PEER REVIEWED

New DPI Data Insights Shaping Future of Global Healthcare Needs

Innovative inhalation therapies and drug delivery are legacies of the COVID-19 pandemic, as pharma and biopharma formulators address growing demands for new healthcare solutions.

Lactose-based dry powder inhaler (DPI) formulations are the most significant form of inhaled treatment for respiratory conditions such as COPD and asthma. Now, they also being used to treat COVID-19, leading to an increase in demand for lactose-based excipients.

Most DPI formulations consist of a micronized active ingredient blended with larger excipient particles, which enhance flow, reduce aggregation and aid in dispersion.

However, the complexity of the formulations required means it can be difficult to understand the impact of individual compounds on the final results.

A multidisciplinary study by DFE Pharma, Hosokawa Micron and Harro Höfliger aims to help manufacturers save time and money in the development process by testing various formulations of magnesium stearate-coated lactose in the blending and filling process.

This 'magic triangle' collaboration, linking global expertise, is part of the new global approach shaping new theories and data to address global healthcare needs.

Formulation specialist DFE Pharma provided different qualities and concentrations of fine lactose to powder processing technology manufacturer Hosokawa Micron.

Baseline levels are established by blending these fine lactose samples without the addition of magnesium stearate. The different lactose particles are then coated with magnesium to allow comparison of impact on filling and blending properties.

The multidisciplinary research extends the findings of previous studies to explore the influence of the different qualities and concentrations of graded powders on the capsule-filling and dosing process.

Its next phase includes the addition of an active ingredient.

By sharing their data-driven insights, the research team is helping generic players stay ahead of the curve and tap into the growing DPI market.

Qualities and combinations of coarse and fine lactose

A dry powder inhaler is a device designed to allow an aerosolized powder to be inhaled into the lungs. It is a replacement for aerosols containing a drug substance suspended in a propellant.

In DPI formulations, the powder properties are very important in relation to the blending with the Active Pharmaceutical Ingredient (API), the filling of the device and the deposition of the API into the lungs.

Most DPI formulations are based on carrier principles. A drug is blended with the lactose which helps improve the handling and the dosing of the API into a device. The lactose will also help to de-agglomerate the cohesive particles so individual particles can be inhaled and enter the lung. The lactose allows the right flowability of the formulation for release from the device.

A formulation strategy always starts with the drug. With asthma and COPD drugs, they have been micronized to make them small enough to be inhaled. These very small particles in very low doses require a working agent to become processable and delivered into a device.

Normally, a pharmaceutical company will have already decided which type of device and filling technology it is going to use. The right lactose grade can then be selected.

Formulators can then test the lactose and blending process and then test the formulation – how is it filled, how is the performance, how is the active getting out of the device and into the lungs?

Previous studies into fine lactose particles, fine particle fraction and dosing have shown if you increase the lactose fine particles you increase the fine particle fraction.

These lactose fine particles can be obtained from various fine lactose grades.

To better understand how these different lactose grades can be used, the DFE Pharma, Hosokawa Micron and Harro Höfliger study selects different fines to test their impact on flow.

Coarse grade Lactohale® (LH) 206 and fine grade Lactohale 210, 230 and 300 are blended with a Nauta blender.

Particle size distribution and flow properties are measured by Schulze tester and FT4 Rheometer.

LH206:LH210 are tested at concentrations of 90:10, 80:20 and 70:30. The same concentrations are run for LH206:LH230. In the case of LH206:LH300 slightly lower concentrations are used – 97.5:2.5, 92.5:7.5 and 87.5:12.5 – because LH300 is a micronized grade of lactose and too many fines can create issues in formulation.

Lactose particle size specification in LH206 is D50 of 75–95 while in the fine grades of 201, 230 and 300 the D50 is 14–19, 7–11 and <5 respectively.

While D10, D50 and D90s are important parameters for DPIs, there are other important factors which can play a role with respect to fine particle fraction and flow properties. These are Q4.5 which are particles below 4.5µm and Q30 which are particles below 30µm.

There is a correlation between Q4.5 and fine particle fraction and Q30 with flow properties.

Looking at the impact of the addition of fines on Q4.5 and Q30, there is a clear linear increase of particles in all cases – as the fines concentration increases there is an increase in particles.

However, there is a stronger impact of LH300 on Q4.5 than Q30 suggesting, if you want to focus on fine particle fraction, LH300 may be able to modulate fine particle fraction to a greater extent.

Selecting the right type of blender for DPI formulations

There is always a need to match the mixing technology and its operational parameters to the specific application, including DPI applications.

In general, for free-flowing materials, a gentle mixing technology is selected while for cohesive materials a more intensive mixing technology is needed.

Free-flowing materials can be mixed in a connective manner by rearranging the particle matrix. Binding forces between the particle are generally weak so a simple gentle mixing will be sufficient for cohesive powders.

Where binding forces are strong, these forces need to be broken and rearranged and this requires energy input. This requires a more intensive mixer.

A Nauta mixer is used for the prevalence in this study.

The mixer can be fixed on top of and directly fit in into a tablet press. The product is charged on the top of the conical vessel and the convective agitation is realised by the combination of the movement of an obit arm and a screw.

The mixing screw is mounted on the top of the arm, a few millimetres from the top wall or from the wall of the vessel to create some clearance and then the screw conveys the powder upwards along the axis of the mixer.

Radial mixing is achieved by the shape of the cone and the arm ensures a tangential mixer.

The speeds used are typically small – between 0.5–2m/s.

Filling technology options and parameter affects

There are two main devices for DPI – blister-based and capsule – which are the focus of this study.

When using a blister-based device and working with cohesive powders like milk-grade lactose then the ideal filling technology is a membrane filler.

However, when using a blister-based device and working with a fairly flexible powder, for example a mixture of sieved and milk-grade lactose, drum-filling technology can be used.

Capsule-based devices are versatile and can be used for both fair flow powder and cohesive powder using either a drum filler or the dosator filling system.

Membrane filling is suitable for dosing volumes from 20mm^3–1,000mm^3 with a dosing range of 10–500mg.

This device features a powder hopper with nozzles attached. Empty pockets come and go towards the dosing station and a vacuum pulls the powder down into the pocket from the nozzle achieving 100% filling to the membrane.

The main advantages are very limited powder spillage on the sealing area and limited powder dust generation during filling. The membrane filling system is a volumetric dosing system wherein pocket size decides the dosing volume.

Drum filling is suitable for dosing volumes from 1mm^3–100mm^3 with a dosing range of 0.5–50mg.

Drum filling again is a volumetric-based dosing system. In this case a drum has a powder hopper with a stirrer inside. The drum moves in a clockwise manner from 12 o'clock to three, six and nine o'clock.

There are two important parameters in drum filling – vacuum pressure and blowout. Vacuum pressure pulls the powder in. Blowout ejects the powder into the capsule after the six o'clock position and cleans the drum of powder retention at the nine o'clock position.

The advantages of are being able to fill a wide range of powders based on flowability, the ability to fill extremely low quantities and high accuracy.

Dosator filling is suitable for dosing volumes from 20mm^3–1,000mm^3 with a dosing range of 10–500mg.

Although this is another volumetric-based dosing system, in this case the dosing volume is dependent on the height between the dosator pin, the dosator sleeve and the powder bed.

A cleaning station applies a vacuum to the pins meaning the cleaning cycle can be decided based on powder properties. The dosator system allows easy adjustment of volume, and thus dosing quantity, and a wide dosing range.

When comparing membrane, drum and dosator filling, the focus is on mean fill weight and relative standard deviation (RSD).

Looking at the impact of the addition of fines on powder flow, there are three important flow properties where researchers found a correlation with the Q30 as well as the filling.

An increase in fines leads to a percentage increase in compressibility and permeability but in flow function there is an inverse relation – flow function decreases as fines increase meaning the powder is becoming more cohesive.

In membrane filling, high RSDs are observed with low fines concentration powders. In drum filling, consistent lower RSDs are observed across all batches. In dosator, consistent lower RSDs are observed except for batches with high fines – LH300 at 12.5%.

An overall comparison shows significant differences in the mean fill weight are observed in the membrane filler – powder characteristics have a high influence on the filling results. In contrast, drum filling displays a low spread on mean fill weight. High RSDs are observed in the membrane filler and the dosator with LH300 while there is a low spread of RSDs in drum filling.

The joint explores the connection between the PSD, the flow properties and the filling systems.

In membrane filling systems there is a very good correlation between Q30 and percentage compressibility and compressibility and mean flow rate suggesting compressibility plays an important role in deciding mean fill weight in the case of membrane filling systems. If particles are modulated below 30 micron the mean fill weight can also be modulated.

There is also a very good correlation between Q30 and permeability. When it comes to permeability versus RSD, when there is a very low permeability there is a high RSD so a certain amount of permeability is needed in powder to have good RSDs with respect to membrane filling systems.

In the drum filling system, there is again a very good correlation between Q30 and flow function and flow function and mean fill.

RSD for drum filling systems is consistently around 2% so there is not a clear correlation. However, it is observed that with very high permeability you may end up with slightly higher RSDs.

With the dosator system, for RSDs no clear correlations are observed for any flow parameters. However, a relationship is observed with regards to RSD and particles below Q4.5 wherein a very high concentration of particles below Q4.5 may result in high RSDs.

This could be because of the high concentrations of LH300 or micronized lactose, there could be electrostatics or because of the cohesivity there could be sticking to the dosator pins which could lead to high variability and could also lead to inconsistency in the powder bank.

If you are using a dosator filling system concentrations of fines become very important.

Summary of phase one findings

Phase one of the study focuses on understanding the impact of the addition of fines on flow properties and filling consistency using different filling techniques.

As fines concentration increases, cohesivity increases for all different grades of lactose. However, different fine grades have different impacts on Q4.5 and on the flow of powders.

A strong relationship between lactose Q30, flow properties and filling is demonstrated.

The drum filler shows the lowest variations in terms of fill weight and RSD. It is a robust system for a wide range of powders concerning flowability and flow function showed good correlation to mean fill weight.

Powder characteristics have a strong influence on the filling results of the membrane filler with percentage compressibility showing good correlation to mean fill weight. Permeability should be higher than 6 mbar at 15Kpa to ensure low RSD values which can be controlled by Lactose Q30.

Dosator filling results in good filling consistency with respect to RSD. However, high RSD was observed with LH206 and LH300 due to the high concentration of fines.

Findings from phases two and three of the study will be presented later this year.

Phase two will present and publish information on the magnesium stearate coating used to coat the lactose formulation and analysis of the flow properties and filling.

Phase three will share the results of adding the API and analysis of the stability of the formulation.

The results will give generic players a head start in the development process and allow them to tap into this rapidly growing market.

This multidisciplinary study is an example of how collaborative working between expert players can benefit the wider pharmaceutical industry, helping generic players stay ahead of the curve and meet the healthcare needs of the day.

Harry Peters

Harry Peters is a specialist in the use of lactose in pharmaceutical applications for more than 10 years. In the last six years at DFE Pharma he has further specialised in the dry powder inhalation field. He is Senior Research Specialist, R&D 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. Together with customers, special lactose grades are developed to optimise the filling and performance of the devices and formulations. Together with universities and industry, new characterisation techniques are explored to further understand lactose in dry power formulations.

Dr. Mohit Mehta

Dr. Mohit Mehta is Director DPI Consulting at Harro Hofliger, Germany.

Dr. IR. Kay Imole

Olukayode I. Imole (Kay) currently works as a process technologist in the research and development department of Hosokawa Micron B.V.