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White Paper

Advantages of Mannitol in Pharmaceutical Granulation Processes – A Comparison of Different Polymorphic Forms

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Granulation is employed during production of oral dosage forms to convert small particles of powder ingredients and the active pharmaceutical ingredient (API) into large, free-flowing, dust-free, compressible granules, ensuring uniform distribution of ingredients throughout the resulting mixture.

There are several granulation processes available; the most widely used in the pharmaceutical industry is wet granulation.

The wet granulation process generally includes blending, wetting, wet mass stage, drying and sizing. Several types of process equipment can be used:

- Low-shear processes use very simple mixing equipment. This approach can take a considerable amount of time to achieve a uniformly mixed state.
- High-shear processes use equipment that mixes the powder and liquid at a very fast rate using high shear forces, and thus accelerate the manufacturing process.
- Twin-screw granulation can continuously manufacture wet granulate powders at higher space-time yield and improved product consistency.
- Fluidized bed granulation is a multiple-step process in which the powders are pre-heated, granulated and dried in the same vessel. This approach allows close control of the granulation process.

Success of a wet granulation process depends on selection of appropriate excipients and choice of suitable process parameters which lead to excellent binding and compaction properties and flow. Among the most widely used fillers and binders in oral dosage forms are lactose, cellulose derivatives and calcium phosphates.

Interest in the use of mannitol as a filler/binder, however, is increasing due to its physicochemical properties such as low hygroscopicity in comparison to other commonly used filler/binder excipients (Figure 1) and chemical inertness as well as its advantageous tableting behavior including compactibility and the ability to form extremely robust tablets.[1] It also has a good taste and mouthfeel enabling its use for chewable, sublingual and orodispersible tablet formulations.

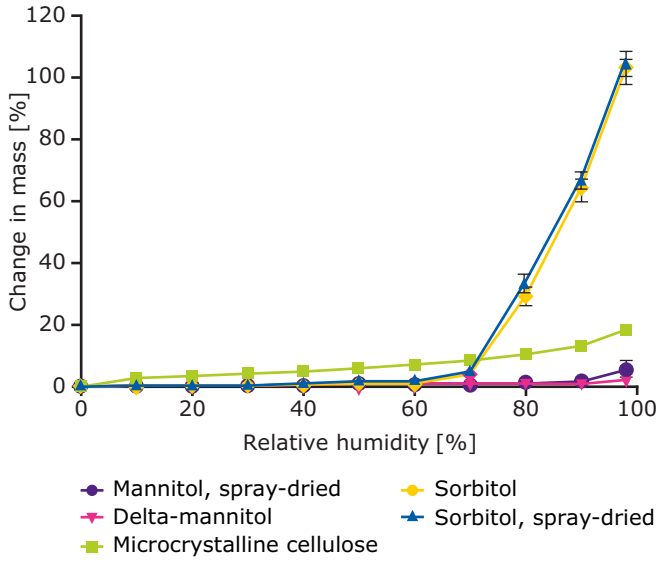

Figure 1.

Hygroscopicity of mannitol in comparison to other excipients commonly used for solid dose formulations.

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Comparison of Galenic Properties of β- and δ-Mannitols

At least three different modifications of mannitol exist denoted as α, β and δ; the β modification is the most stable. However, it was observed that for wet granulation processes, the δ modification shows outstanding properties. During wet granulation, δ-mannitol shows a transformation to the β modification combined with changes in morphology and an increase in surface area by a factor of up to ten. These changes are considered to be major contributing of up to ten factors for improved compaction behavior.[2]

Parteck® Delta M excipient is a delta (δ) polymorphic form of D(-)-mannitol specifically designed for use in wet granulation. While it is monographed as a standard mannitol, Parteck® Delta M excipient transforms into the β polymorph during granulation, creating an increased surface area and a porous structure, which results in increased compressibility (Figure 2).

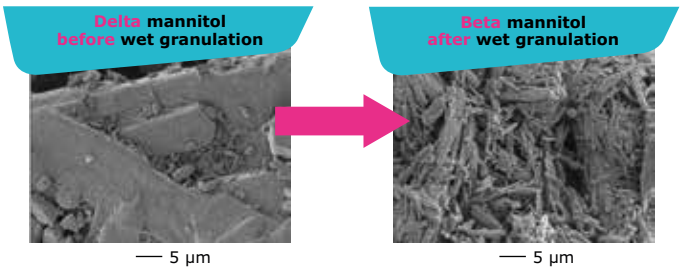


Figure 2.

SEM images showing the transformation of δ-mannitol to β-mannitol during wet granulation. Note the changes in morphology and significant increase in surface area.

Figure 3 highlights the differences in the compression profile (A) and disintegration (B) of wet granulated Parteck® Delta M excipient as compared to standard β-mannitol. For the compression profile study, mannitol was granulated with 10% water and dried, granules larger than 1 mm were removed. Granules were mixed for five minutes with 1.5% magnesium stearate and compressed on a single punch press at various compression forces into 11 mm flat faceted tablets with a final tablet weight of 400 mg. Tablets and granules were analyzed using a standard disintegration tester, tablet hardness tester and BET surface analysis.

The significantly lower disintegration time observed for formulations based on Parteck® Delta M excipient as compared to corresponding formulations with the β modification correlates with the measured Brunauer-Emmett-Teller (BET) surface which is higher for granules of δ-mannitol (Figure 4). As shown in the figure, the amount of granulation liquid used is a critical parameter for creation of the increased surface area.

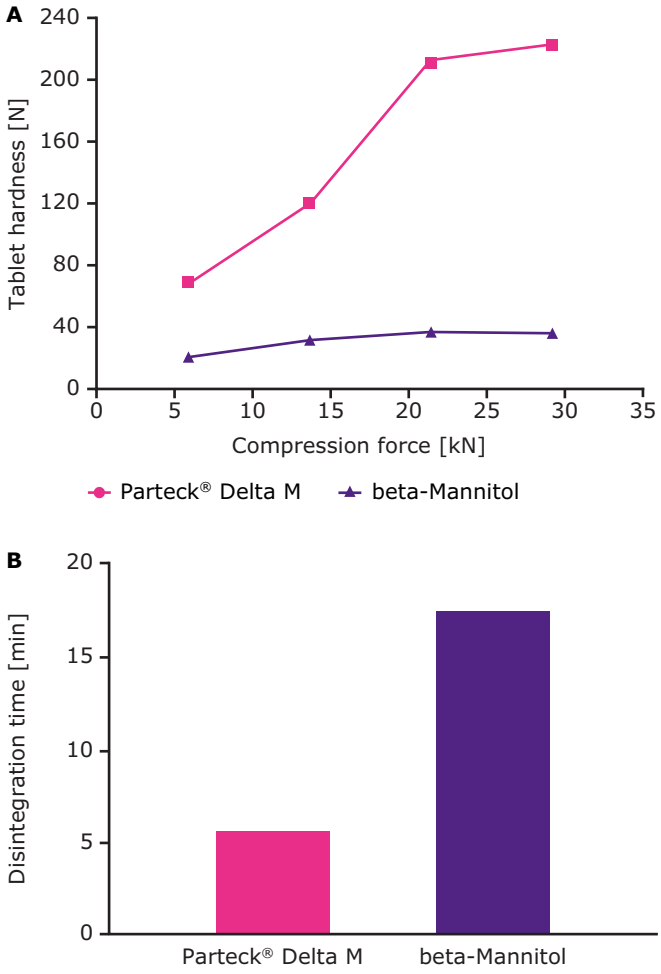


Figure 3.

Compression profile (A) and disintegration (B) of Parteck® Delta M tablets as compared to β-mannitol showing increased tablet hardness and disintegration with Parteck® Delta M excipient.

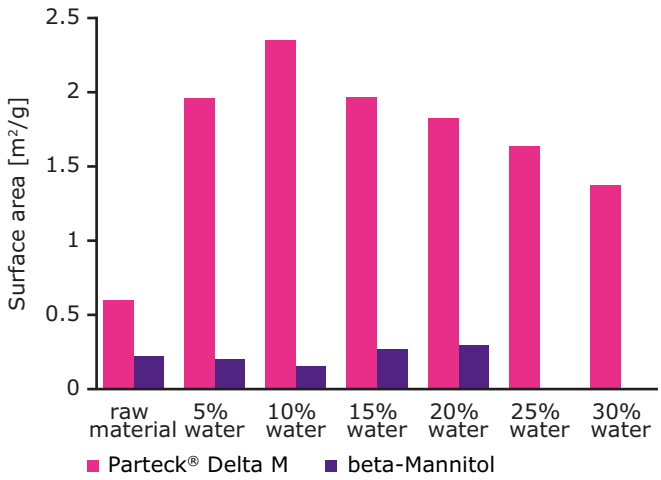


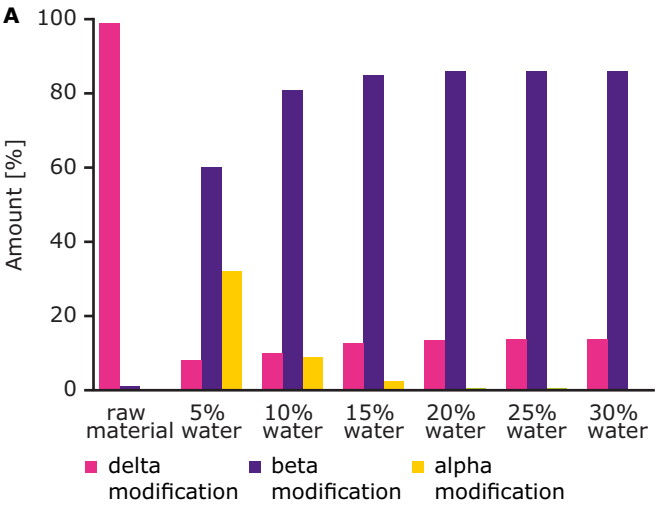
Figure 4.

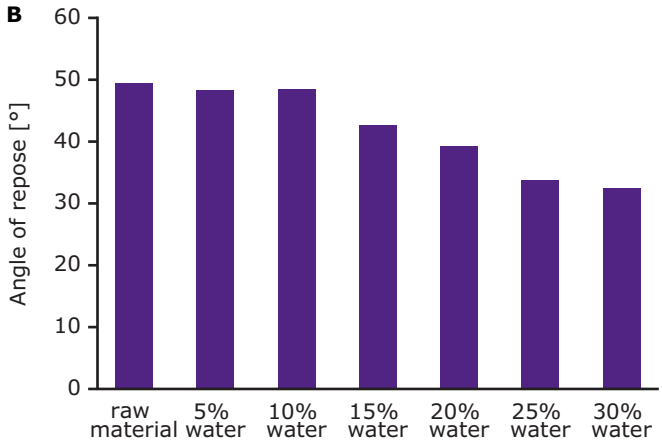
Surface area of δ- versus β-mannitol granulate produced by wet granulation.

Impact of Granulation Method and Granulation Fluid Concentrations on Galenic Properties

In the study described below, varying granulation fluid concentrations (water: 5%, 10%, 15%, 20%, 25%, and 30%, relative to the total amount of Parteck® Delta M) were evaluated for wet granulation with Parteck® Delta M excipient. High shear granulation with up to 25% water was shown to be an ideal means for leveraging the unique properties of δ polymorph mannitol; this approach produced granules with good flow and compression properties and optimized galenic properties of resulting tablets.

Analysis of the crystal modifications showed that at least 10% water had to be added to ensure more than 80% conversion of δ to β polymorph (Figure 5A). This amount depends also on the process applied. Generally speaking, 15% – 20% are recommended for low shear granulation processes while 20% – 25% might be needed for high shear processes. Figure 5B shows that with increasing amounts of granulation fluid used, the flow properties of the resulting granules are improved. Lowest bulk densities are observed with 10% water used, which correlates with the surface area measurement results (see Figure 4 and 5C). By increasing the water concentration to 20% water, the amount of instable α polymorph can be reduced to below 1% – 5% (Figure 5A) while keeping the surface area high (Figure 4) and improving flow properties due to larger granule size at the same time as angle of repose data show (Figure 5B). Tableting trials of the different granulates show that material derived from high shear granulation resulted in tablets with very good galenic properties (high hardness, short disintegration time, low friability, low ejection forces; data not shown). This finding can be explained by the optimization of powder/granules characteristics as indicated by smaller angles of repose and higher bulk density as indicated in Figure 5B and 5C.





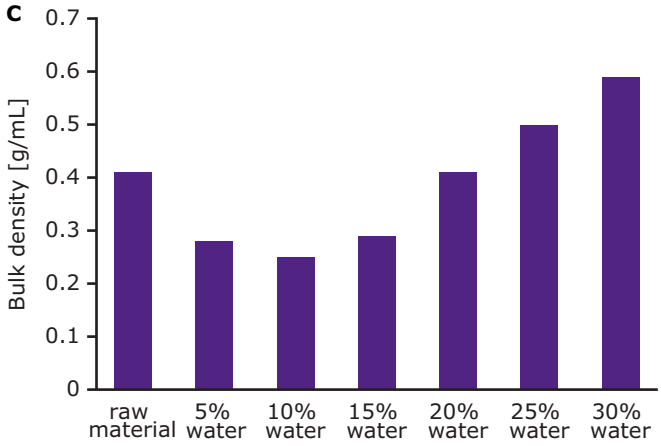


Figure 5.

High shear granulation of Parteck® Delta M excipient with varying amounts of water: A) Crystal modifications, B) angle of repose and C) bulk density of granulated material.

Influence of β- and δ-Mannitol on Dissolution

Fenofibrate is a BCS[3] class II substance, showing high permeability but very poor water solubility. The latter is a potential reason for bioavailability problems in oral dosage forms. Increasing the dissolution rate can support a faster absorption of the API from the gastrointestinal tract and help to overcome bioavailability issues associated with poor solubility; this may result in improved bioavailability *in vivo*. In the following study, the effect of β-mannitol and Parteck® Delta M δ-mannitol on *in-vitro* dissolution of low soluble model API fenofibrate was evaluated. For comparison purposes and to assess the effect of granulation of the tablet performance, four tablet types were created: each of the two mannitol excipients were granulated together with the API (co-granulation) and separately as well, with the API being added to the dried granules (mixture).

The composition and manufacturing process were identical except for the amount of water that had to be optimized for each granulation process. After wetting of the components in a universal mixer, the wet mass was then granulated using a wet granulator with oscillating rotor (mesh size 0.8 mm), tray-dried at 50 °C to a water content < 0.5%, and sieved over a 1 mm sieve. Highly dispersed silicon dioxide and magnesium stearate were added to the dried granules and mixed. Afterwards, the blends were tableted on a single-punch instrumented tablet press equipped with 12 mm biplanar, beveled punches into tablets with a total tablet weight of 500 mg. Compression forces were selected to obtain tablets with equal hardness of 75 ± 5 N for all formulations. The surface area and pore volume of the granules were assessed, and the dissolution behavior of resulting tablets was analyzed.

	Amount [mg/tablet]	Amount [% w/w]
Fenofibrate (D_{50} 18 µm)	100.0	20.0
Mannitol	387.5	77.5
Silicon dioxide, highly dispersed	5.0	1.0
Magnesium stearate	7.5	1.5
Total	**500.0**	**100.0**

Table 1.

Composition of fenofibrate tablets.

Significantly higher dissolution rates were observed for formulations based on δ-mannitol as compared to corresponding formulations with the β modification (Figure 6). The t50% value for tablets with co-granulated fenofibrate based on δ-mannitol was only 23 minutes as compared to the co-granulated β-mannitol at 54 minutes with significantly larger BET surface area. Both granulates showed a very similar particle size distribution (D_{50} values of 109 µm and 82 µm, respectively).[4] For the physical mixtures, the t50% value was 62 minutes for tablets based on the δ-mannitol granulate and 132 minutes for the corresponding β-mannitol, also with a much larger surface area.

The co-granulated formulations performed better than the corresponding physical mixtures. This can be explained by improved wetting effects and a higher dispersion of fenofibrate in the mannitol matrix. The higher dissolution rates observed for formulations based on δ-mannitol correlated with BET surfaces and pore volumes, which are both notably higher for granules of Parteck® Delta M excipient (Figure 7). The findings confirm that the combination of improved wetting and API dispersion characteristics and the surface area increase due to the polymorphic conversion from δ to β during the granulation process result in a significantly higher initial dissolution rate of the API when granulated together with Parteck® Delta M excipient.

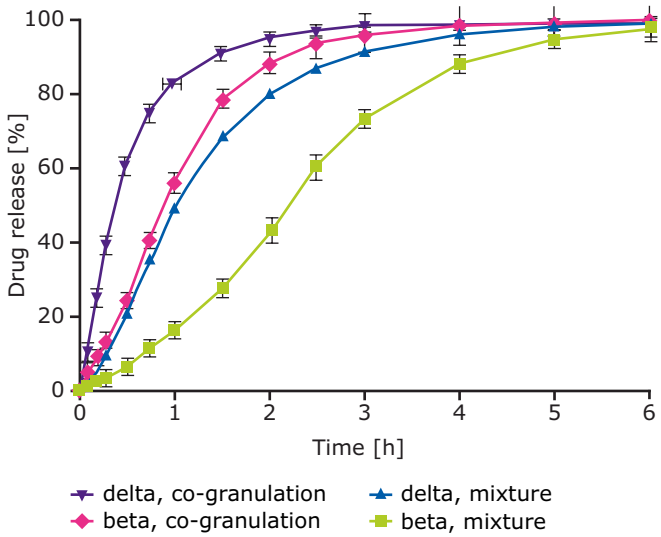


Figure 6.

Dissolution of tablets; δ- vs. β-mannitol mixture vs. co-granulation.

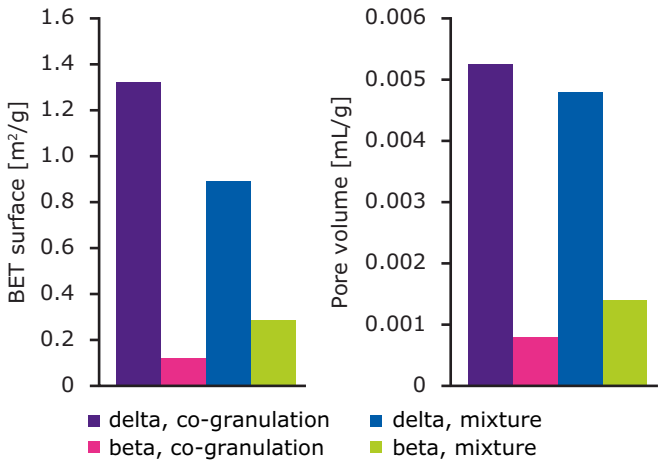


Figure 7.

BET surface area and pore volume of δ- and β-mannitol granulate with fenofibrate.

Wet Granulation with Organic Solvents

If necessary, wet granulation using mannitol with ethanol or propanol is possible. However, Figure 8 shows that the conversion of the polymorphic form takes place to a lesser extent than with water, resulting in a smaller surface area and a corresponding reduction in tableting performance.

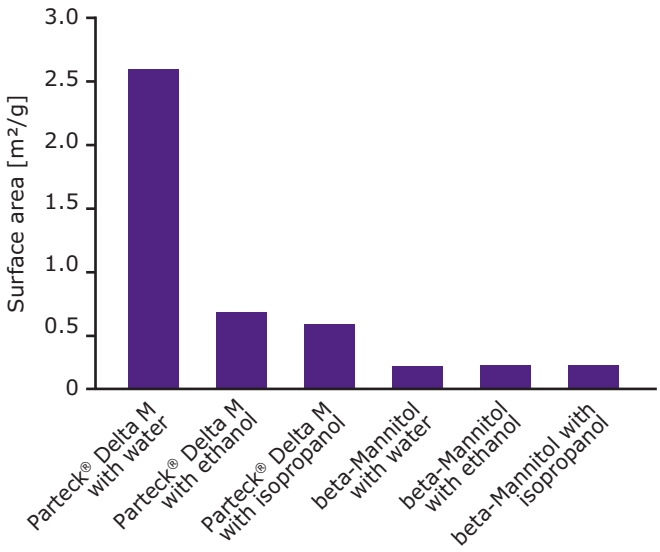


Figure 8.

Surface area resulting from wet granulation of Parteck® Delta M mannitol in comparison to crystallized β-mannitol using different granulation fluids: water, ethanol and isopropanol.

For this reason, the use of δ-polymorphic mannitol with organic solvents does not provide such a benefit as in cases where water is used as granulation fluid. This is why the use of Parteck® M 200 excipient, a spray-dried β-mannitol with excellent compression properties, might be beneficial for wet-granulation processes with organic solvents as it retains its excellent tableting properties and results in very hard tablets with a fast disintegration behavior.

Model API telmisartan was tableted using wet granulation with Parteck® M 200 excipient and ethanol. Telmisartan was dissolved in ethanolic sodium hydroxide solution. Parteck® M 200 and meglumine were wetted with the telmisartan solution in a high shear mixer. The resulting granules were then dried in a fluidized bed granulator and sieved. The dried granules were mixed with croscarmellose sodium, additional Parteck® M 200 and magnesium stearate and tableted at 9 kN using a rotary tablet press equipped with an 8 mm round D tooling punch. Tablet composition (A) and resulting properties (B) are shown in Table 2.

	Amount [mg/tablet]	Amount [% w/w]
Granulation		
Telmisartan	40.0	16.67
Sodium hydroxide pellets	3.5	1.46
Povidone	0.5	0.21
Water	8.0*	*
Ethanol absolute	120.0*	*
Parteck® M 200 (DC mannitol)	162.1	67.54
Meglumine	12.0	5.0
Tableting		
Parteck® M 200 (DC mannitol)	11.4	4.75
Parteck® CCS (croscarmellose sodium)	7.5	3.13
Parteck® LUB MST (magnesium stearate)	3.0	1.25
Total	**240**	**100**

*Solvents are evaporated off during the process.

Tablet properties:	
Compression force [kN]	9
Tablet weight [mg]	240
Weight variation [%]	2.0
Tablet thickness [mm]	3.72
Tablet hardness [N]	130
Friability [%]	0.16
Disintegration time [s]	530

Table 2.

Telmisartan tablet composition and properties following wet granulation with Parteck® M 200 mannitol and ethanol.

Comparison of β- and δ-Mannitol in Fluidized Bed Granulation

In fluidized bed granulation, materials are pre-heated, granulated and dried in the same vessel. This approach allows close control of the granulation process but is a drier mode of operation as compared to high/low shear granulation. To investigate the degree of conversion of Parteck® Delta M excipient from its δ modification into its β modification in a fluidized bed process, different spray rates (26 and 49 g/mL) and inlet air temperatures (65 and 85 °C) were used and the water and β-mannitol content of the resulting granulate was analyzed. As shown in Figure 9, the polymorph conversion is higher with higher spray rates and/or higher inlet air temperatures. Even so, at most 60% of Parteck® Delta M excipient is converted to the β polymorph as compared to 86 – 100% in high shear wet granulation.

Parteck® M 200 excipient is a mannitol already present in its β-polymorphic form with the surface area needed for high compressibility and good flow properties when used with both water soluble and poorly water soluble APIs. In consequence, Parteck® M 200 excipient is the preferred option for fluidized bed applications.

In Figures 10 and 11, directly compressed placebo formulations are compared to directly compressed and granulated model API formulations. For all formulations, Parteck® M 200 excipient and magnesium stearate is used. The model API was chosen as such to represent both water soluble (ascorbic acid) and poorly water soluble (ibuprofen) APIs. It can clearly be seen that the placebo tablets show the best tablet hardness and the tablet hardness is lower for the verum formulations, which is commonly observed for pharmaceutical solid oral dose formulations. When comparing the verum formulation results, granulation leads to higher tablet hardnesses at lower compression forces. At compression forces higher than 15 kN, tablet hardness decreases due to over compression.

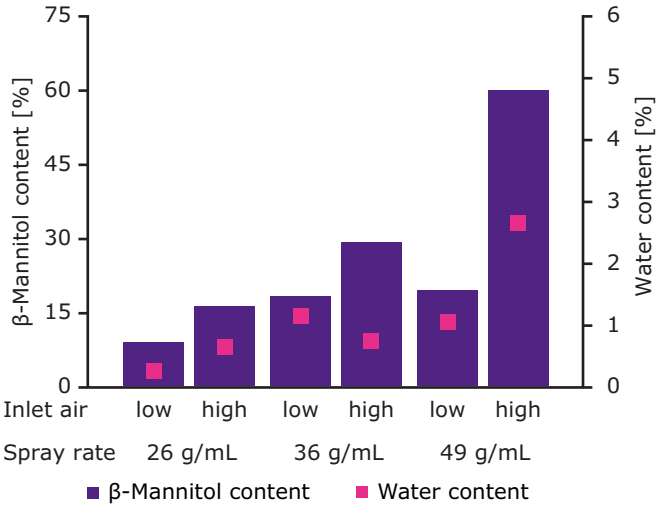


Figure 9.

Correlation of process parameters to polymorphic transformation of mannitol.

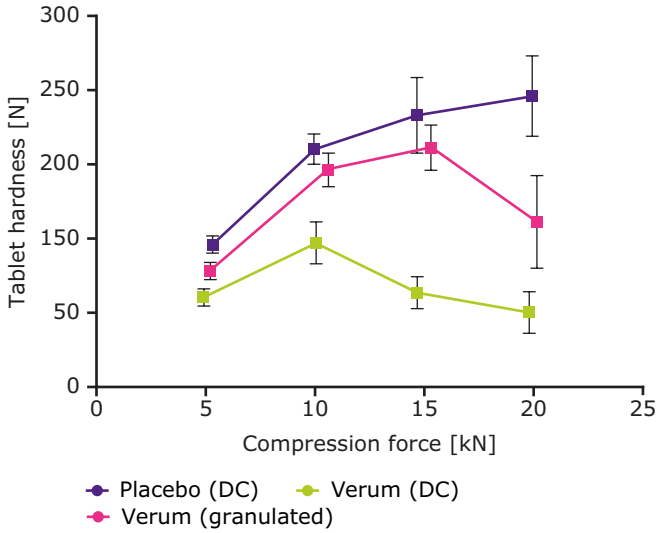


Figure 10.

Compression profiles for directly compressed Parteck® M 200 excipient placebo tablets, directly compressed Parteck® M 200-ascorbic acid tablets (DL 20%), and Parteck® M 200-ascorbic acid tablets (DL 20%) manufactured using a fluidized bed granulation process followed by tableting.

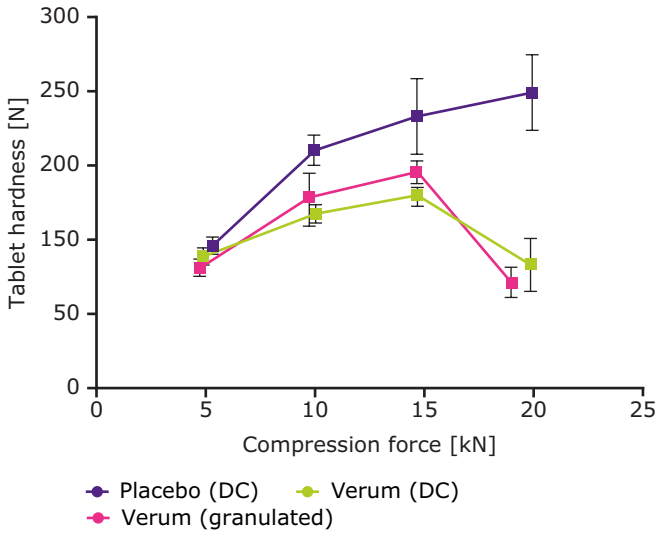


Figure 11.

Compression profiles for directly compressed Parteck® M 200 excipient placebo tablets, directly compressed Parteck® M 200-ibuprofen tablets (DL 5%), and Parteck® M 200-ibuprofen tablets (DL 5%) manufactured using a fluidized bed granulation process followed by tableting.

Conclusion

The success of a wet granulation process depends on use of an excipient with excellent binding and compaction properties. Mannitol is frequently used for this purpose in solid dosage formulations due to its physicochemical properties; it is chemically inert, has good compactibility and low hygroscopicity.[1]

While mannitols in general are increasingly used in pharmaceutical formulations, the Parteck® mannitol family of excipients offers important advantages.

As shown in these studies, standard crystallized mannitol in β-polymorphic form often lacks sufficient binding and tableting properties for use with wet granulation. In contrast, Parteck® Delta M, the only commercially available mannitol excipient in δ polymorph crystals, offers the inertness of mannitol with excellent binding properties, enabling formulators to more easily develop challenging formulations by wet granulation. When fluidized bed granulation is used or granulation with organic solvents is necessary, Parteck® M 200 excipient is an excellent alternative as it offers the surface area required to deliver the desired compaction and flow properties.

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