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White Paper

Advantages of Spray-Dried Mannitol in Roll Compaction Processes

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Pharmaceutical excipients which function as fillers and fillers/binders serve an important role in the formulation of solid dosage forms. Fillers give volume and confer mechanical properties that offer advantages such as flowability and compressibility; these characteristics support ease of manufacturing, final formulation robustness and content uniformity. This is especially relevant in the case of formulations with highly potent, low dose active pharmaceutical ingredients (APIs), as the filler comprises a large part of the final formulation and content uniformity can prove an issue. Several commercially available fillers come with a binder functionality, providing cohesiveness that ensures tablets and granules can be formed with the required mechanical strength and binding. Commonly used excipients include lactose, sorbitol and microcrystalline cellulose.

In recent years, mannitol has gained popularity as a pharmaceutical excipient in solid dosage formulation development and production as a result of several of its physicochemical properties; it is chemically inert, has good compatibility and low hygroscopicity.[1] As result of these properties, mannitol can be used in formulations to produce very robust tablets and as a diluent in rapidly dispersing oral dosage forms.[2] It also has a good taste and mouth feel enabling its use for chewable, sublingual and orodispersible tablet formulations.

A variety of pre-processed and unprocessed grades of mannitol are commercially available for use as an excipient in pharmaceutical formulations, sometimes developed specifically for certain manufacturing processes. For the production of dosage forms for oral administration by direct compression processes, a number of directly compressible grades of fillers are available on the market. In cases in which an efficient direct compression process is not suitable, such as the result of inhomogeneity or separation, dry granulation can be applied as an additional process step before tableting. Dry granulation is used to increase the bulk density of powders, improve flow properties and content uniformity which is essential when processing highly potent APIs; mannitol can serve as a filler/binder for dry granulation by roller compaction. During this process, a powder blend is compacted into a solid mass, a ribbon, typically followed by milling to achieve the desired particle size. Compared to wet granulation, roller compaction can be well used for moisture or heat sensitive APIs as no solvents, liquid binders or elevated temperatures are applied in the process.[3]

This white paper summarizes several studies which explored tableting behavior and comparative compressibility of various pre-processed and unprocessed mannitol grades in dry granulation processes. As a commonly used approach in dry granulation on an industrial scale, the examples focus on roller compaction (also referred to as roll compaction). The roller compaction behavior of different mannitol grades was investigated in placebo formulations or in combination with enalapril maleate as a model low-dose API. Results of these studies reveal differences in performance and can help guide selection of the best mannitol grade for dry granulation processes.

Case Study 1: Tableting Behavior of Spray-Dried Mannitols

Summarized from poster “Roll compaction of mannitol: Tableting behavior of various spray-dried mannitols before and after dry granulation” presented at 2012 AAPS Annual Meeting; data collected in cooperation with Heinrich-Heine University, Duesseldorf, Germany. Authors: CM. Wagner, G. Moddelmog, H. Ohrem, J. Breitkreutz.

This study compared the suitability of different spray-dried mannitol grades for roller compaction and the suitability of the resulting granules for tableting processes.

Materials and Methods

Five spray-dried and commercially available mannitol grades (designated "A" through "E") with similar particle size distributions were selected to explore their suitability for roller compaction and subsequent tableting processes.

Powders were granulated using an instrumented roller compactor (Mini-Pactor® 250/50, Gerteis Maschinen + Processengineering AG) with the specific compaction force set to 2 kN/cm and 10 kN/cm, respectively; the gap between the rolls (1.5 mm) and the roll speed (5 rpm) were kept constant during the process. For unprocessed grades, the roll speed was set to 3 rpm with a gap of 2.0 mm. Ribbons were granulated with a star-granulator using a 1.25 mm sieve. The S_{BET} (Brunauer, Emmett and Teller) surface area of the granules was analyzed by nitrogen absorption (TriStar 3000, Micromeritics Instrument Corporation) and compared to the unprocessed powder.

The granules were mixed with 1% magnesium stearate and compressed on a rotary tablet press (Pressima, IMA S.p.A.) equipped with planar 10 mm punches at compression forces of 3, 6, 9, 12 and 15 kN into tablets with a total tablet weight of 500 mg.

The resulting tablets were characterized with respect to weight, height and diameter; their crushing force was determined using a tablet hardness tester (TBH 210, Erweka GmbH). Tensile strength was calculated according to Fell and Newton.[4] The friability of the obtained tablets was determined according to Ph. Eur. (2.9.7, 7th Edition) using a friability tester (Erweka GmbH).

Results

Tablets formulated using mannitol A and B (Parteck® M 100 and Parteck® M 200 excipients, respectively) achieved the highest tensile strength after direct compression due to the large specific surface area of the raw material (Figure 1, Figure 2). In contrast, mannitol E lacked a sufficient surface area for bonding during tableting and this led to tablets with decreased mechanical resistance. S_{BET} results show that in general, when compared to the raw material, the specific surface area of the granules was increased after roller compaction. This effect became more apparent at high compaction forces and could be detected for every mannitol grade. The increase of granule surface area can be attributed to extensive fragmentation of the brittle mannitol which is more pronounced when higher compaction forces are applied.[5]

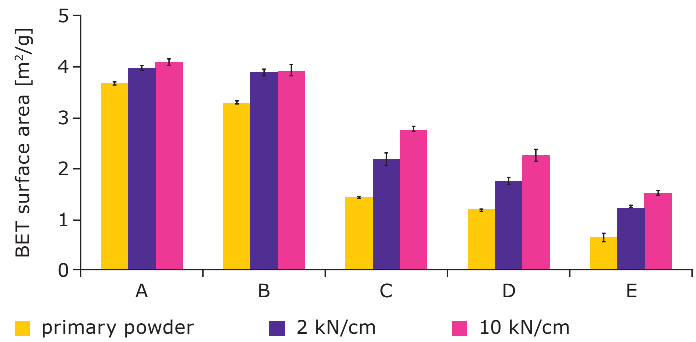

Figure 1.

BET surface area (n = 3) of roller compacted granules in comparison to the powder material.

With increasing compaction forces used in the roller compaction process, a loss of compressibility was observed for all excipients (Figure 2). This effect can be associated with particle size enlargement and the work-hardening phenomenon following roller compaction.[5] As shown in Figure 3, however, both mannitol A and B required less compression force to achieve the desired friability of <1%.

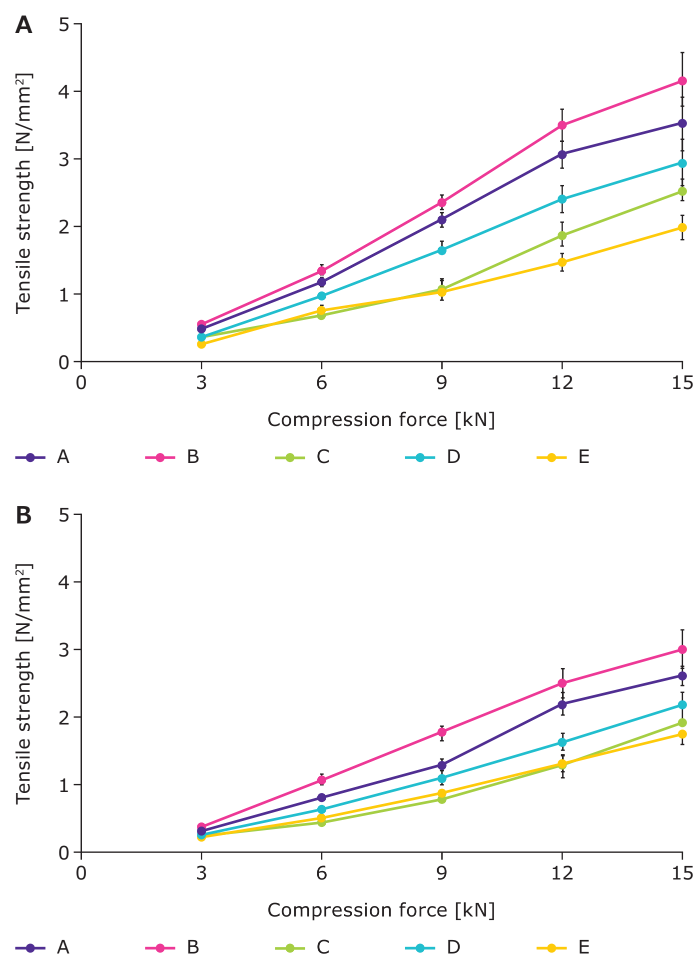

Figure 2.

Tensile strength measurements of tablets made of granules roller compacted at A) 2 kN/cm and B) 10 kN/cm (n = 10).

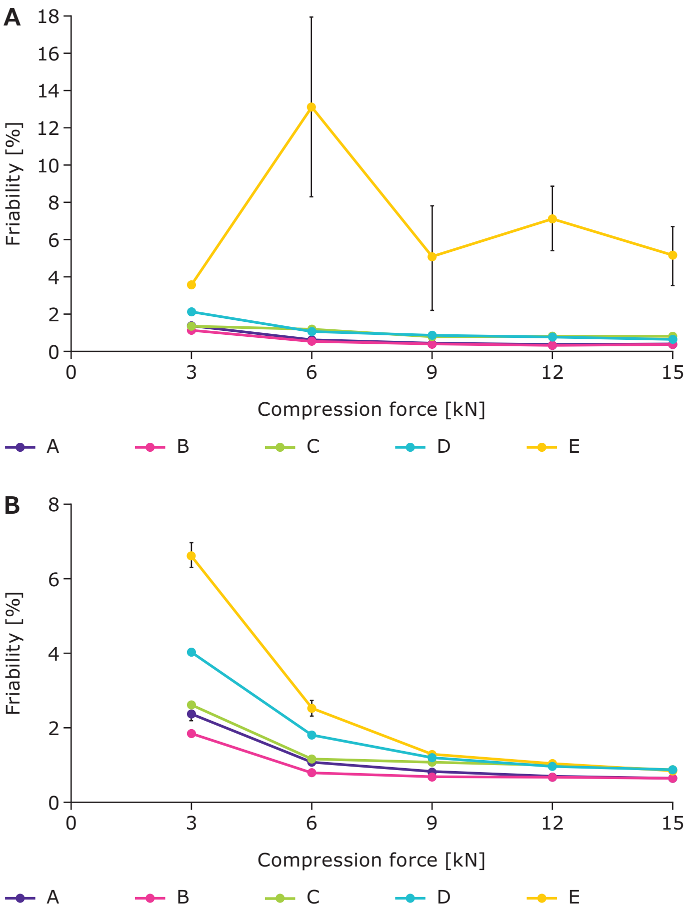

Figure 3.

Friability measurements of tablets made of granules roller compacted at A) 2 kN/cm and B) 10 kN/cm (n = 3). Graph B reproduced from *Wagner CM. Trockengranulierung von Mannitolzubereitungen durch Walzenkompaktierung [Dissertation]. Duesseldorf: Heinrich Heine University Duesseldorf; 2014.*

Conclusion

This study demonstrated that roller compacting spray-dried mannitol grades mostly results in robust tablets but final formulation performance is strongly dependent on the used mannitol type. Parteck® M 100 and Parteck® M 200 mannitols (A and B) were shown to produce granules with the largest surface area and tablets with highest tensile strength and lowest friabilities.

Case Study 2: Comparison of Pre-Processed and Unprocessed Mannitols

Summarized from poster "Roll compaction of mannitol: Comparative compactibility study of various pre-processed and unprocessed mannitol grades" presented at 2013 AAPS Annual Meeting; data collected in cooperation with Heinrich-Heine University, Duesseldorf, Germany. Authors: CM. Wagner, M. Pein, G. Moddelmog, J. Breitkreutz.

The purpose of this study was to compare the roller compaction and tableting behavior of commercially available pre-processed (spray-dried and granulated) mannitol grades and unprocessed crystalline mannitol in its β- and δ-modification.

Materials and Methods

The mannitol grades evaluated included two pre-processed granulated grades, designated "A" and "B", and two spray-dried grades, designated "C" and "D". Crystalline mannitol in the β- ("E") and δ-form ("F") were selected as unprocessed material. In case study 2, mannitol C = Parteck® M 200 excipient.

All powders were granulated and tablets produced and characterized as described as in the first case study. Compression forces of 3–18 kN were applied to produce the tablets.

Results

While roller compaction of mannitol A and B led to tablets with sufficient tensile strength applying compression forces ≥9 kN, granules made of spray-dried raw materials (C and D) were characterized by a superior compressibility and higher tensile strengths even at lower compression forces (Figure 4).

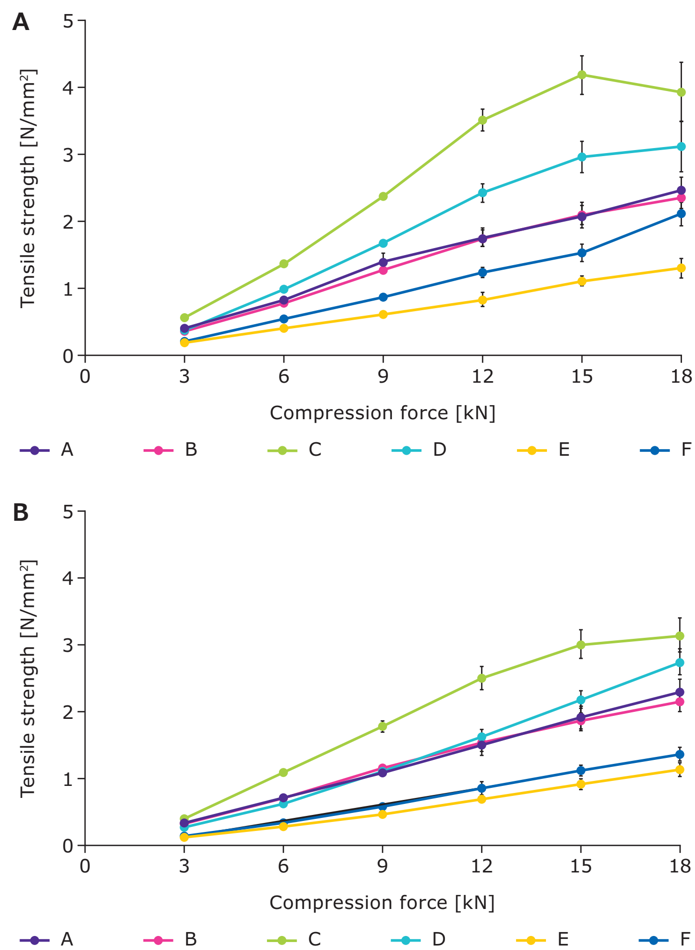

Figure 4.

Compressibility of granules made using unprocessed and pre-processed mannitol grades roller compacted with A) 2 kN/cm and B) 10 kN/cm (n = 10).

As in the first case study, a loss in compressibility was observed for every mannitol grade (pre-processed and unprocessed β- and δ-mannitol) with increasing compaction force used in the roller compaction process (Figure 4); this can be attributed to particle size enlargement and the work-hardening phenomenon.[5]

In comparison to the raw material, the specific surface areas of the granules increased after roller compaction (Figure 5). This effect became more apparent at high compaction forces and can be attributed to the strong fragmentation behavior of mannitol.[6] Tablets of Parteck® M 200 excipient ("C") showed a considerably larger interparticular contact area due to the large BET surface area of both powder and granules (Figure 5) which resulted in higher tensile strength (Figure 4).

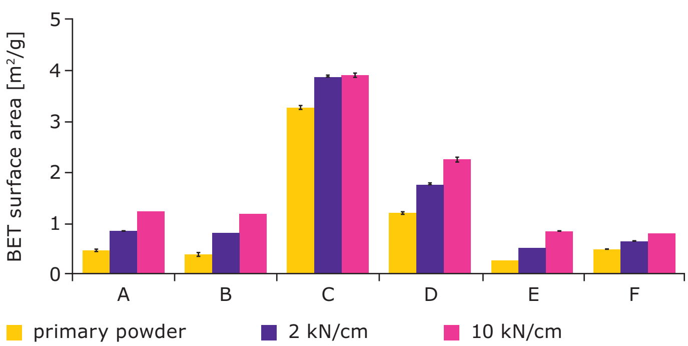

Figure 5.

BET surface area (n = 3) of granules in comparison to the powder material.

Conclusion

This study demonstrated that while roller compaction of granulated starting materials and crystalline δ-mannitol resulted in granules and tablets with desirable properties, the spray-dried grade with the largest surface area (mannitol C = Parteck® M 200 excipient) showed good compactibility during the dry granulation process and exhibited superior compressibility during the tableting process when compressed into the final dosage form.

Case Study 3: Roller Compaction Behavior and Tabletability of Mannitol-Based Enalapril Formulations

Summarized from poster "Applicability of roll compaction for mannitol based enalapril formulations" presented at 2014 PBP World Meeting on Pharmaceutics; data prepared by Heinrich-Heine University, Duesseldorf, Germany. Authors: CM. Wagner, M. Pein, J. Breitkreutz.

The case studies described above demonstrated that unprocessed, crystalline δ-mannitol, spray-dried and granulated grades are suitable for roller compaction. The following study was undertaken to evaluate roller compaction behavior of different mannitol grades in combination with enalapril maleate as model low-dose API as well as the tableting performance of the resulting granules.

Materials and Methods

Enalapril maleate and the different mannitol grades were blended for 20 minutes in a shaker-mixer at 50 rpm.

The powder mixtures were granulated using an instrumented roller compactor (Mini-Pactor® 250/25, Gerteis Maschinen + Processengineering AG) with a compaction force of 8 kN/cm. The gap between the rolls (2 mm) and the roll speed (3 rpm) were kept constant during the process. Ribbons were granulated with a star-granulator using a 1.25 mm-sieve.

Particle size distribution was determined via digital image analysis (Camsizer® XT, Microtrac Retsch GmbH); fines were considered to be particles ≤90 µm. Flowability of the granules was determined as the flowability function (ff) using automated ring shear tester RST-01.pc (Dr. Dietmar Schulze Schüttgutmesstechnik).

The granules were mixed for 2 minutes with 1% magnesium stearate. Tablets with a total drug load of 2.5 mg enalapril maleate and a total tablet weight of 200 mg were produced on an instrumented rotary tablet press (Pressima, IMA S.p.A.) equipped with planar 8 mm punches, using compression pressures of 3–18 kN.

The tablets were characterized with respect to weight, height and diameter; their crushing force was determined using a tablet hardness tester (TBH 210, Erweka GmbH). Tensile strength was calculated as described above. Uniformity of dosage units was evaluated according to Ph. Eur. 2.9.40 and the enalapril maleate content determined by high performance liquid chromatography.

All formulations could be roller compacted to granules and compressed into tablets. Roller compaction of enalapril maleate and spray-dried mannitol yielded granules with low amounts of fines and good flow properties (formulation A and B, with A using Parteck® M 200 excipient; Table 1). In contrast, granules of pre-granulated raw material and unprocessed δ-mannitol were characterized by higher amounts of small particles (formulation C and D, with D using Parteck® Delta M excipient; Figure 6), which is an explanation for the fair flowability in comparison to the good flowability of spray-dried mannitol grades.

	Formulation A	Formulation B	Formulation C	Formulation D
Amount of fines [%]	9.1 ± 0.2	8.6 ± 0.2	18.1 ± 1.2	28.6 ± 0.3
Flow function coefficient ff_c	10.8 ± 1.7	10.0 ± 1.6	6.2 ± 0.3	6.3 ± 0.7

Table 1.

Amount of fines and ff_c-values of the produced granules (mean ± s, n = 3).

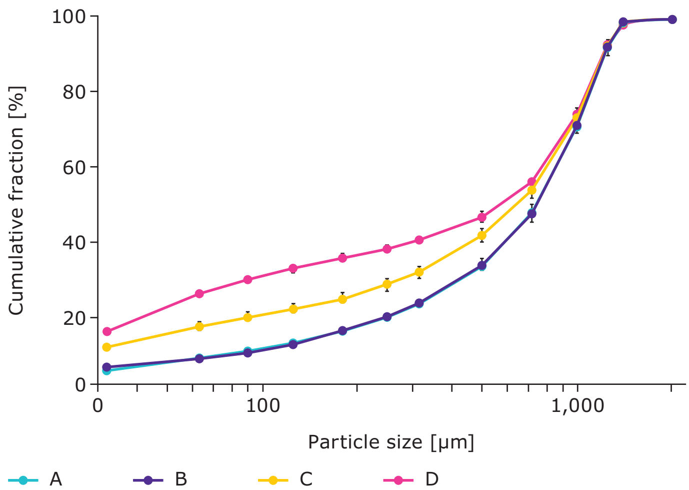

Figure 6.

Particle size distribution of the produced granules (n = 3).

Formulation B granules showed a significantly lower compressibility. Granules containing granulated mannitol and crystalline δ-mannitol also showed reductions in compressibility. Formulation A tablets based on Parteck® M 200 mannitol showed the highest tensile strengths (Figure 7).

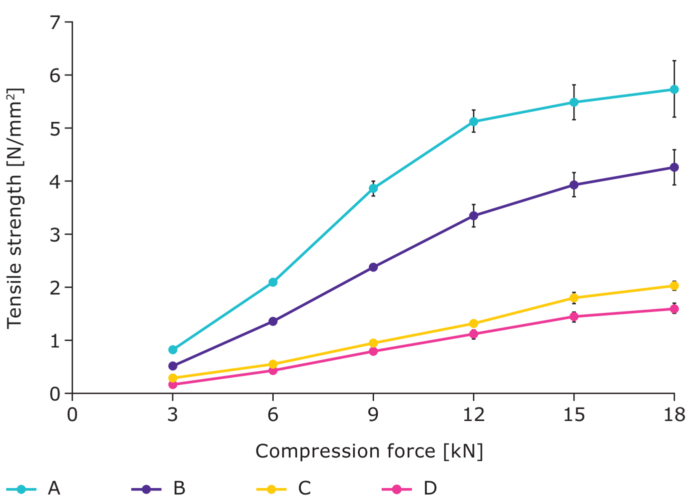

Figure 7.

Compressibility of the produced granules (n = 10).

As shown in Table 2, all tablets assessed for content uniformity met the Ph. Eur. requirements (2.9.40).

	Tablet weight [mg]	API content [% of label claim]	Acceptance value
Formulation A	201.1 ± 1.7	98.4 ± 1.5	3.8
Formulation B	199.5 ± 1.6	97.5 ± 1.2	3.9
Formulation D	202.1 ± 2.5	101.3 ± 3.4	8.2

Table 2.

Acceptance values according to Ph. Eur. 2.9.40 (n = 10) for formulations A, B and D. Data were not available for formulation C.

Conclusion

Enalapril maleate formulations based on the different mannitol grades were successfully produced via roller compaction and had the desired flow properties, an acceptable amount of fines and met pharmacopoeial requirements for content uniformity. Tablets containing granules based on Parteck® M 200 spray-dried mannitol (formulation A), however, showed the highest tensile strengths, very low amount of fines and best content uniformity.

Optimizing a Solid Dose Formulation with Mannitol

The ability to produce high quality tablets relies, in part, on compressibility of solid dose formulations; this, in turn, guides selection of the proper excipient. Achieving the optimum tensile strength is also essential as it ensures that tablets can withstand handling such as when packaged, shipped and used, and at the same time, dissolve properly when taken by the patient. Granulation can be applied if the formulation does not yield satisfactory results via direct compression.

As mannitol becomes an increasingly popular excipient for development of tablets, it is essential to select a grade optimized for both the intended final formulation performance and the formulation process used to yield the desired product characteristics.

While a number of commercially available mannitol options are suitable for dry granulation, the case studies summarized in this white paper highlight important differences among various grades. Performance is strongly dependent on the type of mannitol used; in all cases, spray-dried mannitols produced granules with improved compressibility in comparison to granulated or crystalline mannitol grades, resulting in tablets with higher tensile strength and lower friabilities. When comparing different commercially available spray-dried mannitol grades, a high initial surface area of the mannitol was a critical success factor. Parteck® M excipients showed the highest surface areas before and after granulation. These excipients offered distinct advantages in terms of compressibility and tensile strength of the resulting tablets both in placebo and verum formulations.

In conclusion, it was shown that the selected excipient grade is critical for formulation performance. It was observed in the presented case studies that roller compaction is feasible with satisfactory results with all mannitol grades suitable for direct compression, while grades not designated for direct compression application resulted in granules with lower compressibility in the tableting process and less robust tablets. Directly compressible mannitols with greater surface areas such as Parteck® M 200 excipient produce stronger tablets when roller compaction is used prior to tableting and when applied in direct compression processes.

As such, roller compaction can be successfully applied as a means to improve tableting performance of the selected formulation such as its flow properties or content uniformity of the final dosage form. It is important to note however, that excipient particle properties should be considered early in the formulation development process to ensure a robust final product as well as a smooth transition to commercial scale: If the optimum grade of mannitol is used from the beginning of the process, the resulting final formulation performance will be superior in comparison to processes using other, less suitable grades.

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