DELIVERING SUSPENSIONS WITH MESH TECHNOLOGY

Here, Edgar Hernan Cuevas Brun, Business Development Manager & Scientist, Aerosol Drug Delivery, and Yuan-Ming Hsu, PhD, Research and Development Director, both at HCmed Innovations, discuss the performance of mesh nebulisers for the delivery of suspensions in inhalation therapy.

TREND OF MESH NEBULISERS IN INHALATION THERAPY

Inhalation as a route of administration has been proven to offer a wide range of advantages over other administration routes when it comes to the treatment of diseases that affect the respiratory airways. By locally delivering drugs into the lungs, it is possible to overcome several issues related to systemic side effects as well as to reduce the dose required to achieve a therapeutic effect.[1]

From the three most commonly used devices in inhalation therapy – dry powder inhalers (DPIs), metered dose inhalers (MDIs) and nebulisers – nebulisers are preferable to treat children and older adults who may struggle to co-ordinate the actuation of inhalers or reach a high peak inspiratory flow to guarantee proper lung deposition. With the introduction of mesh technology, extra value was brought to nebulisers thanks to a new mechanism that converts liquid medication into aerosol by the oscillation of a mesh membrane with thousands of tiny pores. Over the past two decades, several companies have worked on mesh nebuliser development – improving these devices and driving them to a mature state that has translated into their major benefits, which include appropriate particle size distribution with aerosol droplets below 5 µm in diameter, silent operation, portability, shorter treatment time and low residue.[2]

It is important to mention that the combination of biologic formulations and mesh nebulisers is further creating a shift in the route of administration of these formulations. The intravenous route is gradually being replaced by inhaled biologics as a new treatment offering for respiratory diseases. This is possible due to the characteristics of nebulisers equipped with mesh technology, which produce low shear forces and heat generation during aerosolisation, especially when compared with jet and ultrasonic nebulisers.[3]

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SUSPENSIONS AND MESH TECHNOLOGY

Most formulations developed for nebulisation are in a liquid state, with a few presented as powders that require reconstitution into liquid form before administration. The vast majority of these formulations are solutions with APIs and excipients homogeneously distributed; however, suspension formulations are also available for inhalation as inhaled corticosteroids (ICSs). These suspensions are heterogeneous mixtures in which the APIs are not fully dissolved in the liquid buffer, clearly differentiating them from the solutions.

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"Customisable mesh nebuliser platforms allow device manufacturers to tailor the mesh components... to make delivery of suspensions more efficient."

When it comes to the use of mesh nebulisers to deliver suspensions, the existence of the suspended fine particles has been associated with a phenomenon called mesh clogging. Mesh clogging is the result of a blockage of the mesh membrane pores, which can adversely affect the aerosolisation of medication, potentially leading to low drug delivery efficiency and extended treatment time.[4] Two commonly used suspension formulations of ICSs for asthma and chronic obstructive pulmonary disease treatment are budesonide and fluticasone propionate. Budesonide's particle size in the formulation medium has been reported to be 2–3 µm in diameter, close to the pore size of the mesh membrane in several mesh nebulisers.[5] Although budesonide and fluticasone propionate have been approved for several years, and are administered via jet nebulisers in many countries, their delivery using mesh nebulisers has been brought into question, leading device manufacturers to specify that their mesh nebulisers should not be used with suspensions.

Besides the classification of formulations into solutions and suspensions, a wide range of physicochemical properties also influence drug delivery efficiency in mesh nebulisers. Viscosity, surface tension and osmolality can greatly affect several aerosol performance parameters and delivery conditions, such as mass median aerodynamic diameter, fine particle fraction (FPF, the percentage of particles with diameter lower than 5 µm), geometric standard deviations (GSDs) and output rate.[6] Other properties, such as pH and temperature, should also be carefully considered as abrupt changes could result in chemical modifications and aggregation of the APIs.[7] Therefore, understanding the properties of formulations is essential for the optimisation of delivery efficiency.

Fortunately, to overcome these issues, customisable mesh nebuliser platforms allow device manufacturers to tailor the mesh components, which may include the membrane's material composition, pore size, thickness and pitch to control aerosol characterisation, as well as the oscillation module and firmware, to operate under different frequencies and amplitudes to make delivery of suspensions more efficient.

DELIVERING FLUTICASONE SUSPENSION WITH MESH NEBULISERS

To examine the delivery performance of two mesh nebulisers with a suspension formulation, the ICS fluticasone propionate 2 mg/2 mL (Flixotide®, GlaxoSmithKline (GSK)) was selected. In 1999, the respiratory division of today's GSK introduced Flixotide Nebules as a nebulised formulation for use with jet nebulisers, specifically targeting adults and children suffering from chronic, severe asthma at a time when fluticasone was only available in DPIs and MDIs.[8] HCmed Innovations explored delivery efficiency of fluticasone by using two of the company's mesh nebuliser platforms. The purpose of the experiment was not just to demonstrate the delivery of fluticasone suspension with mesh nebulisers but also to compare the delivery efficiency between a device operating under continuous output and a breath-actuated device.

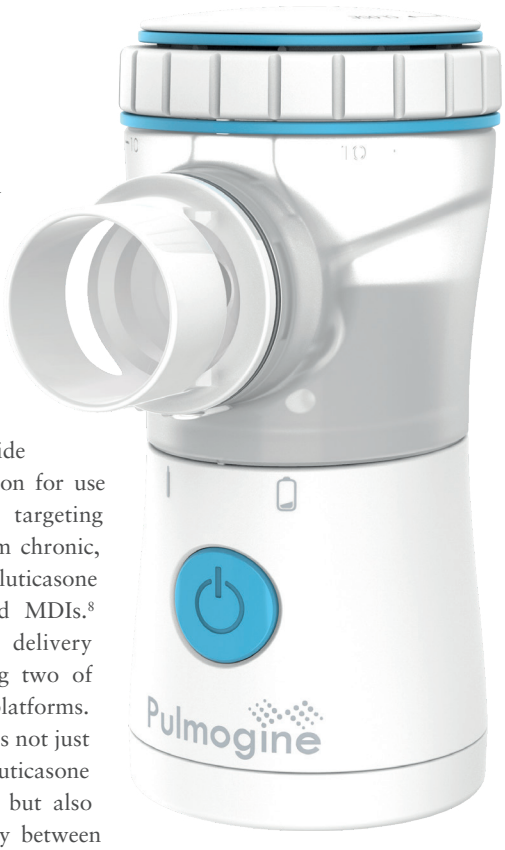

Figure 1: Pulmogine vibrating mesh nebuliser.

DEVICES: MESH NEBULISERS

- **Pulmogine® vibrating mesh nebuliser:** Pulmogine (Figure 1) is a mesh nebuliser that operates under continuous output mode and is able to deliver a wide range of medications. A selected mesh was used in the testing with fluticasone.
- **AdheResp® smart breath-actuated mesh nebuliser:** AdheResp (Figure 2) is a smart mesh nebuliser that counts with Bluetooth connectivity to transfer nebulisation treatment data. This device operates under breath-actuated mode, meaning that aerosol is generated during a fraction of the inhalation phase only. Breath actuation has become an important feature for new high-cost formulations as higher drug delivery efficiency is desirable. The AdheResp platform counts with different levels of customisation to enhance aerosol performance, as well as firmware tailoring to adjust the fraction of time in which aerosol is generated. For comparison purposes in the study, a mesh with the same specifications as the one selected for the Pulmogine device was used in the AdheResp device.

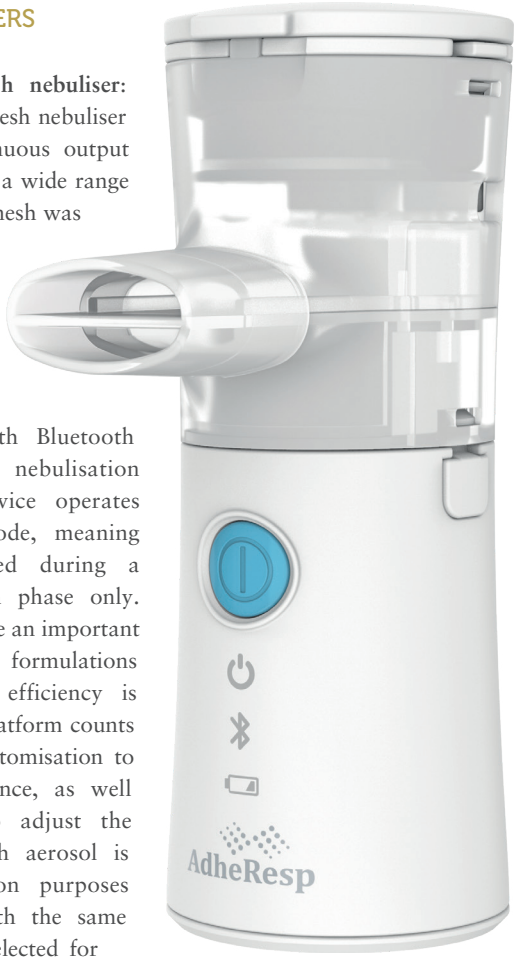

Figure 2: AdheResp smart breath-actuated mesh nebuliser.

Device	DV10 (µm)	DV50 (µm)	DV90 (µm)	FPF (%)	GSD
Pulmogine	1.969 ± 0.072	4.568 ± 0.167	9.775 ± 0.154	54.68 ± 3.61	1.80 ± 0.03
AdheResp	1.630 ± 0.133	3.470 ± 0.363	8.720 ± 0.708	69.13 ± 4.06	2.21 ± 0.46

Table 1: Aerosol particle size distribution measured with Spraytec (mean ± SD).

Testing Procedure and Results

To assess the particle size distribution of the aerosol generated with both devices, a laser diffraction particle size analyser (Spraytec, Malvern Panalytical, (Worcestershire, UK)) was used. A 1 mL fill volume of fluticasone was loaded into the reservoirs to conduct testing in triplicate with each device. The volume median diameter (DV50) for the devices was below 5 µm, which is understood as a parameter to achieve higher lung deposition and which, in time, was supported by FPF values higher than 50% for both devices. Although Pulmogine and AdheResp share the same mesh technology, the mesh orientation – vertical for Pulmogine and horizontal for AdheResp – along with the existence of a chamber in the AdheResp device, were presumed to cause the difference in performance, stressing the sensitivity of aerosol performance towards factors such as airflow. The particle size distribution values are summarised in Table 1.

Delivered dose was assessed using a breathing simulator (BRS2100, Copley Scientific (Nottingham, UK)), which was operated according to the guidelines in the US Pharmacopeia, USP <1601>, to simulate adult breathing pattern (tidal volume: 500 mL; frequency: 15 cycles/min; waveform: sinusoidal; inhalation:exhalation = 1:1). A filter was used to capture the aerosol generated by the devices in the apparatus and a mixture of methanol and water (7:3 in volume) was used to wash the filters and extract the API. Quantification of API was conducted with an ultraviolet–visible spectrophotometer (Lambda 365, Perkin Elmer (MA, US)) at the wavelength 237 nm for which a calibration curve was generated prior to testing.[9] Triplicate assessment with each device was conducted.

The mean delivered dose with the Pulmogine device stood slightly above 37%, demonstrating a good delivery efficiency with the continuous output device. On the other hand, the breath-actuated device, AdheResp, presented a more superior mean delivery efficiency of 72%, close to twice the amount reached with the Pulmogine device. Moreover, by multiplying the delivered dose and FPF, the inhalable fraction – which constitutes the percentage of delivered dose involving droplets with size lower than 5 µm in diameter – of the breath-actuated device was close to 50%, while the continuous output device only reached 20% of the loaded API. Gravimetric measurements of residual mass after nebulisation were negligible for both devices, with barely 3% of the loaded mass remaining in the reservoirs at the end of each treatment.

> "It was demonstrated that breath actuation highly enhanced the delivery efficiency of the formulation, successfully delivering a larger percentage of inhalable fraction, while also reducing the emission of fugitive aerosols."

As aerosol generation only took place during a fraction of the inhalation phase with the AdheResp device, the treatment time was doubled when compared with Pulmogine. Nevertheless, a treatment time of 12 minutes can be considered within a reasonable range for nebulisation treatment. Table 2 summarises the data obtained from the breathing simulation testing.

CONCLUSION

Delivery of suspensions with mesh nebulisers has been questioned for an extended period of time, especially due to the potential blockage that suspensions could cause to the mesh membrane. The two mesh nebulisers assessed in the study showed no significant variations in performance after six runs, maintaining high performance levels. Furthermore, it was demonstrated that breath actuation highly enhanced the delivery efficiency of the formulation, successfully delivering a larger percentage of inhalable fraction, while also reducing the emission of fugitive aerosols. This technology is significantly relevant to the development of drug-nebuliser combination products that involve costly APIs.

Moreover, as the number of biological formulations for inhalation delivery continues to expand, assessing the delivery of suspensions can provide better prospects of what could, in the future, comprise delivery of biological suspensions. This is undoubtedly an important implication, considering that proteins, peptides and nucleic acids may be encapsulated by hydrophobic materials and distributed in the liquid formulations, resulting in the development of new suspension formulations.

Although the devices were tested with a single medication, it would be useful to extend testing to examine delivery performance with other suspensions presenting various properties. Generating sufficient data on the combination of nebulisers and suspensions is an endeavour that HCmed continues to pursue to improve its mesh delivery platforms, as it constitutes the main vehicle to understand the device and drug implications and how they affect one another to achieve higher drug efficiency in the development of new inhalation treatments for respiratory diseases.

Device	Delivered API (%)	Residue (g, gravimetric)	Time (m:s)
Pulmogine	37.30 ± 1.98	0.061 ± 0.050	05:40 ± 0:20
AdheResp	72.01 ± 0.75	0.029 ± 0.004	11:54 ± 0:16

Table 2: Breathing simulation testing and delivered dose quantification (mean ± SD).

ABOUT THE COMPANY

HCmed Innovations is focused on the development of drug-device combination products for inhalation therapy. It develops and manufactures portable vibrating mesh nebulisers that offer a mature customisation platform. This technology enables efficient and reliable nebulisation of different types of medication, including small molecule synthetics and large molecule biologics, as either solutions, suspensions or even difficult-to-deliver high viscosity drugs. The newest products include the incorporation of breath-actuation and connectivity features to enhance drug delivery and reinforce patience adherence.

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ABOUT THE AUTHORS

Hernan Cuevas Brun is Business Development Manager of HCmed Innovations. He has over seven years of experience in the drug delivery field, and holds a BS in Biomedical Engineering from National Tsing Hua University (Taiwan) and a master's degree in business administration. He is responsible for co-ordinating HCmed products' branding and exploring the establishment of new partnerships with global pharmaceutical companies, while also supporting the development of drug-nebuliser combination products. Moreover, he is involved in the development of connected devices, assisting in the company's programmes and establishing alliances with new partners to expand into digital health.

Yuan-Ming Hsu, PhD, is Director of HCmed Innovations, leading the R&D department, and he is responsible for new product development and existing product optimisation. He holds a PhD in Biomedical Engineering from National Yang-Ming University (Taiwan). In addition to working as a researcher at a medical centre in the field of regenerative medicine and controlled-release drug delivery systems, Dr Hsu also gained experience in animal and clinical studies while he was the R&D supervisor in a pharmaceutical company. In the medical device field, he has more than six years of experience of developing class II and III products, including drug-device combination products.