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Exploring the potential of mannitol as an alternative to lactose in dry powder inhalation

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The principle of carrier-based blends is well established in formulations for dry powder inhalation, as it overcomes problems of micronized drug particles often being cohesive and poorly flowable and hence, creating difficulties in powder handling and dosing.¹ In carrier-based blends, micronized drug is adhered on the surface of the carrier and thus, is moved and dosed as if it were a larger particle. For nasal administration, particles larger than 10 µm, probably better than 50 µm, are required to ensure preferential nasal deposition.² Thus, larger particles of carrier-based blends would also be beneficial for deposition. For oral inhalation to the lung, an aerodynamic particle size below 5 µm is needed, hence micronized drug particles in a carrier-based blend must be detached from the carrier upon inhalation. Though not completely understood, the detachment of active pharmaceutical ingredient (API) from carrier particles takes place by dispersion forces that occur during inhalation.

Common strategy: Lactose-based blends

Lactose is the best established material for carrier-based formulations³ and may also act as dispersion modifier if lactose fines are used.⁴ The smooth surfaces of lactose upon crystallization and its unique tomahawk particle shape⁵ render the material very suitable for blending, smooth powder flow and precise dosing. In addition, lactose is a pharmaceutical excipient with minimal safety concerns.⁶

Nonetheless, there are some drawbacks in formulation with lactose that are related to its animal origin, its physical instability with respect to amorphous content⁷ and hygroscopicity, and its chemical reactivity due to its reducing aldehyde group.⁸ This interdicts a combination of lactose and proteins, and necessitates sound control of physical stability during preparation and storage. Further, simple drug/lactose blends do not always lead to desired aerodynamic properties and hence may need further optimization of the carrier.⁹

Benefits of mannitol

These issues are well addressed by the benefits of mannitol, in terms of physical and chemical stability, and are broadened by performance and manufacturing variety. Mannitol is a fully crystalline sugar alcohol with low affinity to moisture and low chemical reactivity.¹⁰ In comparison to other alternative excipient materials that can be considered, such as trehalose or myo-inositol, mannitol is listed as a “generally recognized as safe” (GRAS) substance by the US Food and Drug Administration (FDA) and has already been approved for inhalation as an API and an excipient, depending on the dose (as in Bronchitol [Pharmaxis, AUS] and in Exubera [Pfizer, UK]). The use of mannitol as an alternative carrier to lactose has been addressed by several research groups within the last years and still is of great interest.¹¹ Morphology of particles can affect agglomerate strength and, in turn, the

aerosol performance of a powder at various levels and hence plays an important role.¹² The particle shape of commercially available milled mannitol is elongated or irregular with longitudinal grooves, whereas processed mannitol, commercially available for direct compression applications, is a granule-like, solid material with rough surface structures.¹³ This morphology renders mannitol particles ideal carriers for preparation of highly homogeneous blends with low amounts of micronized drug material without segregation tendencies. However, this may be disadvantageous when it comes to drug particle detachment during inhalation. Mannitol can also be processed by spray drying, resulting in crystalline, more or less spherical particles, which allows preparation of carriers for oral inhalation with tailor-made properties.^{14,15}

Our research group looked at different mannitol qualities and their suitability for carrier-based blends in nasal and oral inhalation.

Case study 1: Processed mannitol for carrier-based nasal dry powder formulations

Spray-dried microparticles (mean particle size (x_{50}) of 2.7 µm) were produced from chitosan to enable delivery of a protein (bovine serum albumin, BSA, as a model drug) to the nose by a dry powder nasal sprayer. Initial experiments with a nasal cast model¹⁶ showed that pure microparticles were not preferentially deposited

in the nasal cavity, but will pass the nose due to their excellent aerodynamic properties. Hence, carrier-based dry powder formulations with spray-dried particles and different mannitol qualities (45-90 μm sieve fraction of Pearlitol 200 SD and Pearlitol 160 C, Roquette, France) were assessed with respect to their ability to fix the microparticles and force them to deposit in the cast model. The intention was that the blend should become entrained by the air released from the active nasal powder reservoir device (the PowderJet from RPC Formatec, Mellrichstadt, Germany), however, microparticles should not get detached from the carrier.¹⁷ It was shown that spray-granulated mannitol with its rough surface structure was able to adhere the spray-dried particles, efficiently leading to highly homogeneous blends. The powder blend was delivered from the device, but dispersion power was low enough to keep the drug particles on the carrier, leading to small post-nasal fractions below 10%.¹⁸ Interestingly, this does not exclude the use of such blends for oral inhalation, as dispersion forces in an oral inhaler are much higher. It was shown in another study that particle-engineered mannitol is a versatile carrier for oral dry powder inhalation.¹⁹

Case study 2: Tailored mannitol particles for carrier applications in oral inhalation

Spray drying on a pilot-scale spray dryer has been utilized to produce mannitol particles of varying geometric size, shape and surface microstructure.²⁰ These particles were tested as carriers in carrier-based blends with spray-dried, spherical salbutamol sulphate and budesonide particles, with respect to their aerodynamic performance *in vitro* (determined as fine particle fraction [FPF], with an aerodynamic size below 5 μm , utilizing the NGI and the Novolizer device). It was shown that the performance of spray-dried mannitol particles as carrier particles was dependent on the interplay of drug and carrier properties. Particle shape (round

versus indented) had the principal impact on the FPF, as drug particles accumulated in indentations were hindered from detachment by the air flow.²¹ This effect was more pronounced for hydrophilic drugs than hydrophobic drugs, due to more distinct interactions between drug particle and carrier. An additional effect was seen for rough surface microstructures, which increased the contact points for spherical drug particles and with this, decreased the FPF. Carrier size was without significant effect for spherical shaped carriers, but FPF decreased for larger carrier particles if indentations occurred simultaneously. These results can foster selection of the best carrier properties for a specific need and production thereof by spray drying.

Conclusions

Results support the use of processed mannitol in carrier-based blends for inhalation. Depending on the active pharmaceutical ingredient, the route of delivery, intended deposition and delivery device, the optimal mannitol carrier for a defined delivery objective can be selected from different commercial qualities or from tailor-made spray-dried particles. Its relatively low hygroscopicity and chemical reactivity offer additional benefits, which broadens its possible application for a wide range of APIs including proteins.

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