uniform.

The mechanical energy pushes the liquid drug formulation through a silicon chip with micro-nozzles. The nozzles form liquid jets that break up into small respirable droplets. As a result, a slow-moving mist with a high fine particle fraction is produced.

The size of the pores or channels in the nozzle determines the droplet size, which will impact the area in the lung that the drug is deposited. By synchronising the patient's breathing with the actuation, the droplets can mix with the inhalation air stream to form a slow-moving cloud of soft mist. Inhalation of a slow-moving cloud means that less of the dose is deposited at the back of the throat, and a higher proportion of the drug is deposited in the lung.[10]

SMIs are both environmentally friendly and have a long spray duration, making it easy for patients to co-ordinate their breathing. Correct inhaler technique is important for optimal delivery of the drug to the lungs and peripheral airways. For paediatric and geriatric patients, who may have difficulties with inhalation technique, SMIs may simplify treatment administration, thereby improving deposition in the lung.

UNDERSTANDING PREFILLED SYRINGE INHALERS

Prefilled syringe inhalers (PFSIs) are one type of soft mist inhaler. In these devices, the formulated drug solution is stored within a prefilled syringe (PFS). When actuated, the syringe plunger is pushed forward, applying pressure in the PFS, which forces liquid to flow to the spray nozzle unit where it is aerosolised and inhaled by the patient. To avoid inconsistent dosing, this pressure must be applied in a controlled way. This can be achieved with spring-loaded devices that apply pressure smoothly and accurately over time.

Although PFSI devices are not yet available on the market, they offer exciting opportunities for the future. PFSIs have the advantage of being potentially available as both single-use and reusable devices. To reuse, the PFS can be simply switched out for a new one and the mouthpiece disposed of and replaced. As a result, they are ideal for use in clinical environments, clinical trials for investigational drug products and single dose treatments.

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WHERE SMIs CAN ADD VALUE

It is clear that SMIs offer a number of distinct advantages for patients, including ease-of-use, portability and a high percentage of lung deposition. Using SMIs can also be advantageous when developing drugs compared with other devices.

Suitable for Biologic Formulations

Most biologic drugs currently in clinical development are in liquid form to streamline formulation processes. As a result, SMIs offer distinct advantages for many biologic drugs requiring delivery to the lungs. Using a fill-finish platform of glass PFSs with the soft mist nozzles already mounted in, PFSI manufacturing can also offer good stability of the drug formulation and improved shelf-life, even for complex biologic drugs. In addition, SMIs allow the effective aseptic filling required for biologic products.

Increased Drug Delivery Potential

Many COPD sufferers rely on multiple medications, each requiring its own delivery device. SMIs can be used to deliver multi-API drug formulations, easing administration of multiple medications and potentially improving patient compliance. However, drug formulation for solutions containing multiple APIs can be challenging.

Although conventional SMIs are generally suited to low doses, PFSIs can also be used to deliver both low and high doses, further increasing their potential.[11,12]

Gentle Aerosolisation for Sensitive Drug Products

SMIs can present an alternative to certain types of nebulisers for the delivery of biologics. The ultrasound, vibration and cavitation methods used in nebulisers to create aerosols can damage proteins, such as antibodies and lipid-based nanoparticles, and lead to shear degradation.[13] SMIs can be designed with specialised nozzles that limit shear forces and are gentle on fragile formulations.

"SMIs such as PFSIs offer sustainability as they can be reused – drug storage modules (syringes) can be easily switched out or refilled."

Sustainability

SMIs such as PFSIs offer sustainability as they can be reused – drug storage modules (syringes) can be easily switched out or refilled. This means the device could be used for the administration of multiple therapies.

CONSIDERATIONS FOR CUSTOMISING SMIs

Despite the benefits SMIs offer, there is still a need to overcome certain challenges in development, particularly surrounding formulation and optimisation for device compatibility. For different drugs, SMIs will need to be carefully customised to deliver efficient treatment. Maintaining sterility in the container throughout repeated use without using preservatives is also a challenge for liquid systems when compared with dry powder inhalers.

Formulation Development Considerations

Ensuring dose uniformity is particularly challenging for drug products delivered via the inhalation route. Inhaled delivery of aerosols is generally influenced by the patient's inhalation flow and the consistent release of a predetermined volume not of the drug but of the drug formulation.

To minimise dosing variability, care must be taken to avoid blocking the nozzle, which could impact the particle size and mist formation. This can occur as a result of irreversible agglomeration or caking of particles in solution due to inadequate formulation. As the API would no longer be evenly distributed in the solution, this could be further detrimental to dose uniformity.

Device Considerations

The aerosol particle size characteristics of the aerosolised drug will affect the amount of drug that reaches the lungs, and therefore the efficacy achieved. By adapting the method used to generate fine particles and their size, drugs can be delivered more precisely. For example, drug particles with a diameter of 2–5 µm will more likely be deposited in the peripheral airways and small bronchioles, whereas larger particles will be deposited in the upper airways.

Additionally, lung deposition when using certain SMIs has been shown to be significantly higher at a slow flow rate with a larger particle size compared with high flow rate with a smaller particle size. As a result, the flow rate is also important to consider when optimising delivery and should be considered in conjunction with particle size.

By engineering the nozzle to optimise particle size distribution, adjusting the nozzle pore size and selecting a suitable built-in flow limitation for the device, efficient delivery to specific areas of the lungs can be achieved.[14]

"The inhalation drug market is growing quickly, with many inhalation products currently in development or at clinical trial."

WHAT'S IN STORE FOR THE INHALATION SEGMENT?

Advancements in inhalation product design and engineering have improved the precision and accuracy of dosing while enabling delivery of a wider range of drug formulations. Consequently, the inhalation drug market is growing quickly, with many inhalation products currently in development or at clinical trial.

Furthering this growth relies on cost-efficient and effective drug delivery devices. SMIs represent an ideal solution with several advantages over traditional inhaler devices and have the potential to make inhalation a viable option for a wider range of drugs than ever before.

ABOUT THE COMPANY

Resyca is a joint venture between Recipharm and Medspray (Enschede, the Netherlands) and a sister company to Recipharm, forming part of Recipharm's Advanced Delivery Systems business unit.

Resyca acts as a single hub to deliver next-generation SMI devices that are ideal for the delivery of both small and large molecules, and designed to optimise lung deposition whilst minimising oropharyngeal deposition.

Resyca's innovative SMI technology platform consists of both PFSI devices and clinical devices that can be filled on the spot, speeding up clinical investigations. Development, manufacture, filling, assembly and packaging take place within Recipharm Group.

Recipharm is a leading contract development and manufacturing organisation in the pharmaceutical industry employing almost 9,000 employees. Recipharm offers manufacturing services for pharmaceuticals in various dosage forms, production of clinical trial materials and APIs, pharmaceutical product development, and development and manufacturing of medical devices. The company manufactures several hundred different products to customers ranging from big pharma to smaller research and development companies and operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US, and is headquartered in Stockholm, Sweden.

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ABOUT THE AUTHORS

Wilbur de Kruijf is General Manager and Chief Technology Officer at Resyca, based in Enschede, the Netherlands. Mr de Kruijf has a background in medical product design and human factors engineering. Prior to joining Resyca, he held a role at Medspray for 15 years, developing micro-spray nozzles and aerosol devices based on that technology. Mr de Kruijf has experience working with design consultancy firms developing a range of medical devices, such as wheelchairs, hospital beds, x-ray scanners and drug delivery devices.

Bernhard Müllinger is the General Manager and Chief Operations Officer of Resyca and is based in Munich, Germany. Mr Müllinger has experience with smart nebuliser devices and has worked in this industry for most of his career. He has extensive knowledge in medical device development and clinical development of combination products. Prior to joining Resyca, Mr Müllinger worked at Vectura (Chippenham, UK), Activaero (Gemunden, Germany), which was acquired by Vectura in 2014, Inamed-CRO (Munich, Germany), Asklepios Clinic (Hamburg, Germany) and Helmholtz-Zentrum (Neuherberg, Germany).