SELECTION OF EXCIPIENTS FOR DRY POWDER INHALERS

As dry powder inhalers need a carrier to help with ensuring the drug is effectively delivered, interest has been focused on developing inhalation-grade lactose for this purpose. Harry Peters, Product Application Specialist Inhalation, and Gerald Hebbink, PhD, Scientist, both of DFE Pharma, look at which selection criteria to use to ensure the best grade of lactose is used for each dry powder inhalation formulation.

Dry powder inhalers (DPIs) have become very popular for dosing of medications to patients, especially those suffering from respiratory diseases. Most DPI formulations contain a carrier to improve the handling of the powder and to control the deposition of the drug into the lungs.[1,2]

Excipients like lactose, mannitol, sorbitol, erythritol, anhydrous glucose, trehalose and fumaryl diketopiperazine (FDKP) have been investigated as carriers for use in DPI drugs.[3,4] Some of these excipients are hygroscopic and are therefore not suitable for combination with every drug.[3]

Most formulations in the market use alpha-monohydrate lactose, which has been widely accepted by regulatory authorities.[5] However, health authorities do require extra testing and controls for some parameters, compared with the use of lactose in oral dosage forms. Therefore, inhalation-grade lactose has been developed and is the preferred excipient for the use in DPI formulations.

During the R&D process for a DPI project, it should be understood what kind of functionality needs to be addressed with the lactose. Also in view of quality by design (QbD) regulations,[6,7] the critical attributes of a DPI formulation that determine the functionality should be understood. A number of attributes of excipients have been identified.[8] In this article several selection criteria are described that will determine which grade of lactose is optimal for any specific DPI formulation.

DRUG PROCESSING

Most inhaled formulations contain a highly potent pharmaceutical active that has been micronised and is dosed in low concentrations. Handling of micronised actives is a challenge due to agglomeration. To improve the handling, a carrier is added to de-agglomerate the active during blending. Almost all inhalation-grade lactose would give this functionality. The criterion to be evolved is that the surface area of the lactose is sufficient to de-agglomerate the active particles that stick to the lactose surface.[9] Furthermore, the amount of powder that can be inhaled should be considered.

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DEVICES

Dry powder inhalation devices on the market can roughly be divided into three groups: capsule devices, blister devices and reservoir devices. The first step in a development process of a DPI is the selection of a device. Subsequently, the most important parameters for the selection of the optimal lactose grade are the filling platform, dosing of the drug out of the device and deposition of the drug in the lungs.

Once the device has been selected it has become clearer what the filling platform of the formulation could look like and what type of lactose is needed to fill and empty the device.[10]

One of the challenges for the formulator is to fill a device with the drug and obtain content dose uniformity. Filling systems nowadays can consistently fill small volumes of approximately 5 mg on commercial production scale. Since dosages of some actives are below 1 mg, the formulator will have to increase the mass of the powder with a carrier to ensure proper filling. Formulations containing more than 95% lactose are therefore quite common.

Harry J W Peters
Product Application Specialist
Inhalation
T: +31 545 256703
E: Harry.Peters@dfepharma.com

Dr Gerald A Hebbink
Scientist
T: +31 545 256611
E: Gerald.Hebbink@dfepharma.com

DFE Pharma
Kleverstrasse 187
47574 Goch
Germany

www.dfepharma.com

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Filling Reservoir Devices

Reservoir devices are often filled with a good flowing carrier, because the dosing of the formulation is metered by the device. The metering system requires sufficient flow and constant density of the powder to achieve good content dose uniformity. Good flowing lactose grades with constant density are recommended to be used in these types of devices. The mean particle size will mostly be in the range of 100–200 µm. Good flowing lactose grades are obtained mainly by sieving processes.

Filling Blister Devices

Blisters can be filled with different techniques. All techniques require that the powder stays in the pocket of the aluminium-seal of the blister before it is sealed. Therefore, the powder properties of the formulation should be non-dusting and slightly cohesive. Cohesiveness of the lactose can be increased by milling the lactose or by addition of fine lactose grades to the formulation.

Filling Capsule Devices

The type of lactose chosen here is dependent on the filling system. Capsule filling devices, like drum fillers and piston fillers, will require more cohesive, milled-grade lactose grades.[11] Tamper filling or other volume filling techniques like the "pepper shaker", however, require a free-flowing powder.[12] Sieved lactose grades will in general meet these criteria.

DRUG DEPOSITION

Literature describes that for specific devices the amounts of fine lactose particles plays a significant role in the deposition of the drug.[13,14] Especially for the generic formulator, it is a challenge to meet the requested deposition with the same dose of drug, particularly when using a different device. The parameters that a formulator can use to optimise the deposition are restrained by the design of the device and expanded by the various lactose grades.[15]

DESIGN OF EXCIPIENT

From these selection criteria for excipients, it becomes clear that the excipients need to be designed specifically. There are several ways to do this, such as chemical and mechanical surface modifications.[16,17] However, the most common technique of manipulating particle size distributions of lactose is through milling and sieving operations. By combining several of these techniques, as illustrated in Figure 1, a plethora of lactose grades can be designed.

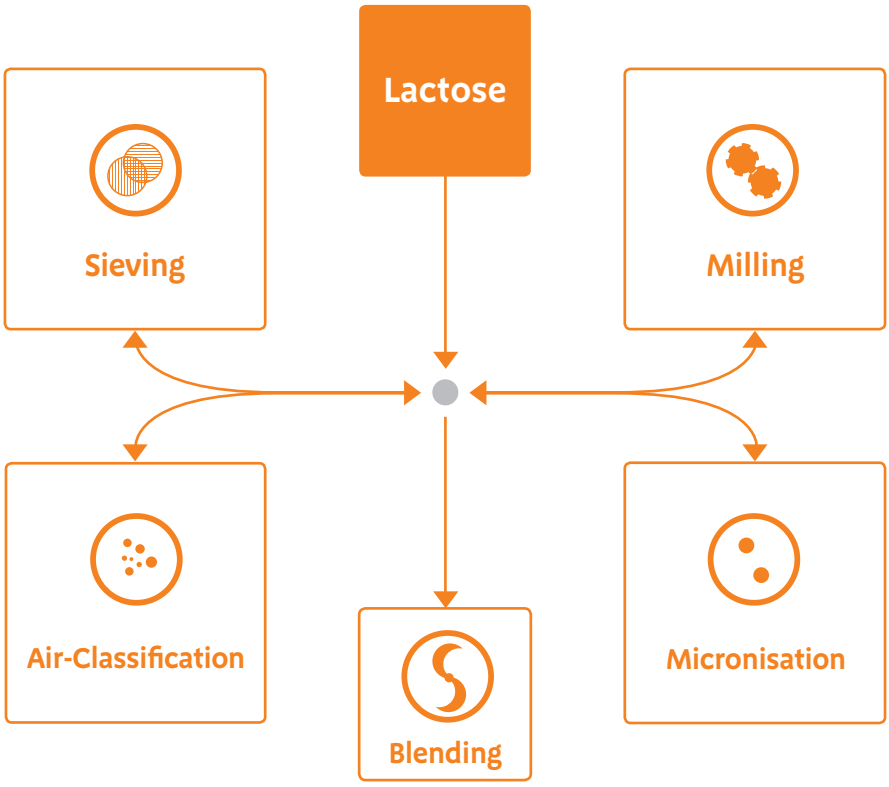

Figure 1: Unit operations and combinations thereof for the design of lactose particle size distribution.

CONCLUSION

The selection of the optimal inhalation lactose grade is based on the device, the filling platform, the concentration of the active, processing of the active and the required deposition of the drug in the lungs. Each formulation will therefore need the excipient to be designed to meet the specific requirements mentioned above. Although this selection is often empirical, support of an experienced excipient supplier can speed up the development process.

REFERENCES

1. *Pilcer G, Amighi K, "Formulation strategy and use of excipients in pulmonary drug delivery". Int J Pharm, 2010, Vol 392, pp1–19.*
2. *Weers JG, Miller DP, "Formulation design of dry powders for inhalation". J Pharm Sci, 2015, Vol 104, pp3259–3288.*
3. *Steckel H, Bolzen N, "Alternative sugars as potential carriers for dry powder inhalations". Int J Pharm, 2004, Vol 270, pp297–306.*
4. *Rahimpour Y, Kouhsoltani M, Hamishehkar H, "Alternative carriers in dry powder inhaler formulations". Drug Discov Today, 2014, Vol 19, pp618–626.*
5. *Edge S, Kaerger JS, Shur, J, in Handbook of Pharmaceutical Excipients 6th ed (eds. Rowe RC, Sheskey PJ & Owen SC) pp362–364, Pharmaceutical Press, 2009.*
6. *Yu LX, "Pharmaceutical quality by design: product and process development, understanding, and control". Pharm Res, 2008, Vol 25, pp781–791.*
7. *Yu LX et al, "Understanding pharmaceutical quality by design". AAPS J, 2014, Vol 16, pp771–783.*
8. *Kinnunen H, Hebbink G, Peters H, Shur J, Price R, "Defining the critical material attributes of lactose monohydrate in carrier based dry powder inhaler formulations using artificial neural networks". AAPS PharmSciTech, 2014, Vol 15, pp1009–1020.*
9. *Ferrari F et al, "The surface roughness of lactose particles can be modulated by wet-smoothing using a high-shear mixer".*

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AAPS PharmSciTech, 2004, Vol 5, e60.
10. *Grasmeijer F, Grasmeijer N, Hagedoorn P, Frijlink HW & Boer AH de, "Recent advances in the fundamental understanding of adhesive mixtures for inhalation". Curr Pharm Des, 2015, Vol 21, pp5900–5914.*
11. *Sim S et al, "An insight into powder entrainment and drug delivery mechanisms from a modified Rotahaler®". Int J Pharm, 2014, Vol 477, pp351–60.*
12. *Edwards D, "Applications of capsule dosing techniques for use in dry powder inhalers". Ther Deliv, 2010, Vol 1, pp195–201.*
13. *Kinnunen H et al, "Extrinsic lactose fines improve dry powder inhaler formulation performance of a cohesive batch of budesonide via agglomerate formation and consequential co-deposition". Int J Pharm, 2014, Vol 478, pp53–59.*
14. *Kinnunen H, Hebbink G, Peters H, Shur J, Price R, "An investigation into the effect of fine lactose particles on the fluidization behaviour and aerosolization performance of carrier-based dry powder inhaler formulations". AAPS PharmSciTech, 2014, Vol 15, pp898–909.*
15. *Grasmeijer F et al, "New mechanisms to explain the effects of added lactose fines on the dispersion performance of adhesive mixtures for inhalation". PLoS One, 2014, Vol 9, e87825.*
16. *Singh DJ et al, "Preparation and evaluation of surface modified lactose particles for improved performance of fluticasone propionate dry powder inhaler". J Aerosol Med Pulm Drug Deliv, 2015, Vol 28, pp254-267.*
17. *Williams D, "Particle Engineering in Pharmaceutical Solids Processing: Surface Energy Considerations". Curr Pharm Des, 2015, Vol 21, pp2677–2694.*

ABOUT THE AUTHORS

Harry Peters is a technical support 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 started working as R&D manager and product application specialist for inhalation grade lactose. He advices 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 iniversities and industry, new characterisation techniques are explored to further understand lactose in dry power formulations.

Gerald Hebbink is a chemist who has been working with lactose for the pharmaceutical industry for over eight years. He has been specialising in lactose for inhalation within DFE Pharma in close collaboration with industry partners and with universities all over the world. This has resulted in co-authorship of peer-reviewed papers on lactose, from production to application.

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