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Unveiling the Path of Nebuliser Platforms for Combination Product Development

With the objective to providing more efficient and user-friendly solutions for inhalation therapy, companies developing mesh nebulisers have adopted customisable platforms to fulfil an important unmet need in the market. As new therapies are developed, an increasing number of new biologic formulations in liquid form require the use of nebulisers.[1] This fact has gradually reignited the interest in these delivery systems. Among the nebuliser types, mesh nebulisers utilise a mesh plate to aerosolise liquid medication, offering an effective and portable solution for localised drug delivery, while reducing systemic adverse effects.

Formulations and nebulisers require an appropriate degree of tailoring to achieve higher delivery efficiency and adherence. Therefore, identifying the right formulation-nebuliser fit during early feasibility studies or at the pre-clinical stage greatly benefits the overall development; however, formulation-nebuliser combination implementations can be initiated at different stages of the development process. Nowadays, customisable mesh nebuliser platform developers can assist pharmaceutical companies in navigating several aspects of this journey through integrated services and solutions.

Formulation Implications

When working on a new drug-nebuliser combination product, understanding the formulation physiochemical properties as well as the delivery system characteristics are fundamental to succeed.

Candidate formulations for an active pharmaceutical ingredient (API) may present different physicochemical properties such as viscosity, surface tension, osmolality, pH, and others.[2] These differences are commonly related to the excipients and solvents in the formulations as well as the API concentration. When it comes to inhaled formulations, the combination of these elements is crucial as they could affect how the formulation is aerosolised.

On one hand, excipients can help to stabilise the API in the formulation or in the case of biologics even protect the API from stress forces.[3,4] However, their concentration can impact the viscosity and/or surface tension among other properties, making it challenging for mesh nebulisers to aerosolise the formulation.[5] This can be observed with high viscosity or low surface tension formulations. The same can be said about the concentration of the API, with typically higher concentrations resulting in more difficulties for aerosolisation.

Due to the situations mentioned above, the selection of a suitable candidate formulation during early development is critical for the appropriate matching with the delivery system. When identifying nebulisers as the desired delivery platform, focusing on delivery performance for the selected formulation can derisk the combination product development as well as potentially shorten timelines. Moreover, for biologics, stability and activity post-nebulisation is critical to lead to therapeutic effect, making mesh nebulisers a desirable option to deliver these large molecules as heat and shear forces are minimal when compared to other types of nebulisers.[6]

Customisable Mesh Nebuliser Platforms

Mesh nebulisers generate aerosol by the means of a mesh plate. These mesh plates can be made of several materials such as nickel, nickel-palladium alloy, stainless steel, and others.[7] Each plate has thousands of pores through which the liquid medication passes turning it into droplets throughout the aerosolisation process. In active mesh nebulisers, a controller works as the driving mechanism that sends a signal to the mesh module, which oscillates of the mesh component.

Other than the mesh plate and driving mechanism, which are directed linked to the performance, the device design and the indicators play a key role when it comes to usability factors. Aspects that are essential from a human factor perspective and to an extend also relevant to patient adherence.

Customisable mesh nebuliser platforms have the capability to tailor most if not all the features of common mesh nebulisers and incorporates new ones that add extra value. When it comes to the delivery of biologics, which are known to be more costly APIs, the implementation of some of more innovative features is fundamental. A clear example is the implementation of breath-actuation, because it can significantly increase drug delivery efficiency and reduce fugitive aerosol emission.[8]

Some of the most important customisable features are (Figure 1).

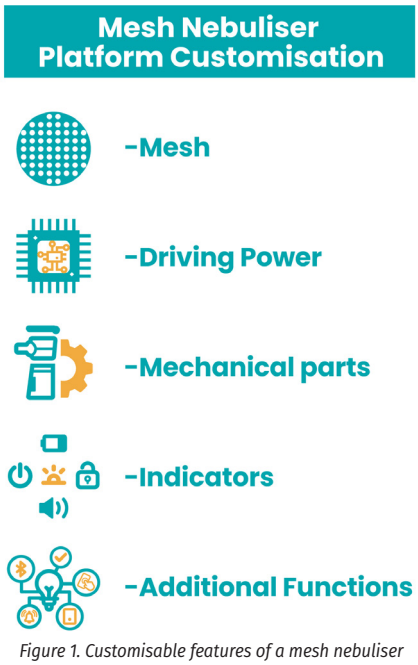

Figure 1. Customisable features of a mesh nebuliser platform

- **Mesh Plate / Mesh Module:** other than utilising different materials for the mesh plates, an ideal pore size can be identified to better fit the delivery requirements of a formulation. For some difficult-to-deliver formulations, the geometry of the plate can also be adjusted along with the plate thickness and pitch (distance between two pores). When it comes to the modules, some platforms claim to offer distinct mesh modules for different types of formulations.

- **Driving Power:** platforms can be flexible to adjust the driving power that oscillates the mesh plate with the aim to increase delivery output or to deliver highly viscous formulations. This type of modification may require a combination of hardware and software components within the controller of the nebuliser to be applicable in the tailored device.

- **Mechanical Parts:** to accommodate the needs of some specific population groups based on their age, or indication, and treatment requirements, platforms can adapt their mechanical components to match ergonomics or functional parts. Some examples are the modifications on the medication container fill space, aerosol chambers volume, button size, etc.

- **Indicators:** a combination of visual, auditive, and tactile feedback can commonly be incorporated to customisable nebuliser platforms. Some platforms already contain and can further accommodate additional LED indicators, add vibration for defined functions, or even include a speaker/buzzer to guide patients during treatment. Because of their nature, these modifications inquire both hardware and software modifications.

- **Additional Functions:** functions such as breath-actuation, activation, and connectivity can be adjusted, enabled, or disabled, depending on the requirements. Some platforms can further adjust the trigger span during the inhalation stage or incorporate guiding systems to ensure an ideal lung deposition.

Finding the Right Fit: Formulation-Nebuliser Combination

For formulation-nebuliser combination development, the earlier the product begins to be developed as a combination, the better chances to derisk some of the steps. However, a balance between cost and derisking is usually follow by sponsoring companies. It is for this reason that in some developments, and more particularly during a proof-of-concept phase, pharmaceutical companies would opt to use off-the-shelf nebulisers in early stages.

There is still a certain degree of unawareness that the development of a drug-specific nebuliser with a nebuliser platform does not require the development of a completely new device. Some of the main nebuliser platforms already count with fully developed or approved standard devices in highly regulated markets. This status guaranties their immediate use in early clinical studies, providing robust devices that can be customised at later stages to fulfil additional requirements. Moreover, some nebuliser platform developers also offer special kits that contain a range of configurations that are readily available for testing, thus facilitating the selection of candidate formulations with suitable device configurations. The configurations in the development kits may include different pore size ranges, aerosol chambers, or driving powers.

For the actual initiation of the development process of a formulation-nebuliser combination a feasibility study needs to be conducted. This step is fundamental to understand how the two parts of the combination product interact. A common feasibility study may include aerosol characterisation and delivery performance, which can be summarised as follows.

- **Droplets Size Distribution (DSD):** the test relies on the use of a laser diffraction particle size analyser for a quick assessment that provides key values such as volume median diameter (VMD), fine particle fraction (FPF), and geometric standard deviation (GSD). No API quantification is conducted.

- **Aerodynamic Particle Size Distribution (APSD):** by using a cascade impactor, the mass median aerodynamic diameter (MMAD) is computed on the basis of the amount of API that is collected at different stages of the system, with each stage being defined by a specific size cut-off. This process is commonly suggested for higher accuracy when working with suspensions. However, the process is lengthier and requires assay methods for API quantification.

- **Delivery Performance:** commonly conducted by using a breath simulator, several performance parameters are computed with this study, including emitted dose, delivered dose, output rate, treatment time, and residual mass. Although gravimetric methods can be applied, quantification assays need to be in place to obtain delivered dose performance which is suggested to both continuous output and breath-actuated mesh nebulisers.

- **Other Tests:** particularly for biologics, post-nebulisation studies to assess the integrity of the molecules after aerosolisation is indispensable. Due to the potential impact of stress forces (e.g. shear forces) stability and activity assays are required to understand if the aerosolisation process may have led to aggregation, denaturation, etc.

The list above can serve as a general rule for understanding overall combination performance; nonetheless, to ensure that this information is meaningful, developing methods with the correct setups for combination product testing is essential. Consequently, working with companies offering customisable platforms as well as experienced contract research organisations (CROs) is a necessity to ensure the generation of meaningful data.

At the end of this stage, a selected match, or it some cases a narrow down among the possible options, is expected to identify a suitable candidate formulation and customisable platform (Figure 2). From here on, mesh platform developers can map the customisation development based on performance requirements for the drug-specific nebuliser.

Figure 2. Right fit for formulation-nebuliser combination product

Customisable Nebuliser Platform Implementation

Identifying an initial match for a combination product is the first major step moving towards the product customisation. From a device perspective, the standard nebuliser of a platform is sufficient for preclinical studies, including toxicology assessment or even to enter clinical studies, such as a Phase 1 prior to customisation. Subsequently, customisation of combination products can start at different stages. Some of the most common scenarios for the implementation of customised drug-nebuliser combination products is listed as follows:

- **Pre-clinical Stage:** the most ideal case as previously described maps a development in which the formulation and nebuliser are paired at an early preclinical stage, accelerating the development and shortening the overall full path. These combinations may require prompt commitment and upfront payments when it comes to bounding to a platform in the beginning, but in the long run could significantly reduce further expenses thanks to the mature stage of the combination product.

- **Clinical Stage:** it is common change devices between Phase 1 and Phase 2 clinical trials. These changes may be due to the several factors, but the reluctance of working with a platform in the early beginning thus opting for more conventional nebulisers and unexpected supply availability of certain products are the leading reasons. On either case, a bridging study is fundamental to compare aerosol characterisation, while justifying the means for the switch. All customisations can be implemented at this stage. From Phase 2 and onwards justifying a device switch may be more complex, requiring bioequivalence and in some cases repeating pivotal studies. The final pathway may vary and can be highly dependent on the territory where the product will be launched.

- **Marketed Stage:** for marketed products, switching to new devices is also possible. However, the process may require extensive safety data, bioequivalence, and in most cases conducting additional clinical trials with the new customised nebuliser.

At each one of the stages, companies offering customisable nebuliser platforms provide the needed support for the development of the device, which extends from technical documents for filing clinical trial approvals or regulatory filings to device supply and training when required. These integrated services go beyond the development process, reaching to the commercial stage for which scaling up is a key factor during development as well as post market surveillance support (Figure 3).

Business Perspective and Other Implications

When it comes to the business-related matters, the development process can be segmented in different stages, especially for the early-stage development in order to derisk. For initial feasibility studies, the supply of devices under a material transfer agreement or a feasibility study proposal to trigger the performance assessment is sufficient to begin the collaboration. At this stage, the purpose is to evaluate a potential long-term collaboration, and therefore, the commitment to an agreement may be premature.

As soon as positive results are recorded in a feasibility study, the tailoring of a customise platform can commence. This opens the path to negotiating a development or licensing agreement that may significantly vary according to the scope of the project. The definitions of field (related to the API and indication), territory, and exclusivity combined to the level of customisation of a mesh platform are some of the contributors that shape the device and development milestones, royalties, and other development activities. They often comprise late pre-clinical tests, clinical studies, and part of what would be the commercial supply; nonetheless, it is usual to have commercial agreements being executed at later stages to cover activities related to commercial supply terms and distribution. For projects that are initiated in between clinical stages, the milestones may also be adjusted to adapt to the stage of the project.

There are cases in which the commercial strategy is not fully defined during the earlier stages. For these situations, there are also other alternatives that would focus on more specific tasks such as clinical trials. Clinical supply or even research agreements are options that allow for a shorter-term collaboration as the development and/or commercial strategy is outlined. Commonly, milestones would concentrate on tasks that could be completed within shorter periods and with lower costs for the sponsoring side.

Due to the difference among development projects, there is no one-size-fits-all strategy from the business nor the development perspective. Nonetheless, this allows for room to hold discussions and negotiation between the formulation and nebuliser platform parties to come to an agreement that fits the expectations of both parties.

Empowering Drug-Nebuliser Combination Products

The success of a drug-nebuliser combination product development is subject to multiple factors, starting with the right pairing of the formulation and nebuliser. Formulation combined with mesh nebuliser platforms can further optimise delivery performance allowing to derisk the development process and potentially shorten timelines.

New drug entities, including small molecules and biologics, can significantly benefit from customisable solutions as the development and/or implementation could take place at different stages of the combination product development. Pharmaceutical companies can then feel reassured of having a partner that can assist with the device part from either technical or regulatory perspective. Nowadays, paving the track for a more efficient development has

Figure 3. Fully integrated pathway for drug-nebuliser combination product

become an option thanks to the integrated services of mesh nebuliser platform developers, who can support throughout the entire development process to market access.

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