COLLABORATION AIMS TO ACCELERATE DEVELOPMENT PROCESS IN DPI FORMULATION

Here, Harry Peters, Senior Product Application Specialist (Inhalation) at DFE Pharma, explains how the collaboration between DFE Pharma, Hosokawa Micron and Harro Höfliger can help manufacturers save time and money in the development process for dry powder inhalers, enabling them to tackle unmet needs and unleash the potential of the significant market opportunity presented by dry powder inhalers.

Lactose-based dry powder inhaled (DPI) formulations are well established in the market for the treatment of respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD). There is now a growing trend towards developing DPI formulations that are ternary mixtures including magnesium stearate as well as lactose and APIs. However, the development process for such formulations is complex.

Successful delivery of an API into the lungs depends on many interconnected factors during the production process. The smallest change in the formulation can have a major effect on the end result. DFE Pharma, Hosokawa Micron (Doetinchem, Netherlands) and Harro Höfliger (Allmersbach im Tal, Germany) have joined forces to set up a multidisciplinary study to generate valuable data-driven insights as the basis for offering better advice and support to pharmaceutical companies.

COMPLEX OPPORTUNITIES

Lactose-based DPI formulations are in growing demand. The worldwide prevalence of asthma, which is primarily treated with DPIs, appears to be rising.[1] Increasingly, doctors are using inhaled medications to treat the symptoms of covid-19.[2] Both conditions are global health issues, and neither is going away any time soon. As such, drug developers and generics manufacturers are increasing their focus on DPIs in a bid to tackle this unmet medical need.

DPIs allow patients to inhale an aerosolised powder into their lungs. Formulation considerations include how the powder properties blend with the API, as well as how they affect device filling and the deposition of the API into the lungs.

Most DPI formulations consist of an active ingredient, micronised to a size suitable for inhalation and blended with a

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larger excipient, usually lactose. They tend to be based on carrier principles – the drug is blended with the lactose, which helps to improve the handling and the dosing of the API into the device. The lactose also helps to de-agglomerate the cohesive particles, so that individual particles can be inhaled and enter the lung, as well as enabling the right flowability of the formulation for release from the device.

Of course, how excipients behave in the final formulation depends on all manner of variables. For example, previous studies in fine particle fraction and dosing have shown an increase in lactose fine particles also increases fine particle fraction. This presents developers with a challenge of trial and error when selecting the right lactose for their product. Formulators will test the effect of different grades and blending processes on metrics such as filling, performance and delivery, until they find the right one for them.

JUMPSTARTING DPI DEVELOPMENT

DFE Pharma's joint research project with Hosokawa Micron and Harro Höfliger aims to overcome this time- and resource-hungry trial-and-error step, thus accelerating the development of much needed new DPI products. This "magic triangle" collaboration links global expertise in formulations, excipients, powder processing and manufacturing technology. It expands on the findings of previous work exploring the influence of differing qualities and concentrations of graded powders on the capsule-filling and dosing process with and without magnesium stearate.

By sharing the data-driven insights of the three-phase study, the research team aims to help generic players stay ahead of the curve and tap into the growing DPI market.

- **Phase I:** Establish baselines by blending varying fine lactose samples without the addition of magnesium stearate
- **Phase II:** Blend samples coated with magnesium stearate and compare the results to baseline
- **Phase III:** Blend samples with active ingredients and compare results.

Thus far, the team have completed and published the results of Phase I. Phase II data will be published in the coming months.

THE STORY SO FAR

In Phase I of the study, the team focused on understanding the impact of the addition of fines on flow properties and filling consistency, using different filling techniques. It was found that, as fines concentration increases, cohesivity also rises in all different grades of lactose. However, different fines grades have different impacts on Q4.5 (particles below 4.5 µm), Q30 (particles below 30 µm) and the flow of powders. There was also a strong relationship between lactose Q30, flow properties and filling.

The drum filler showed the lowest variation in terms of fill weight and relative standard deviation (RSD). As such, the team concluded that it was a robust system for a wide range of powders with respect to flowability. Additionally, flow function showed good correlation to mean fill weight.

Powder characteristics had a strong influence on the filling results of the membrane filler, with percentage compressibility showing good correlation to mean fill weight. The team concluded that permeability should be higher than 6 mbar at 15 Kpa to ensure low RSD values that can be controlled by lactose Q30. The team also found that dosator filling results in good filling consistency with respect to RSD, though high RSD was observed in lactose grades with a high concentration of fines.

In the second phase of the study, trials were conducted using different grades of lactose fines with different mixing/blending speeds and times, and both with and without a magnesium-stearate coating. While the analysis is being finalised, the team can already conclude that the addition of magnesium stearate to lactose changes the flowability.

The study is now moving into its final phase, which will be conducted at Harro Höfliger's state-of-the-art facility using DFE Pharma's lactose and Hosokawa Micron's powder mixing technology. APIs will be added to formulations using high-shear blending. The result will be analysed for flow properties, blend uniformity, assay, emitted dose and aerodynamic particle size distribution. The team, who are expected to publish their results later this year, will also carry out short-term stability studies.

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ENRICHING THE KNOW-HOW ON DPI FORMULATION TO ACCELERATE THE DEVELOPMENT PROCESS

DPI formulations hold life-changing potential for patients the world over. Tackling the unmet need triggered by the increasing prevalence of conditions such as asthma and covid-19 is a huge opportunity for the pharma industry. By sharing the data from this project, DFE Pharma, Hosokawa Micron and Harro Höfliger hope to help the sector leapfrog the costly, time-consuming trial-and-error part of the formulation process and carve out a shorter path to market. The results from this research will strengthen the understanding of the coating process and the correlation between lactose quality, blending, flowability and dosing, as well as provide practical advice for pharmaceutical companies.

ABOUT THE COMPANY

DFE Pharma is a global leader in pharmaceutical excipient solutions. The company develops, produces and supplies high-quality functional excipients for use in the pharmaceutical, biopharmaceutical and nutraceutical industries for respiratory, oral solid dose, ophthalmic and parenteral formulations. The company's excipients are used in numerous medicinal and nutraceutical products, including covid-19 vaccines and treatments.

DFE Pharma's excipients play an essential role as fillers, binders and disintegrants, as well as in stabilising active ingredients for release in a predictable and effective manner into the patient's system. With over a century of experience and more than 450 people worldwide in over 100 countries serving more than 5,000 customers, DFE Pharma is committed to supporting (bio)pharmaceutical and nutraceutical companies in their journey to improve patients' lives.

ABOUT THE AUTHOR

Harry Peters has been working as a specialist in the use of lactose in pharmaceutical applications for more than 15 years. In the last six years at DFE Pharma, he has further specialised in the dry powder inhalation field. Mr Peters is Senior Product Application Specialist (Inhalation), having started working as R&D manager and Product Application Specialist for inhalation grade lactose. He advises formulators of dry powder inhalers about the use of inhalation grade lactose.

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