New Developments in Spray-Dried Lactose

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Spray-dried (SD) lactose was introduced to the pharmaceutical market in the 1960s as an excipient that enables direct compression of formulations in a simple manufacturing process (1). To this day, lactose remains one of the most popular excipients for active pharmaceutical ingredients (APIs) whose dose makes them suitable for direct compression. Several manufacturers make and sell SD lactose, and a pharmaceutical formulator must understand the variables that control performance to select the right grade for an application. This article begins with a description of the structure of SD lactose, followed by a review of the variables that can affect its compressibility, and concludes with a look at a possible next-generation product.

The structure of SD lactose

SD lactose is created by spray-drying a suspension of crystals of α-lactose monohydrate (primary particles) in a saturated aqueous solution of lactose. The resulting product is then sieved to yield a narrow-size distribution, which is

Recent advances in spray-drying technology have led to the production of new directly compressible lactose grades with distinct advantages.

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Figure 1: The structure and typical particle-size distribution of SD lactose.

Compressibility. Crystals of α-lactose monohydrate that are large enough to flow reasonably well for direct compression are not particularly compressible (3). It is a brittle material that fragments on compaction (4), although other studies have shown that it has a low fragmentation propensity (5). The compression behavior changes from brittle to ductile when the particle size is reduced to 45 µm or smaller (6). Different sieve fractions of crystalline α-lactose monohydrate have different compaction behaviors—finer fractions generally form stronger compacts at a given compaction pressure (3).

Compaction properties of SD lactose are influenced by the particle size of the primary crystals. Primary particle size can be determined by disruption of the SD agglomerates by sonication in a nonsolvent such as saturated isopropanol, followed by size analysis of the resulting suspension using a technique such as laser diffraction.

The data in Figure 2 show the compaction of 15 experimental
grades of SD lactose that vary in their primary particle size and amorphous content (7). In this example, tablets of 500-mg weight and 13-mm diameter were made using a compaction force of 10 kN. The results of this study indicate that decreasing the primary particle size results in substantially harder tablets over the range of amorphous contents, including the samples that were made with 15% amorphous lactose as in a typical commercial product.

The latest generation of SD lactose exploits this phenomenon. Figure 3 shows the compaction profiles of two commercial products with median primary particle sizes of 34 µm and 20 µm. Both products contained 17% amorphous lactose and were equilibrated at 30% RH before compression. The SD lactose was lubricated with 0.5% magnesium stearate, and the tablets were compressed at 250-mg weight using 9-mm punches on a Kilian rotary press. The product containing the finer lactose produced tablets that were 30–50% harder with the same compaction force, which is a potentially important gain for some difficult-to-compress formulations.

It is well known that compaction properties of many excipients are affected by their water content. For example, the use of microcrystalline cellulose (MCC) can lead to an increase in tablet strength and a decrease in porosity after exposure to moisture, in which the water acts as an internal lubricant within individual microcrystals (8). Moisture has a greater, more complex effect on the compaction of SD lactose.
than it does for MCC. Figure 4 shows the compaction of a mixture of 99.5% SD lactose and 0.5% magnesium stearate at three different water activities using compaction forces of 10–20 kN. As water activity increases from 0.1 to 0.3, there is an increase in tablet hardness at every compaction force, but as water activity is increased further to 0.6, the tablet hardness declines dramatically. This is explained as follows. Atmospheric water is absorbed predominantly by the hygroscopic amorphous lactose fraction, and the initial increase in hardness again is thought to be a result of lubrication by water. However, water content affects the glass transition temperature ($T_g$) of amorphous lactose, and at a critical value, the $T_g$ will drop below ambient temperature. When this occurs, the amorphous material changes from its glassy state to a rubbery state, at which point mutarotation and crystallization to $\alpha$-lactose monohydrate occurs. At ambient temperatures, this transition occurs at water activities of 0.45–0.5. Crystallization by this mechanism is apparent both as a reduction in the content of $\beta$-lactose in the SD lactose and, more important for the formulator, as a reduction in compressibility of the excipient.

Typically, SD lactose is shipped from the manufacturer with a water activity of 0.15 and packaged in protective containers to minimize water uptake. These precautions enable a two-year expiration date to be applied.

**The next generation**

Recrystallization of amorphous lactose may be regarded as undesirable, even if it is controlled by suitable packaging. Therefore, the stabilization of the matrix of SD lactose can be beneficial. A suitable technique for this is rapid recrystallization.

Crystallization to $\alpha$-lactose monohydrate as described in the previous section is relatively slow depending on the mutarotation process. Recently, it has been discovered that under certain conditions of temperature and humidity, fast crystallization of amorphous lactose can occur, not to $\alpha$-lactose monohydrate, but to a stable mixed $\alpha/\beta$ crystal form of lactose in which the $\beta$-lactose content of the amorphous matrix is maintained (9). Thus, it is possible to produce a version of SD lactose in which the primary part-
cles are embedded in a stable mixed crystal matrix rather than in an amorphous matrix. This material is known as stabilized SD lactose.

The moisture sorption isotherm of stabilized SD lactose at 20 °C is compared with those of α-lactose monohydrate and conventional SD lactose in Figure 5. The hygroscopicity and recrystallization of the amorphous fraction of conventional SD lactose are apparent in its isotherm. There is a rapid increase in water content from 20 to 50% RH, at which point crystallization occurs and the water content decreases again. In contrast, stabilized SD lactose exhibits no such transition as the water content increases only slightly between 20 and 90% RH. Therefore, stabilized SD lactose represents another potential step in the development of improved direct compression excipients.

References