Smart Breath-Actuated Mesh Nebulisers for Combination Products

Innovative breathing technologies have helped bring solutions to patients worldwide. One of these is smart breath-actuated nebulisers that can improve adherence by monitoring safe and effective use

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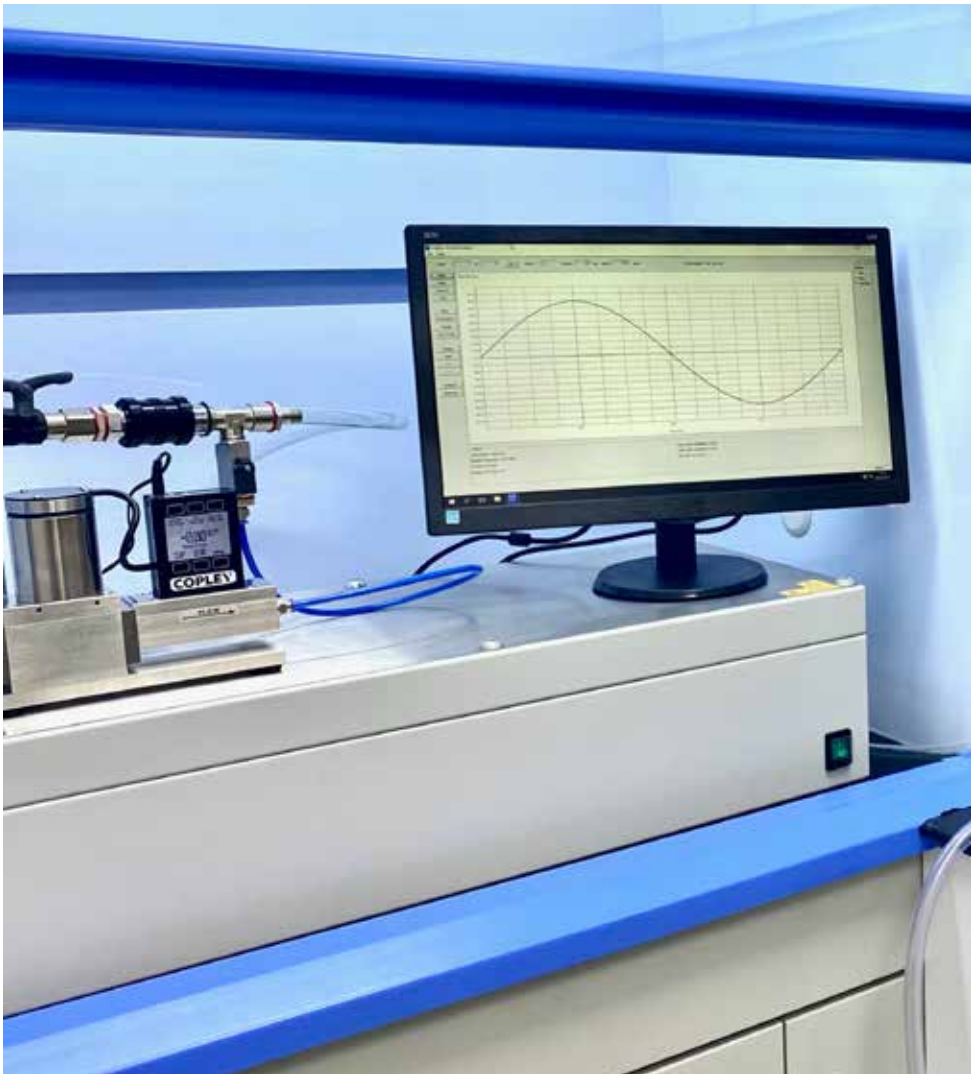


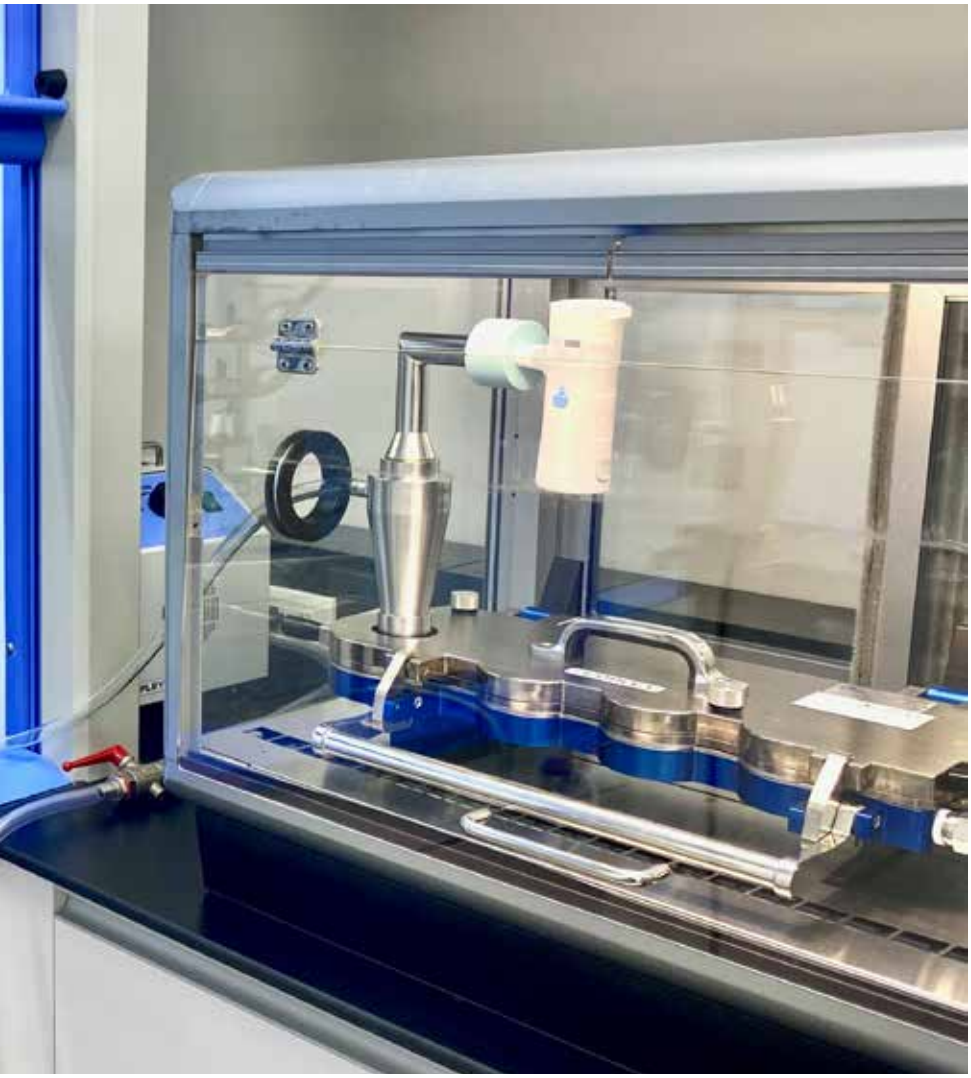
As in several other industries, the Internet of Things (IoT) has also found its place in the medical industry. The medical IoT with connectivity functions offers the opportunity to improve patient adherence. In the respiratory field, more specifically in inhalation therapy, this constitutes a major contribution. Low adherence can be observed in different types of treatment, as patients may not always comply with their prescription. However, in inhalation therapy, this is further attenuated by the potential mishandling of devices, which results in even lower levels of adherence (1).

Smart devices arise as a solution that supports the monitoring and tracking of treatment, educating and encouraging patients to adhere to their treatment and benefit from it.

These smart solutions can be presented as either add-ons (e.g., smart caps) or be incorporated within the nebulisers. Bluetooth has become one of the top choices for the connectivity environment that links smart nebulisers to mobile devices. Some of the main functions include storage of treatment information,

alarm reminders, test evaluations, and educational materials (2).

Breath-actuation technology is another main feature encountered in innovative mesh nebulisers. It consists of a mechanism that triggers aerosol generation during a specific period of the inhalation phase only. The idea behind this function is to reduce the amount of aerosol that is otherwise emitted directly into the environment, and to enhance drug delivery efficiency (3). By combining hardware and software, it is possible to activate the aerosolisation of liquid formulations during the most optimal intervals of the breathing pattern, which, besides improving the delivered dose, also helps in the reduction of fugitive aerosol emission, which may be hazardous to those around patients receiving their inhalation treatment (4).



Formulation and Device Combination

The features and customisation capabilities offered by mesh nebulisers, along with the incorporation of connectivity and breath actuation, have created an ideal environment for the development of drug-nebuliser combination products, where there is incentive for both pharmaceutical companies and mesh nebuliser manufacturers to partner and develop state-of-the-art solutions that can improve existing treatments and initiate novel approaches for rare diseases (5). This development requires both parties to build an understanding of the chemical and physical properties of the drug formulation, including the excipients, and the specifications of the mesh nebuliser that can be tailored to combine with a product that delivers optimal performance.

To find the right fit for the combination product can be a strenuous process. In many cases, formulations may have been developed by pharmaceutical companies before performing tests on a specific nebuliser. This then requires looking for a nebuliser that can provide the best performance to aerosolise the existing formulation. Directly testing over-the-counter (OTC) devices used to be the common pathway; however, the newly developed smart breath-actuated nebulisers offer customisable characteristics to enhance drug delivery based on the formulation properties. Viscosity, surface tension, osmolality, molecular weight, and drug stability are some of the properties that should be taken into careful consideration. Therefore, direct initial discussions between pharmaceutical companies and nebuliser manufacturers may become the new standard procedure for the development process. In the future, an even more ideal scenario may include the development of drug formulations and devices from the initial steps to have flexibility on both factors of this equation.

Several drug-nebuliser combination products using mesh technology have been launched in the past decade. Most of these products target the treatment of lung diseases with antibiotics. The treatment of *Pseudomonas aeruginosa* infections in cystic fibrosis patients has been covered by a series of combination products, which include active pharmaceutical ingredients (APIs) such as aztreonam and levofloxacin (6-7). Mycobacterium avium complex (MAC) lung disease has also found supportive treatment with a combination product that is based on an innovative liposomal formulation, containing amikacin as the API (8).

When it comes to smart breath-actuated mesh nebulisers, there are not many examples of combination products that have been fully developed at this point. It can be assumed that this is due to the fact that these devices are newer,

and that the development process can take several years. However, there is currently a combination product that incorporates the latest technologies to treat pulmonary arterial hypertension (PAH) in conjunction with the API iloprost (9).

Development Process and Commercialisation

The first stage in the process of developing drug-nebuliser products consists of *in vitro* studies that aim to assess the feasibility of nebulising the drug formulation with a specific nebuliser. Several nebulisers can be tested at this stage to find the most suitable combination that could achieve higher performance outcome.

As clinical trials can be costly, pharma companies may narrow down the candidate devices during the *in vitro* testing. The selection process may then be driven by candidates that can provide optimal performance or offer tailoring capabilities to improve the performance over the standard platforms. Once a nebuliser has been selected, optimisation of devices may be performed before setting up animal studies for toxicology purposes.

After optimising the combination product, clinical trials can be initiated. In most cases, a Phase I study intends to evaluate safety and maximum tolerable dosage on either healthy volunteers or people suffering from a specific condition. During this phase, different dosages may be considered, and the performance of the device is closely monitored before moving onto the next phase. Phase II and Phase III studies later focus on the efficacy of the drug formulation being delivered and the observation of adverse effects. In between these phases, final modifications can be performed to fulfil commercial requirements.

The commercialisation stage involves the rollout of the product, which is normally presented in two separated packages – a device and a drug package. Device packages are often delivered as part of the starter kit, while drug packages are sent on a monthly basis, and include the medicine along with additional mesh components and handsets. The additional meshes and handsets are used to replace the used ones according to specific periods of time, ranging from one to several weeks, in order to guarantee optimal performance. The defined performance is quantified in prior durability studies of the combination product. Lastly, the distribution and sales of the final product is done according to the agreed terms between the pharmaceutical and device partners.

Regulatory Implications

Regulatory compliance and certifications are a fundamental part of the development of medical devices and combination products as they set the requirements for the final product. Mesh nebuliser manufacturers are expected to be ISO 13485:2016 certified and produce devices with good manufacturing practice (GMP) compliant standard operating procedures.

Different markets count on their respective regulatory pathways for product approval in which mesh nebulisers are mostly classified as Class

II medical devices. In this context, the new European Union Medical Device Regulation (EU MDR 2017/745) has established a formalised system that interconnects the quality management system, risk management, documents, and other records, and it is compulsory for CE marking, as well as for the distribution of products within the EU market. On the other hand, in the US, the FDA 510(k) clearance is required to sell and distribute a medical device in the US market. This documentation contains safety, technical, and performance information that demonstrates substantial equivalence to a legally marketed device.

When it comes to combination products, the Centre for Drug Evaluation or Research and Centre for Biologics Evaluation and Research of the FDA is assigned to lead the review, relying on granting permission through the investigational new drug (IND) or new drug application (NDA) programmes. Separately, for the device alone, the Centre for Devices and Radiological Health is consulted, where the submission for review can be conducted as a device module in the NDA or IND, or a separate 510(k) (10). It is important to highlight that human factor and usability studies for the device should be conducted in parallel in Phase II to have the final version that will be utilised in Phase III clinical trial.

The MDR provides new information and regulatory requirements for the drug-device products (11). However, as these products are not physically combined, they can either be co-packaged or sold separately attaining to cross-references between information of the two products.

The addition of smart functionality also includes regulatory requirements that are linked to data security (12-13). This is essential as treatment and personal data of patients is stored in cloud platforms for sharing between patients and medical practitioners. Health Insurance Portability and Accountability Act (HIPAA), GDPR, and the California Consumer Privacy Act (CCPA) describe rules for privacy protection that should be taken into consideration when developing connected medical devices. Moreover, the International Medical Device Regulators Forum has also added into the guidelines for cybersecurity the standards UL 2900-1:2017 and UL 2900-2-1:2017, which refer to general requirements for software cybersecurity and particular requirements for network connectable components of healthcare and wellness systems, respectively.

Prospects

Smart breath-actuated mesh nebulisers have the potential to become the preferable choice for drug-nebuliser combination products. The continuous growth of these products may impulse the creation of novel and more efficient treatment solutions that would cover a wider range of diseases, using inhalation therapy as the main administration route. In order to succeed, close collaboration between pharmaceutical companies and mesh nebuliser manufacturers is indispensable.

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