Excipients in DPI Formulations

Understanding how lactose and other excipients can affect formulation performance

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Because most conventional dry powder inhaler (DPI) products contain an extremely small dose of active pharmaceutical ingredient (API) in the form of a very fine, highly cohesive powder, the majority of DPIs rely on excipients, especially lactose, to overcome formulation performance problems. Although a few DPIs, such as AstraZeneca's Turbohaler Pulmicort budesonide product, include no excipients at all, the majority of dry powder formulations contain inhalation grade lactose. The selection of specific characteristics of the lactose used, as well as the use of ternary excipients, can have a significant impact on handling, dose reproducibility, and respiratory deposition efficiency.

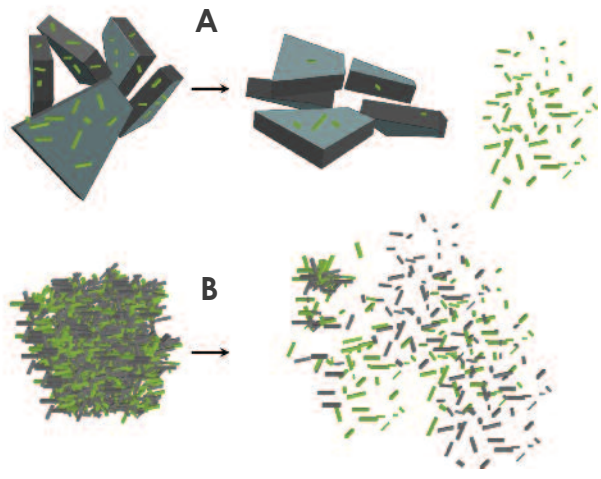
In order to ensure that an inhaled drug avoids impaction in the upper tracheal region, API particles must have an aerodynamic diameter less than 6 (m. Particles in this size range have a high surface area to mass ratio, making these powders highly cohesive and adhesive. APIs for inhalation are therefore usually very difficult to handle. Furthermore, DPIs usually contain therapeutic doses of less than 500 mcg, below the resolution of most fillers and checkweighers, so metering pure API into capsules or blisters would present major challenges even if the powder flowed freely. The addition of lactose increases flowability and adds enough bulk to outweigh the variability of filling and checkweighing equipment, allowing for greater uniformity.

Lactose/API mixtures can take one of two forms: agglomerated systems or carrier systems. Both types of mixture bind the micronized drug to form larger particles that flow more freely, can be weighed more easily, and are less likely to stick to the insides of the inhaler device than would API alone. In agglomerated systems like that in AstraZeneca's Oxis formoterol formulation, a fine grade of lactose having a similar particle size to that of the API is added to create a spheronized mass. The more common method involves using larger excipient particles that form ordered mixes with the much smaller drug particles adhering preferentially to the carrier (Figure 1A). Glaxo SmithKline's Ventolin (salbutamol sulfate), Novartis's Foradil (formoterol), and Vectura's Clickhaler (budesonide or formoterol), for example, all use excipient carrier systems.

The aerodynamic diameter of either the agglomerate or carrier is too large for the product to reach the bronchioles, so the drug must be liberated from the lactose particles in order to achieve an effective deposition. For agglomerates, the force supplied by the device and/or the patient's respiration deagglomerates the mixture or detaches the API from the carrier, resulting in an inhalable form of both the active ingredient and the excipient (Figure 1B). However, in carrier systems, detaching the API from the carrier requires overcoming relatively high interfacial forces that bind the mixture together. The device and/or patient may not be able to generate enough force to overcome the adhesion; as a result, most dry powder inhalers have inherently poor aerosolization efficien-

Figure 1

Schematic representation of (A) carrier based DPI formulation and (B) agglomeration based DPI formulation prior to and post inhalation.



cies, with many marketed products having respiratory fine particle fractions of less than 30% [1].

Despite the fact that consistent dosing represents a critical issue with major potential consequences, the pharmaceutical industry has not historically made overall respiratory deposition efficiency of DPI products a core priority. However, recent studies have suggested that the choice of lactose supplier and/or batch can result in significant differences in performance with low dose formulations [2-4], leading to a new focus on improving the aerosol performance and dose reproducibility of conventional DPI formulations. Modifying the size and morphology of lactose carriers, along with the addition of ternary excipients, can greatly enhance the efficiency and consistency of API deposition.

The mechanisms of carrier systems

Achieving higher respiratory fractions of API in carrier based formulations requires an understanding of the mechanisms influencing the aerosolization process. In the ordered mixtures typical in dry powder formulations, the larger lactose carrier contains regions of high and low adhesion termed "iso-energetic regions" or "active sites" [5, 6] that preferentially attract micronized drug particles and that may correspond to peaks and clefts on the carrier surface, variations in surface chemistry due to crystalline face orientation, and/or the presence of crystalline-amorphous domains (Figure 2).

Variations in surface energy on the carrier result in variable adhesive forces between the lactose and the API particles adhering to the carrier during the dynamic mixing process. As a result, different levels of energy supplied by the inhaler device or generated by the patient's respiration will result in varying amounts of therapeutic dose deposition, especially as the API dose is reduced [7]. In some cases, the adhesion potential of certain sites on the carrier may exceed the energy generated during the inhalation maneuver, and drug particles adhered to those sites will remain attached to the carrier. For very small doses, those irreversible adhesions can create a significant reduction in the percentage of drug deposition.

Modifying excipient systems to enhance performance

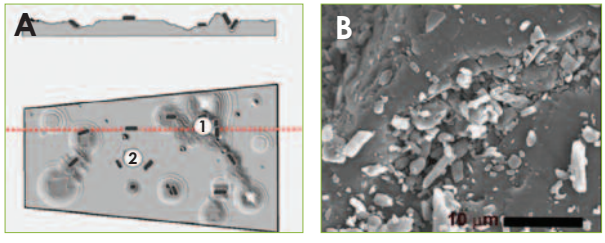
Early DPI systems used standard excipient grade lactose, but increased regulatory awareness of product specifications and an improved understanding of carrier behavior have led to the availability of lactose products specifically designed for inhalation formulations. Selecting the optimum grade of lactose for the formulation has become easier since a number of suppliers are now offering multiple size classifications and forms [7]. These new grades offer specific characteristics required for DPI formulation and in most cases are produced independently from their bulk excipient counterparts (Table 1).

A number of studies that have demonstrated improved aerosol performance in carrier-DPI systems with the addition of fine excipient particles, and many suppliers now offer microfine and milled lactose as part of their inhalation grade lactose portfolios as a result. Fines, usually lactose with an aerodynamic diameter of less than 10 (m [8-11], may be added directly to the formulation [9, 11] or by milling the carrier [12, 13] prior to the addition of the API. Either way, fines addition generally results in increased API respirable fraction. For example, when finely milled lactose was added at a concentration of 10% by weight to a carrier blend of bovine serum albumin (BSA), the fine particle fraction after aerosolization increased by almost 20% [11]. Another study produced similar improvements in aerosolization efficiency for salmeterol xinofoate with equivalent quantities of added fines [9]. Two other recent studies have demonstrated that milling large lactose particles to achieve a higher fines content prior to mixing improves aerosol performance in the carrier/API mixture. For example, Young et al. demonstrated that milling-induced fines concentrations of 5% resulted in a 10% increase in FPF [12].

The mechanism for the improved aerosolization with the addition of fines is not well understood, though two possibilities have been suggested: 1) excipient fines fill high-energy sites on the larger carrier particles, displacing the API to lower-energy sites or 2) excipient fines form multiple agglomerates with the API, dispersing relatively easily during the aerosolization process. In all likelihood, both processes are present and play significant performance modifying roles depending on the size of the dose and the specific formulation.

Figure 2

(A) Schematic of the distribution of active sites on the surface of a lactose carrier and (B) electron microscopy image of API particles filling a



Modification of the carrier surface

Another method for improving aerosolization involves modifying the surface of a lactose carrier to optimize the geometry of the carrier/API contact. Studies have shown that aerosol performance of a micronized API correlates to the rugosity of the carrier due to differences in the relative contact area between the two types of particles [4]. The morphology of the carrier determines the orientation of the smaller particles on its surface; the greater the contact area between the carrier and the micronized drug, the greater the adhesion. When the interstices in the carrier surface are smaller than the smallest face of the API particles, the drug may have little contact with the lactose and therefore relatively low adhesive force. The number of irreversibly filled active sites is greatly reduced, and the API particles detach relatively easily. Larger clefts, on the other hand, may allow for contact by multiple API surfaces, increasing adhesion and irreversible attachments (Figure 3).

The surface morphology of lactose is generally inconsistent, leading to an uneven distribution of high energy sites. A number of studies have therefore focused on reducing the heterogeneity of the carrier surface by "smoothing," etching or controlled crystallization [14-17]. Increasing the homogeneity of the carrier's surface geometry can generate a more even distribution of energy, resulting in greater consistency and a fewer irreversibly filled sites. One recent study found that controlled etching of lactose carrier particles resulted in fewer high activity sites when compared to untreated carriers of similar size [14].

One smoothing technique utilizes the addition of ternary agents during high shear mixing. The addition of magnesium stearate, as in the Trinity-Chiesi dry powder formulation of BDP-Pulvinal, has been shown to improve aerosolization by reducing interfacial energy and the resulting API-carrier adhesion [15, 16, 18-21]. In one study, high shear mixing of magnesium stearate with lactose resulted in a significant decrease in the adhesion of beclometasone diproprionate (BDP) to the carrier surface as measured by colloid probe microscopy [16]. Compared to an untreated lactose/BDP carrier system, the mixture with magnesium stearate produced a fourfold increase in fine particle dose [16]. In another study, magnesium stearate improved the aerosolization of salbutamol sulphate from a lactose carrier, with up to a 15% increase in FPF [19].

Conclusion

The choice of excipient used will continue to play a major role in DPI product performance. With excipient companies focusing on specific inhalation grade

Table 1

Inhalation grade pharmaceutical lactose suppliers

Supplier	Product name	Grades available	Specification
DMV international	Respitose®	Customer specific grades and sieve classifications	Sieved, milled, granulated, spray dried, anhydrous, micronised
Friesland Foods, Domo®	Lactohale®	LH100 LH200/201 LH300 Customer specified grades	Sieve classified Milled Microfine
Meggle	Inhalac®	70 120 230 Customer specified grades	d0.9 = 200 μm d0.9 = 150 μm d0.9 = 100 μm
Sheffield Ingredients	Anhydrous NF inhalation Monohydrate NF inhalation	40M 40M 80M 120M 120MS	Sieve classified

material, a greater range of specific excipient grades with defined performance parameters are likely to become commonplace in the future. Due to the flurry of research within the DPI sector, an increased understanding of API-carrier interactions will allow a focus on developing new technologies/excipient systems that result in improved API aerosol performance with reproducible emitted dosing.

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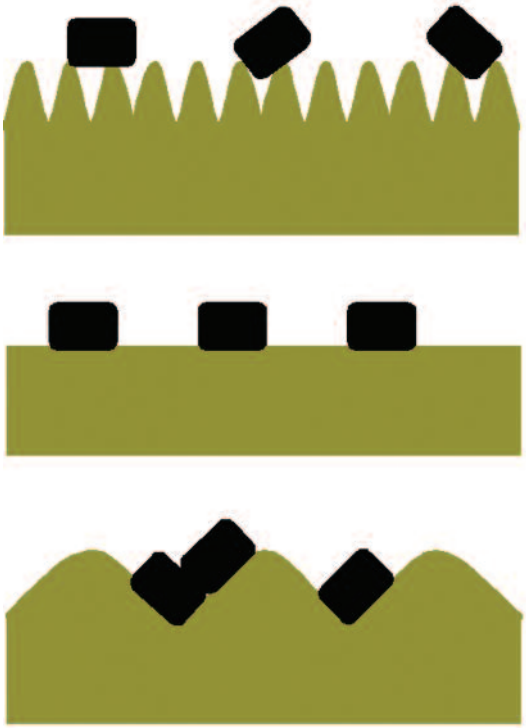
Figure 3

Schematic of API particle interactions with carriers of different rugosity. Top to bottom indicates increasing contact geometry and reduced API aerosol performance



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