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Nebulize High Value Therapeutic Drugs

THE VALUE OF CUSTOMISABLE MESH NEBULISER PLATFORMS IN COMBINATION PRODUCT DEVELOPMENT

In this article, Edgar Hernan Cuevas Brun, Business Development Manager & Scientist, Aerosol Drug Delivery, and Yuan-Ming Hsu, PhD, Research and Development Director, both at HCmed Innovations, look at the advantages of customisable nebuliser platforms for new combination products.

Advancements in inhalation therapy during the last decade have enabled the pharmaceutical industry to overcome some of the challenges commonly associated with the delivery of drugs to the respiratory airways and the lungs. In the past, dosing limitations resulting from inconsistent delivery of APIs, as well as the variability of patients' physiological and anatomical conditions across different population groups, were frequently reported as shortcomings of the inhalation administration route. Thanks to innovative technological approaches and research, there is a growing understanding of the importance and benefits of the inhalation route, along with the significant influence of formulation-device interaction.[1,2] Likewise, the establishment of standardised aerosol characterisation and drug delivery studies has also supported the evolvement of this field.[3]

During this period, the implementation of new regulatory pathways and guidelines for market approval filing has further increased confidence in the direct delivery of drugs to the lungs, especially for the treatment of respiratory diseases and conditions that could benefit from the faster absorption of APIs into the bloodstream via the thin alveolar-capillary barrier in the lungs. The result of these findings is shaping a more solid route for the development of inhaled drug-device combination products, with pharmaceutical companies and device manufacturers working on innovative treatment options that focus on optimising drug delivery efficiency and repeatability.

As new formulations are developed with consideration given to drug-device interactions, device manufacturers are transitioning into becoming contract development and manufacturing organisations (CDMOs) that offer customisation platforms for the delivery of inhalable formulations. Nowadays, these platforms can fulfil requirements ranging from aerosol properties and delivery efficiency to intuitive usability functions that satisfy human factors needs for the patient population target. Consequently, in the drug-nebuliser combination product space, CDMOs are developing mesh nebuliser platforms to add value to the development process. These customisable platforms are being developed to support innovative inhalable treatments, which range from the delivery of small molecules to biologics.

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DRUG-NEBULISER IMPLICATIONS AND DEVELOPMENT

For the development of drug-nebuliser combination products, identifying the unmet needs for the target population is one of the key initial steps for development, both for the formulation of the drug substance and the selection of the device. Dry powder inhalers may be more suitable for populations that do not exhibit significant difficulties reaching a specific inhalation flow rate, whereas nebulisers are preferable for patients who are not able to reach the necessary flow peak for actuation.

While small molecules are thought to be easier to deliver than large molecules, suspensions and highly viscous formulations, each formulation interacts with a delivery system in a unique way. Biologics and liposomal formulations are often classified as the most susceptible groups to drug-device interaction. Biologics have been reported to aggregate or lose activity, particularly when exposed to detrimental forces during delivery, while liposomes can burst prematurely, releasing the API.

As mitigating mechanisms, formulating solutions or suspensions with suitable excipients and solvents is essential, as is selecting a suitable delivery platform that can fulfil the delivery requirements. For this reason, drug-nebuliser development is paving a new path in which both formulation and device can be tailored from an early stage to achieve more positive delivery outcomes and increase the likelihood of a successful development.

Establishing the efficacy and therapeutic effect of a combination product constitutes the central point of the development. In many cases, this is primarily related to the efficacy of the API and the aerosol performance; however, usability and human factors studies have shown another increasingly valuable aspect for the success of new therapies – compliance. From here, the possibility to tailor a device extends beyond aerosol delivery and characterisation, via a customised user interface and functionality that can accommodate the needs of diverse population groups, such as children, young adults and the elderly, each one presenting a different set of needs when it comes to the device's ergonomics, indicators and feedback mechanisms.

Forged on these principles, and due to the existing demand and development spectrum, a CDMO offering customisable platforms should be capable of offering flexible, yet mature, customisation options as the basis of its combination product development, thereby supporting pharmaceutical companies from an early stage.

MESH NEBULISER BENEFITS AND SELECTION SCOPE

Active mesh nebulisers are devices that rely on the oscillation of a mesh membrane to transform a liquid medication into aerosol. This process has been shown to generate less heat than ultrasonic nebulisers and lower stress and shear forces than jet nebulisers. As such, mesh nebulisers are often described as a more suitable option for delivering molecules that are susceptible to detrimental forces, while also delivering them in a shorter time and with lower residual mass. However, the performance and specifications of devices from different manufacturers have shown that there is a wide range of outcomes that can occur even with the same mesh technology base. Therefore, selecting the appropriate mesh nebuliser for a new formulation or even group of candidate formulations can be challenging.

Exploration of device selection is often initiated with a feasibility study to gain an understanding of aerosol characterisation performance and the stability and activity of the API post-nebulisation, especially with biologics. During this step, the interaction of the device and formulation should be studied and development further reinforced. Meanwhile, the formulation's physicochemical properties, such as viscosity, surface tension and osmolality, among others, may be some of the driving factors of its aerosolisation characteristics. Equally, from the device perspective, the mesh membrane specification, power consumption and other electrical and mechanical components form the aspects that contribute to the drug-device interactions.

Considering these aspects, the requirements from the pharmaceutical company and the device CDMO are heavily intertwined, but can be simplified with a customisable platform product – a product with an essential foundation in aerosol performance but that is only considered completed after adding other factors, such as usability, connectivity and activation options.

ADDED VALUE OF A CUSTOMISABLE PLATFORM

A customisable platform can effectively facilitate and shorten the development process of a drug-nebuliser combination product, as well as support the initial feasibility assessments. During the feasibility assessment, pharmaceutical companies looking for a mesh nebuliser to deliver candidate formulations can avoid investigating a series of over-the-counter products by using a nebuliser platform that can be tailored to a range of specifications. This can result in a device that is a better match for the candidate formulation in the early stages of development before getting into more specific customisation options later on, adding significant value to the development process.

Feasibility Study

At HCmed Innovations – a CDMO focused on mesh nebuliser platforms and devices operating under continuous (Pulmogine®) and breath-actuated (AdheResp®) modes (Figure 1) – identifying the ideal

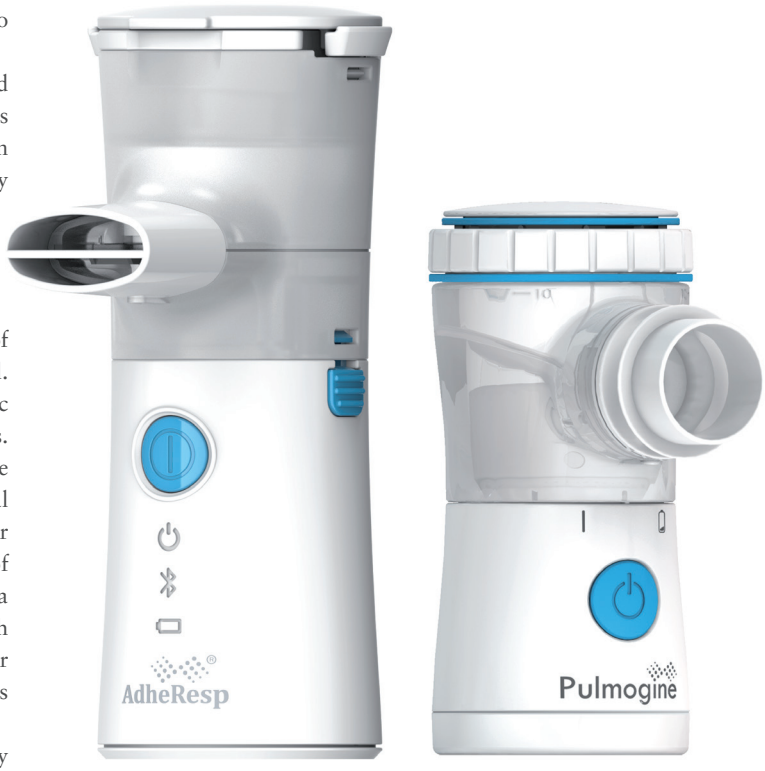

Figure 1: HCmed's AdheResp smart breath-actuated nebuliser and Pulmogine vibrating mesh nebuliser.

Pulmogine Development Kit

Group 1: Small Pore Size Meshes x 3
Group 2: Medium Pore Size Meshes x 3
Group 3: Large Pore Size Meshes x 3

AdheResp Development Kit

Group 1: Small Pore Size Meshes x 3
Group 2: Medium Pore Size Meshes x 3
Group 3: Large Pore Size Meshes x 3

Figure 2: AdheResp and Pulmogine nebuliser development kits for early feasibility assessment.

device mode at an early stage is essential for future development and can reduce the burden that would otherwise result from testing both nebuliser platforms.

For each nebuliser platform, the feasibility study process starts with the development kits, which are presented as a standard set of nine nebulisers divided into three groups based on their mesh pore size specification (Figure 2). By grouping three devices of each specification in the same group, repeatability can be investigated, providing an insight into the initial aerosol delivery performance parameters, including volume median diameter or mass median aerodynamic diameter, as well as fine particle fraction, geometric standard deviation, output rate, delivered dose, delivery rate and overall treatment time. Furthermore, the same kit can be used to confirm the stability of the molecule and compare the therapeutic activity of the API both pre- and post-nebulisation as part of a preliminary assessment. Additionally, by performing the assessment within the same platform, it is possible to generate a comprehensive set of data that could later add more value to the development process.

Design Customisation and Development

Once the aerosol delivery has been assessed and positive results have been obtained for the most optimal formulation-device combination, further customisation planning, including aspects other than aerosol characterisation, can commence. In the case of HCmed's platforms, there are several modifications and features that can be implemented, depending on the degree of customisation required.

As part of the development plan, input requirements are defined for customisation of the features associated with specific development timelines. The degree of customisation then becomes the primary element driving the timelines for development and deliverables, as agreed upon with the pharmaceutical company.

The customisation options cover aspects at both the firmware and hardware levels. The most common customisation features include:

- **Aerosol Performance and Delivery:** Mesh membrane specification is one of the key components that directly influences aerosol characterisation. Although an initial selection is done in the feasibility study as part of the exploratory work, additional testing is required to identify the most suitable specification range and pore size. Available in both Pulmogine and AdheResp platforms.
- **Power Consumption:** The power that drives the oscillation of the mesh membrane can be tuned within an upper and lower limit, altering the output rate of the device, thereby adjusting the treatment time and delivery rate. Available in both Pulmogine and AdheResp platforms.
- **Container Fill Volume:** The maximum capacity of the container's fill volume can be customised to suit the dose to be delivered. Simultaneously, container modification can also address changes to the residue. Available in both Pulmogine and AdheResp platforms.
- **User feedback:** Both nebuliser platforms use LED indicators to provide feedback on the device operation. Additional LED indicators, as well as audible, tactile and visual feedback, are also possible. The AdheResp platform includes an embedded vibration feedback mechanism that indicates when the device is activated, aerosol generation is triggered and treatment is completed.
- **Activation:** By bonding a specific drug to the device, delivery can only be accomplished after activation with a specific tag via near field communication technology. The key purpose of this function is to avoid misuse of the device to deliver formulations other than the intended one. This function can be enabled or disabled as needed. Only available in the AdheResp platform.
- **Connectivity:** Bluetooth connectivity enables the transmission of data between the nebuliser and a mobile device. Data such as time sets, battery status and pressure during breathing can be readily transmitted during treatment. With the support of a third-party cloud, this information could be shared with physicians, healthcare professionals, patients and medical facilities. Currently, only available in the AdheResp platform.

The customisation scope of HCmed's nebuliser platforms has evolved to fulfil several input requirements that can satisfy the needs of different patient populations, taking into account the indication and age group. This enables the customised device to cover all the aspects that are related to the user characteristics of the group being treated.

As some of the modifications may lead to changes that significantly depart from the standard Pulmogine and AdheResp platforms, additional design validation and verification may also be required. During this process, the customised device's functionality, reliability and performance are checked in order to generate the corresponding technical documentation package for submission.

When considering clinical implications, the use of the platforms' standard devices can be readily applied in early stages, enabling

"When considering clinical implications, the use of the platforms' standard devices can be readily applied in early stages, enabling easier bridging in later clinical phases."

Figure 3: Nebuliser customisation scope for combination product development from early feasibility assessment to commercialisation.

easier bridging in later clinical phases. Once the technical documentation for the customised device has been fully generated, it can be incorporated into the combination product development – most commonly prior to a Phase II study – to complete the subsequent steps in verifying the treatment's safety and efficacy.

Regulatory, Supply and Post-Market Surveillance

Although customised devices that have been tailored for the delivery of a specific formulation require their own exclusive documentation packaging, part of the technical documentation can be adapted from the platform's standard version. HCmed's nebuliser platforms, Pulmogine and AdheResp, come with complete technical documents that have been used in submissions for the standard devices. These documents can be referenced or leveraged for the customised device to a certain degree, which provides two key advantages:

1. Assurance that a device operating with the same technology has been approved and is fit for its intended purpose, leading to higher confidence in the success of a customised version.
2. Speeding up the timelines for producing the development and technical documentation.

While there are specific regulatory pathways for each country or region, the fundamental design history file is adequate for reference. In the US, the submission of a combination product of a drug with a specifically customised device is highly encouraged by the US FDA. To facilitate the submission, the filing is driven by the drug formulation without requiring separate approval for the device. The CDMO plays an essential role in the market access filing process for the final product.

The next key milestone is the scaling up of the product ready for commercialisation. The existence of standard products within a customisable platform results in a faster and more reliable ramp up for mass production. This stage fundamentally relies on the experience and technology, which is developed through a reliable supply chain and ensures quality assurance for the release of the final product. A CDMO, such as HCmed, can secure the production numbers of the customised nebuliser to co-package with the drug or adapt to other commercialisation strategies, depending on the territory.

Finally, once the product is marketed, the job of a mesh nebuliser CDMO partner is to provide further appropriate post-market surveillance for the device components. The CDMO's ultimate goal is to consolidate its commitment to the combination product developed with a pharmaceutical partner to provide the best possible treatment to patients.

CONCLUSION

The advantages provided by the adoption of a customisable nebuliser platform in new combination products extend from as early as the feasibility phase, continue throughout the development phase and reach all the way to final commercialisation (Figure 3). The platform approach facilitates the overall process for combination product development, shortening timelines and increasing the probability of success, with CDMOs able to create value from their existing platforms.

At HCmed, the company's commitment to and flexibility in customising its Pulmogine and AdheResp platforms constitutes its main contribution for pharmaceutical companies looking for mesh nebuliser platforms to deliver inhalable drugs, from small molecules

to biologics. As new treatments are developed with the aim of being directly delivered to the lungs, it is expected that the partnership between pharmaceutical companies and CDMOs will remain part of the foundation for drug-nebuliser combination product development.

ABOUT THE COMPANY

Founded in 2014, HCmed Innovations is a contract development and manufacturing organisation that provides high-quality and cost-effective vibrating mesh nebuliser technology and services to support global pharmaceutical partners in the development of drug-nebuliser combination products for inhalation therapies. HCmed offers mature customisable mesh nebuliser platforms to enhance drug delivery. The company's technology enables efficient and reliable nebulisation of different types of medication, ranging from small-molecule synthetics to large molecule biologics, as either solutions, suspensions or even difficult-to-deliver high viscosity drugs. Its latest platform includes the incorporation of breath actuation and connectivity features to enhance drug delivery and monitor patient adherence.

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