Directly compressible lactose: general considerations.

DMV International
The ingredients of success

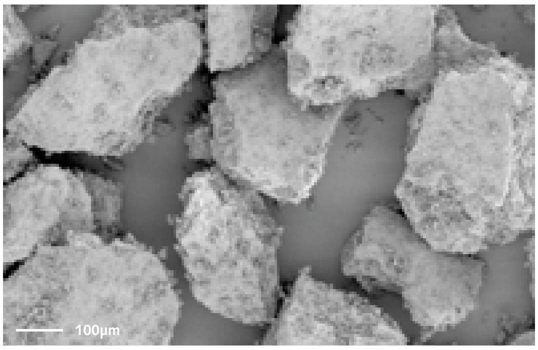
Summary

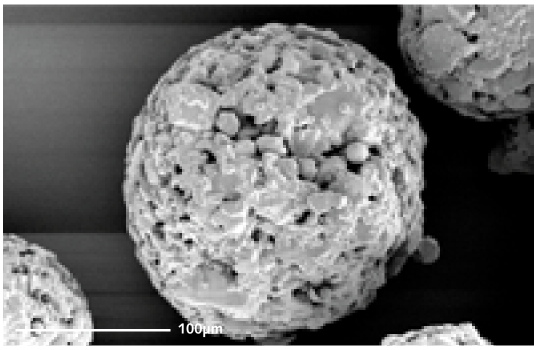
Lactose monohydrate in a fine form can be compressed into hard tablets, but it exhibits poor flow. The goal of the secondary processes that convert lactose into directly compressible grades is to maintain the inherent compressibility of fine lactose, whilst improving the flow.

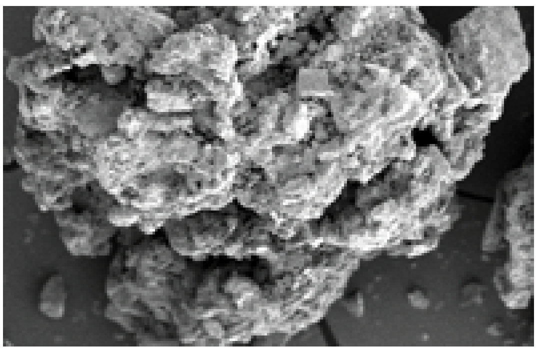
This is done by three means:

- Spray drying gives spherical agglomerates that exhibit excellent flow and compaction properties.
- Granulation gives irregular agglomerates that flow well and compress well.
- Roller drying gives lactose mainly in the anhydrous β-form with excellent compaction properties.

This introduction to directly compressible lactose describes these three processes, and shows how each processing technique influences the properties of the products.







Introduction

Lactose is processed in three different ways in order to make it directly compressible. These three processes are:

Process	DMV Products
Spray drying	Pharmatose DCL11
	Pharmatose DCL14
Fluid bed granulation	Pharmatose DCL15
Roller drying	Pharmatose DCL21
(anhydrous lactose)	Pharmatose DCL22

Before a description of each of these three processes, two introductory sections are included in this article, the first dealing with isomers of lactose and the second briefly describing the compression properties of lactose. These sections form the basis for a more detailed understanding of direct compression lactose.

Isomers of lactose

Lactose is a disaccharide consisting of a galactose and a glucose unit. It exists in two isomers differentiated by the orientation of the hydroxyl group at position 1 (circled) in the glucose unit (see figure 1).

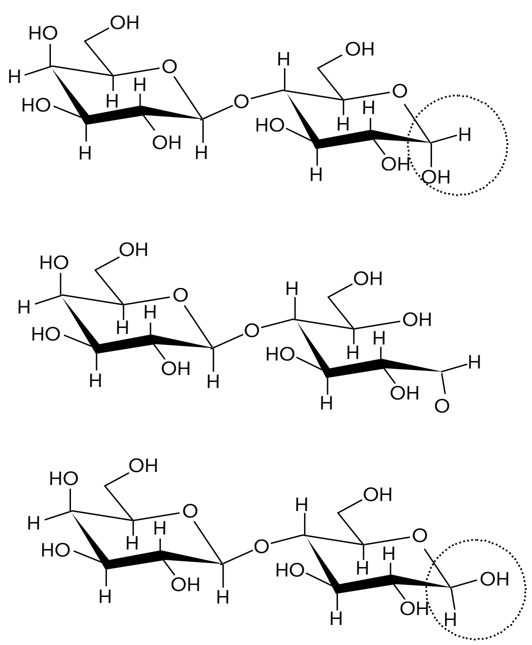


fig. 1: α-Lactose (top) and β-lactose (bottom).

In aqueous solution, these two isomers exist in equilibrium. The equilibrium value is temperature dependent, but between 0°C and 100°C the β-/α-lactose ratio varies from 62/38 to 58/42, irrespective of which isomer is used to form the solution[1]. The interconversion (mutarotation) of the isomers takes place through an open ring intermediate (the middle structure in figure 1) and the equilibrium can take a few hours to establish at room temperature[1]. The two isomers have different solubilities in water, and this property is important in determining how lactose crystallizes from aqueous solution. Below 93.5°C, a solution that is saturated with α-lactose is not saturated with β-lactose, and therefore below 93.5°C α-lactose monohydrate crystallizes. Conversely, above 93.5°C a solution that is saturated with β-lactose is unsaturated with α-lactose, and on crystallization the anhydrous β-form predominates[1].
When lactose is crystallized quickly there is little opportunity for mutarotation, and both α-lactose and β-lactose are present.

Mutarotation in solution and the crystallization characteristics of lactose solutions are important factors in the production of directly compressible lactose.

Compaction of lactose

Lactose compacts predominantly by brittle fragmentation, but individual crystals do not show a particularly high propensity to fracture on compression[2]. The consequence of this property is that the surface area increase on compaction is limited, and when relatively coarse free flowing lactose monohydrate crystals are compressed the increase in surface area available for bonding is insufficient to form hard tablets. On the other hand, finely milled lactose monohydrate, which possesses enough surface area for good tablet formation, does not flow at all well. One approach to the production of directly compressible lactose is therefore to utilise the good inherent compressibility of fine lactose monohydrate within larger, better flowing secondary particles formed by granulation or by spray drying. A second approach is to modify the crystal form of lactose into something more brittle, so that more extensive fragmentation on compaction leads to more surface area for bonding. This material is roller dried anhydrous lactose.

The means of manufacture of these three forms of directly compressible lactose, some variations that are possible within each process, and the properties of the resulting products are discussed briefly in the next three sections.

Spray dried lactose

Manufacture

Spray dried lactose is formed by spray drying a suspension of α-lactose monohydrate in an aqueous lactose solution. The two lactose components of the suspension result in two different components of the product. On spray drying the dissolved lactose component dries almost instantaneously, and therefore no significant mutarotation of the lactose occurs. Thus, this fraction gives rise to a significant proportion of β-lactose in the final product. Additionally, the rate of drying means that there is little or no opportunity for crystal formation and the dissolved lactose results in an amorphous component in the product. The crystals of α-lactose monohydrate that are originally suspended are unchanged during the spray drying process and appear in the final product embedded in the amorphous matrix of α- and β-lactose.

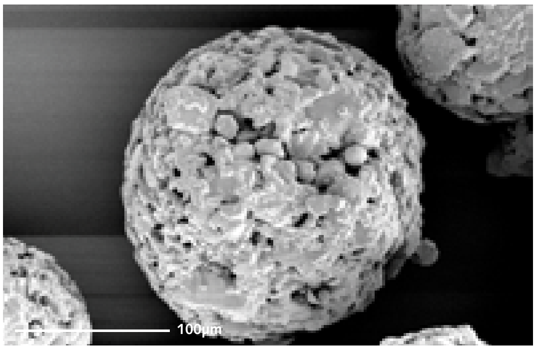


fig. 2: A spray dried lactose particle.

Figure 2 shows an SEM photograph of a typical spray dried lactose particle, where the fine crystals of α-lactose monohydrate can clearly be seen embedded in the amorphous matrix. The nearly spherical shape of the particle is characteristic of the spray drying process. Typically, spray dried lactose contains about 80% to 85% of crystalline lactose and 15% to 20% of amorphous lactose.

Properties

The flow properties of spray dried lactose are excellent, a result of the narrow particle size distribution and the spherical nature of the particles. Thus spray dried lactose typically exhibits an angle of repose of 31° to 33°, and a Flodex index of about 4mm to 6mm. The Flodex Index represents the smallest circular hole through which a powder will consistently flow[3].

Compression of spray dried lactose is, in part, influenced by the particle size of the embedded crystals of α-lactose monohydrate[4] (hereafter referred to as the primary particle size or PPS), and the advantage of reducing the primary particle size of spray dried lactose is shown in the compression profiles in figure 3.

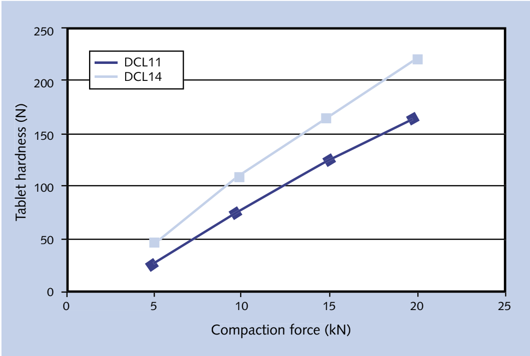


fig. 3: Typical compression profiles of Pharmatose DCL11 and DCL14.

These profiles were generated by compression of Pharmatose DCL11 (PPS typically 35µm) or DCL14 (PPS typically 23µm) lubricated with 0.5% magnesium stearate. Both Pharmatose DCL11 and DCL14 give hard tablets, but Pharmatose DCL14, with a finer primary particle size, has superior compression properties.

The amorphous fraction of spray dried lactose compresses by plastic deformation, and it is plasticized by water. The effect of plasticisation is shown in figure 4, where spray dried lactose has been conditioned at 10%, 30% and 60% RH before compression.

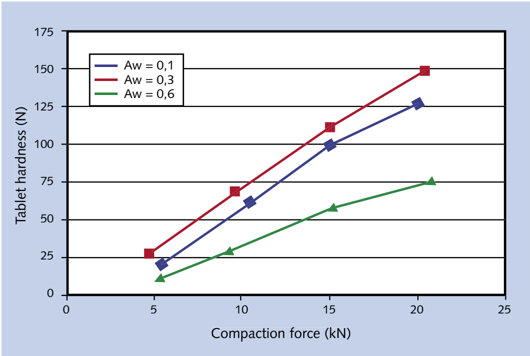


fig. 4: The effect of relative humidity on the compression of spray dried lactose.

There is an improvement in compression up to 30% RH conditioning, but then a decrease at 60% RH. The explanation is that at 30% RH the extra water is acting as a plasticiser allowing more deformation of the amorphous content. At 60% RH however, the amorphous material can crystallize to α-lactose monohydrate. For this reason Pharmatose DCL11 and DCL14 are supplied in protective packs to prevent water ingress into the product and thus to prevent crystallization of the amorphous fraction.

In summary, spray dried lactose is particularly suitable when excellent flow and compression properties are required. Pharmatose DCL14 should be used where extra compressibility is needed. The protective packaging for Pharmatose spray dried products is an important stability factor.

Granulated lactose

Manufacture

Granulated or agglomerated lactose is made by granulating crystals of α-lactose monohydrate with water or a lactose solution in a fluid bed processor. As with spray-drying, there is little chance for mutarotation of the dissolved lactose during the granulation process, and therefore a matrix containing both α- and β-lactose is formed. Unlike spray-dried lactose however, this matrix is not amorphous.

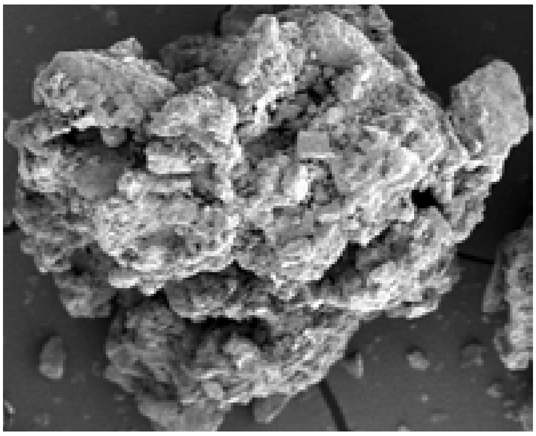


fig. 5: A particle of granulated lactose.

Figure 5 shows a scanning electron micrograph of Pharmatose DCL15. The most obvious difference from spray-dried lactose is the less regular appearance of the particles, a result of the fluid bed processing technique.

Properties

Fluidised bed granulation is the preferred technique for manufacture of granulated lactose for an important reason. The bulk density of lactose granules affects their compression properties, porous low density granules giving harder tablets than high density granules[5], and fluidised bed granulation is therefore well suited to the production of low density granules.

The β-lactose content of granulated lactose is determined by the relative amounts of lactose crystals and lactose solution used in manufacture, a higher proportion of solution resulting in a higher β-lactose content, and this has a bearing on the compressibility of the granules. Figure 6 shows the compaction profiles of granulated lactose with different β-lactose contents.

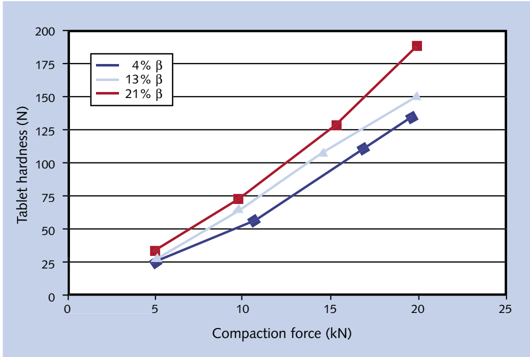


fig. 6: Compression of granulated lactose with different β-lactose contents.

It appears that the granules with the higher content produce harder tablets. However, it must also be noted that increasing the β-lactose content gives a decrease in water content by Karl Fischer, and the granules containing 21% β-lactose fall outside the European and US pharmacopoeial specification for this parameter. Taking this into account, Pharmatose DCL15 was developed to contain the highest β-lactose content consistent with official requirements.

Because the granulated lactose does not contain an amorphous fraction it is relatively insensitive to moisture.

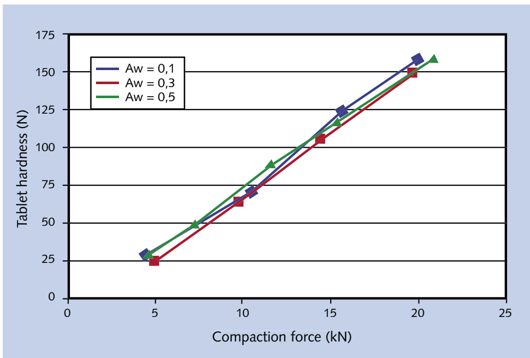


fig. 7: Effect of relative humidity on the compression of granulated lactose.

Compare figure 7, which shows the effect of conditioning granulated lactose, to figure 4 which is the equivalent for spray dried lactose. Compression of Pharmatose DCL15 is very much independent of moisture content.

Roller dried anhydrous lactose

Manufacture
The manufacturing process for anhydrous lactose is quite different form conventional granulation or spray drying. An aqueous solution of lactose is applied to a heated roller above 93.5°C, resulting in rapid drying of the solution and the formation of film of anhydrous lactose rich in the β-isomer.
This film is removed from the roller, milled and screened to give the final product.

A scanning electron micrograph of Pharmatose DCL22 is shown in figure 8 where the structure of milled flakes is apparent.

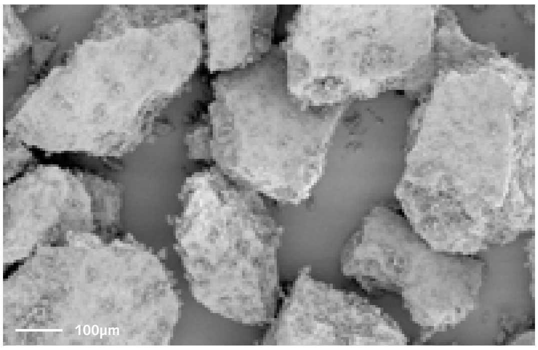


fig. 8: Particles of Pharmatose DCL22.

Roller dried anhydrous lactose contains the highest β-lactose content of all types of directly compressible lactose, typically 75% to 80%, resulting in different compaction properties.

Properties

The shape of the particles of roller dried lactose suggests that the flow will not be as good as that of spray dried lactose, and this is indeed the case. However, flow can be significantly improved by careful control of the milling and sieving process, and hence the particle size distribution.
This difference can readily be demonstrated by comparison of Pharmatose DCL21 which typically has a Flodex Index of 18-24mm, with the free flowing version Pharmatose DCL22 which typically has a Flodex Index of 6-8mm.

On compaction, roller dried anhydrous lactose fragments more readily than α-lactose monohydrate. This was shown by measurement of the specific surface area of tablets made from these two materials. The increased fragmentation propensity, compared to α-lactose monohydrate, results in more surface area for bonding, and consequently harder tablets[2]. The brittle nature of roller dried anhydrous lactose has further advantages for scale up of a formulation. Firstly, it has a very low lubricant sensitivity ratio, this property being defined as the reduction of tablet strength formed from granules lubricated with 1% magnesium stearate compared to tablets formed from unlubricated powder[5]. Robustness to lubricant effects is also demonstrated by a magnesium stearate mixing time study[6], and data adapted from this publication are shown in figure 9.
Microcrystalline cellulose gives the hardest tablets initially, but it shows more sensitivity to mixing time than either spray dried or anhydrous lactose.

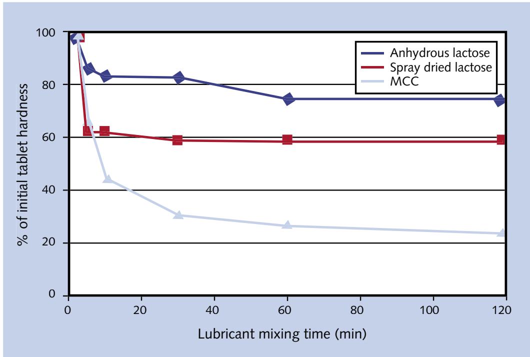


fig. 9: The effect of magnesium stearate mixing time on tablet hardness. Adapted from Bolhuis et al[6].

Secondly, brittle materials tend to exhibit low strain rate sensitivities[7]. Strain rate sensitivity (SRS) is determined using a compaction simulator and is defined as:

$$SRS = \frac{100*(Py_2 - Py_1)}{Py_1}$$

Where Py_1 and Py_2 are the yield pressures determined at punch velocities of 0.033mm.s^{-1} and 300mm.s^{-1} respectively. Higher values of SRS are typical of materials that deform plastically. Very brittle materials such as dibasic calcium phosphate have essentially no strain rate sensitivity.

Material	Strain rate sensitivity
Spray dried lactose	19.2
Anhydrous lactose	20.3
Microcrystalline cellulose	38.9
Mannitol	46.4
Maize starch	49.3

table 1: Strain rate sensitivity of a number of common excipients, from Rowe et al[7].

From the table it can be seen that both spray dried and anhydrous lactose have low SRS values.

Comparison of three types of directly compressible lactose

The above discussion is intended to allow the formulator to select the preferred type of directly compressible lactose for a particular purpose. Important properties for direct compression are compression and flow, and these are summarized for the five Pharmatose DCL excipients in figures 10 and 11 respectively.

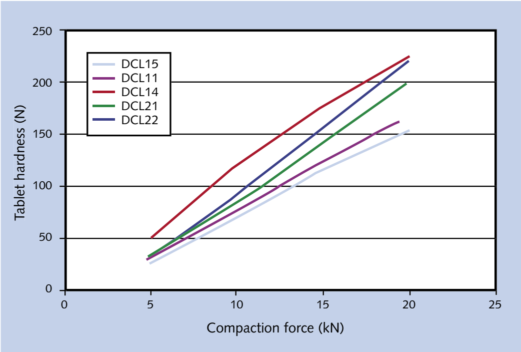


fig. 10: Comparative compression profiles of Pharmatose DCL excipients.

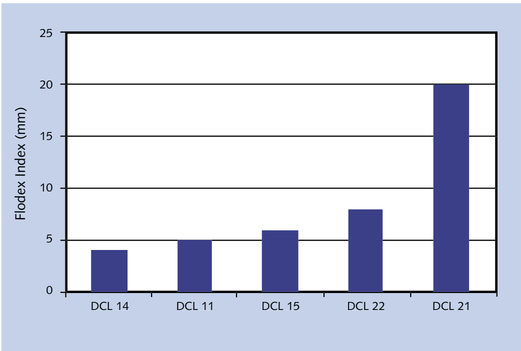


fig. 11: Comparative flow properties of Pharmatose DCL excipients.

Spray dried lactose, particularly Pharmatose DCL14, has excellent compression and flow properties, and is a good choice when both of these aspects are important. But as discussed above, the compaction properties of spray dried lactose may change according to the relative humidity to which it has been exposed.

Spray granulated lactose (Pharmatose DCL15) is not sensitive to relative humidity and is a good choice for many applications where the superior flow and compaction of spray dried lactose is not needed.

Anhydrous lactose also has excellent compression properties, and with Pharmatose DCL22 the traditional drawback of anhydrous lactose (modest flow) has been overcome.

References

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