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Roll compaction of granulated mannitol grades and the unprocessed crystalline delta-polymorph

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ABSTRACT

In pharmaceutical industry dry granulation by roll compaction (RC) gains in importance since the process is cost-effective and continuous. Additionally, mannitol as excipient received more and more attention due to its numerous advantages becoming apparent particularly in orodispersible drug formulation. So far, RC behavior of the commonly used fillers microcrystalline cellulose and lactose has been described in several studies. The purpose of this project was to investigate and to compare RC behavior of both pre-processed D-mannitol grades and unprocessed δ-D-mannitol. Therefore, two granulated mannitol qualities were dry granulated and the compactability of the granules was determined subsequently. It could be shown that the use of granulated raw material leads to granules with acceptable particle size distribution and amounts of particles ≤90 μm. Robust tablets with acceptable tensile strength (2 kN/cm batch, mannitol type A 1.39 ± 0.19 N/mm^2, mannitol type B 1.27 ± 0.06 N/mm^2, applying 115 MPa compression pressure) were produced. Compared to a spray-dried mannitol, granulated raw material leads to tablets with inferior mechanical resistance. One reason for this observation is the smaller specific surface area of granulated raw material (0.46 ± 0.03 m^2/g and 0.38 ± 0.04 m^2/g, respectively to 3.27 ± 0.03 m^2/g) and the resulting granules. Unprocessed D-mannitol in the δ-modification exhibits lower compactability than both pre-processed grades. Higher specific compaction forces (10 kN/cm) during dry granulation have to be applied to achieve granules with adequate flowability (ff$_c$-value 10.13 ± 1.15). Tablets with low abrasion and appropriate disintegration time could be still produced.

1. Introduction

Dry granulation by roll compaction is a widely used technology in various industry branches including mineral, food, chemical, or agricultural industry [1,2]. Also in the pharmaceutics the continuous agglomeration process plays an important role due to its numerous advantages. As in other granulation techniques the purpose of roll compaction is the increase in bulk density of powders, the improvement of flow properties, and the prevention of segregation, which is particularly important for processing highly potent active pharmaceutical ingredients (APIs). But furthermore, RC enables the processing of moisture or heat-sensitive drugs/excipients. A cost-intensive recovery of organic solvents or water is not required, which makes the process environmentally friendly and limits the number of process steps. Scale-up issues are rare [3]. Nevertheless, major challenges of this technology are a large amount of fine particles caused by e.g. a leakage of uncompacted material between the roller seals and the work-hardening phenomenon, which describes the resistance of a material against any subsequent deformation step [2,4]. In several investigations, a decrease in tensile strength of tablets processed by RC in comparison to tablets made from the virgin powder was observed [4–7]. To overcome these problems a couple of strategies have been reported in literature. Bultmann [8] observed that multiple roll compaction of microcrystalline cellulose (MCC) leads to a decreased amount of fines, improved flow properties and optimized particle size distribution. However, crushing forces of the subsequently prepared tablets decreased. To diminish the loss in compactability Herting and Kleinebudde [9] decreased the particle size of the raw material (MCC) and obtained tablets with higher tensile strength.

The most commonly used fillers in dry granulation are various grades of MCC and lactose [10]. But also maize starch, magnesium carbonate, calcium hydrogen phosphate or sorbitol can be used [10]. This study focuses on the roll compaction behavior of mannitol, which is a widely used excipient in various pharmaceutical dosage forms and food products. In pharmaceutical preparations it is mainly used as a diluent in tablet formulations, e.g. chewable tablets. In lyophilizates mannitol acts as a filler to produce a homogeneous, fluffy cake [11]. It is highly soluble in water, well tolerated and exhibits a low drug interaction potential. Because of its sweet taste and its pleasant texture

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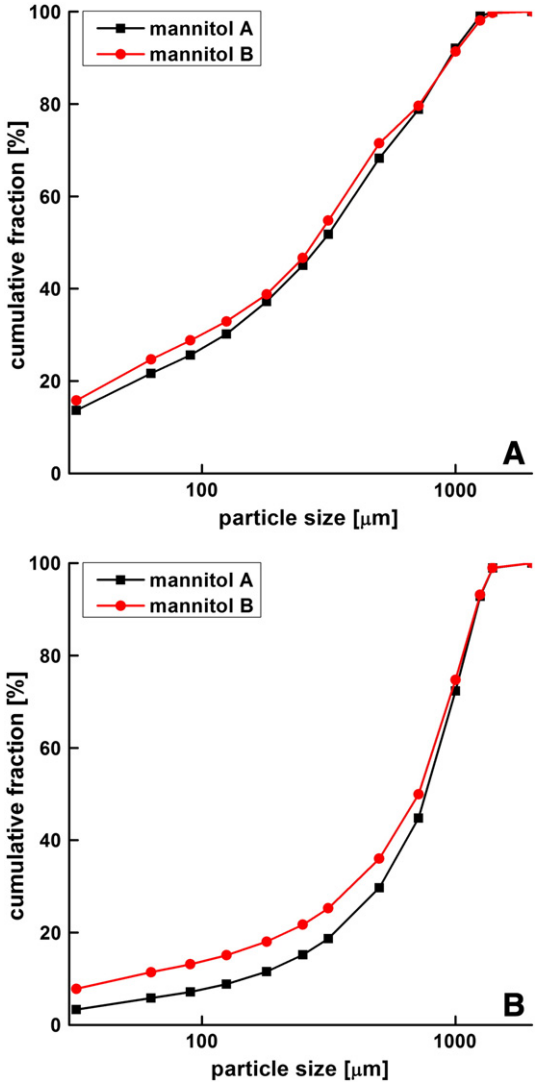

Fig. 1. Particle size distribution of granules roll compacted with (A) 2 kN/cm and (B) 10 kN/cm (n = 3, mean).

(mouth feel) [11], the hexahydric alcohol became the key excipient in dispersible and orodispersible formulations. Particularly in pediatrics and geriatrics rapidly disintegrating and dispersing tablets can overcome deficient swallowing ability of the patients and play a very important role to improve patient's compliance [12,13].

Various mannitol grades are available on the market. For direct-compression pre-processed grades such as spray-dried and granulated mannitol are utilized. But also unprocessed mannitol can be obtained at least in two different polymorphic forms. In a previous study unprocessed β-mannitol was roll compacted and the compactability of the resulting granules was investigated [14]. Low compactability and insufficient disintegration behavior of the tablets were observed. Thus, the compactability behavior of various spray-dried grades was determined in order to find out whether pre-processed grades are more suitable for dry granulation. It was shown that the beneficial properties of the pre-processed grades observed in direct-compression could be transferred to RC and subsequent tableting.

The aim of this study was to investigate whether unprocessed δ-mannitol exhibits enhanced compactability behavior after dry granulation compared to a β-mannitol. Furthermore, RC behavior and tabletability of granulated mannitol grades as further pre-processed mannitol qualities should be examined.

2. Materials and methods

2.1. Materials

All materials were used as received and were stored for equilibration at 21 °C and 45% relative humidity (rh) at least for two weeks. As pre-processed D-mannitol the granulated grades Mannogem® 2080 (mannitol *A*) from SPI Pharma, New Castle, USA and Pearlitol® 300 DC (mannitol *B*) from Roquette, Lestrem, France were used. As an example for a spray-dried mannitol quality, Parteck® M 200 (mannitol *C*) from Merck Millipore, Darmstadt, Germany was chosen. For the investigation of the unprocessed mannitol, a β-modification (D(−)-mannitol) and a δ-modification (Parteck® delta M) both from Merck Millipore, Darmstadt, Germany were used. Magnesium stearate (Parteck® LUB, Merck Millipore, Darmstadt, Germany) was utilized as lubricant for tableting.

2.2. Methods

2.2.1. Roll compaction

The experiments were carried out using an instrumented roll compactor (Mini-Pactor®, Gerteis, Jona, Switzerland) equipped with two smooth rolls of 25 cm diameter and 2.5 cm width. The unprocessed mannitol grades were roll compacted applying a specific compaction force of 2, 6, and 10 kN/cm. The gap between the rolls (2 mm) and the speed of the rolls (3 rpm) were kept constant during the process. For the pre-processed grades the gap between the rolls was varied to 1.5 mm and compaction forces 2 and 10 kN/cm were applied. After adjusting a constant gap ribbons were directly granulated using a star-granulator with a 1.25 mm sieve. The oscillating granulator was operated at a rotor speed of 40 rpm clockwise and 60 rpm counter clockwise.

2.2.2. Sampling

In order to obtain representative sampling all granules were divided into samples of required size using a rotary sample divider (PT, Retsch Technology, Haan, Germany).

2.2.3. Particle size

The particle size distribution of the raw materials and the granules was determined by digital image analysis using Camsizer XT® (Retsch Technology, Haan, Germany). Therefore, the X-Jet module was chosen

Table 1
ff_c-Values and amount of fines of the produced granules ($n = 3$, mean ± s); friability ($n = 3$, mean ± s) and disintegration time ($n = 6$, mean ± s) of the tablets.

Batch	Mannitol A		Mannitol B	
	2 kN/cm	10 kN/cm	2 kN/cm	10 kN/cm
ff_c-Value	5.35 ± 0.18	9.40 ± 0.42	3.85 ± 1.13	8.80 ± 1.4
Amount of fines [%]	25.6 ± 3.2	7.2 ± 0.3	28.8 ± 0.3	13.1 ± 0.6
Compression pressure	Tablet friability [%]			
	2 kN/cm	10 kN/cm	2 kN/cm	10 kN/cm
38 MPa	3.28 ± 0.05	4.12 ± 0.15	2.46 ± 0.05	2.95 ± 0.05
76 MPa	1.28 ± 0.05	1.65 ± 0.03	1.05 ± 0.02	1.12 ± 0.02
115 MPa	0.91 ± 0.02	1.08 ± 0.06	0.83 ± 0.03	0.81 ± 0.01
153 MPa	0.70 ± 0.01	0.87 ± 0.04	0.75 ± 0.03	0.72 ± 0.02
181 MPa	0.64 ± 0.02	0.69 ± 0.05	0.72 ± 0.05	0.62 ± 0.06
229 MPa	0.60 ± 0.03	0.73 ± 0.06	0.66 ± 0.03	0.56 ± 0.02
	Disintegration time [s]			
38 MPa	58 ± 5	69 ± 20	171 ± 55	139 ± 37
76 MPa	96 ± 9	327 ± 36	392 ± 58	383 ± 50
115 MPa	126 ± 8	448 ± 46	438 ± 11	512 ± 49
153 MPa	198 ± 22	546 ± 37	475 ± 47	542 ± 37
181 MPa	333 ± 18	522 ± 101	477 ± 48	516 ± 35
229 MPa	572 ± 51	580 ± 42	540 ± 22	622 ± 60