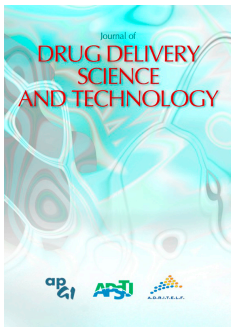

Evaluation of different types of mannitol for dry granulation by roller compaction

Luca Palugan, Saliha Moutaharrik, Micol Cirilli, Andrea Gelain, Alessandra Maroni, Alice Melocchi, Lucia Zema, Anastasia Foppoli, Matteo Cerea

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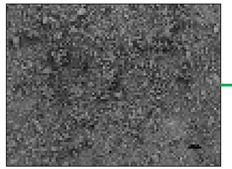
Different mannitol grades

Fine powder

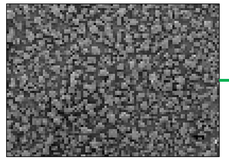


Mannitol PO

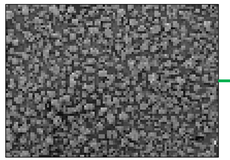
Granular

Mannitol GR

Spray dried



Mannitol EZ



Mannitol XL

Dry granulation

Roller compaction

F_{RC} 15, 30, 45 kN

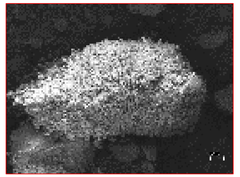
Ribbons

Milling

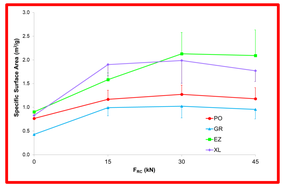
Granules

Evaluation of granules

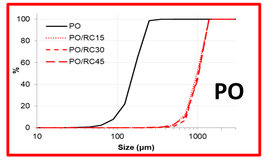
SEM

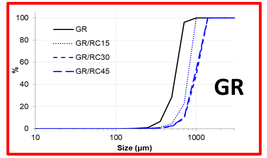


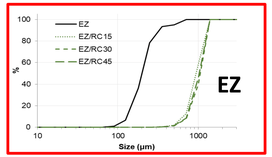
Specific surface area

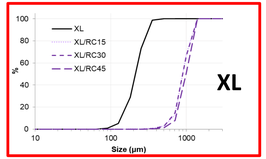


Particle size analysis

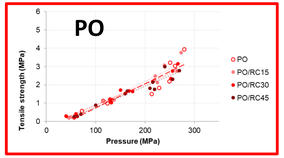


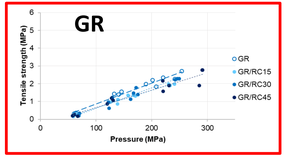


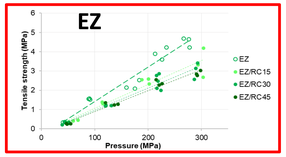


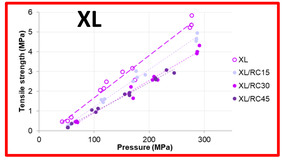


Ability to compaction









Evaluation of different types of mannitol for dry granulation by roller compaction

Luca Palugan[1], Saliha Moutaharrik[1], Micol Cirilli[1], Andrea Gelain[2], Alessandra Maroni[1], Alice Melocchi[1], Lucia Zema[1], Anastasia Foppoli[1]* and Matteo Cerea[1]

[1]Università degli Studi di Milano, Dipartimento di Scienze Farmaceutiche, Sez. Tecnologia e Legislazione Farmaceutiche "Maria Edvige Sangalli" via G. Colombo 71, 20133 Milano, Italy
[2]Freund-Vector Corporation, European Lab, via Enrico Mattei, 2, 20852 Villasanta (MB), Italy
* Correspondence: anastasia.foppoli@unimi.it

Abstract: Dry granulation by roller compaction (RC) is a continuous manufacturing technology increasingly used in the pharmaceutical industry for improving bulk density and flowability of powder mixtures or for preventing segregation issues of highly potent drugs prior to tableting. Dry granulation is ideally applied to moisture and heat sensitive drugs with added benefits also in terms of costs and lower equipment footprint. Mannitol is a polyol widely used in pharmaceutical formulations: particularly in orally dispersible tablets and powders and chewable tablets, where its high solubility and pleasant organoleptic properties make it an excipient of choice. Mannitol is available in several grades with different technological characteristics for adapting to various applications. In view of the use of mannitol for the formulation of active ingredients with poor flowability and compaction, the present work was aimed at analyzing the properties of the different commercial types of mannitol when used for dry granulation by roller compression to obtain tablets. Mannitol raw materials and granules prepared by roller compaction at different pressure were characterized for particle size distribution, bulk density, flow properties, specific surface area and ability to tableting. Granules with proper size (500-1500 µm), increased bulk density and adequate flow properties could be obtained. Increased specific surface area of the granules suggested a fragmentation of the particles during roller compaction even at relatively low processing pressure confirming the brittleness of the materials. For all materials tested, satisfactory properties for enabling tableting process were shown.

Keywords: roll compaction; dry granulation; mannitol; brittle material; compaction ability; work-hardening

1. Introduction

Dry granulation is a rather established manufacturing technology, traditionally used in the pharmaceutical industry for improving bulk density and flowability of powder mixtures or for preventing segregation issues of highly potent drugs prior to tableting [1–5]. The choice of excipients for the granulation process is essential to allow the powder agglomeration process, and it can contribute to the success of further processing steps, as in the case of the tableting process. In this context, the use of hydrophilic diluents, or the introduction of wetting agents, can easily compensate for solubility characteristics and improve the dissolution rate of poorly soluble active ingredients [6–8]. Compared to wet granulation, dry granulation avoids the use of any liquid binder, so it is ideal for use with moisture and heat sensitive drugs with added benefits also in terms of costs and lower equipment footprint. In addition, relying on the approach that exploits high-density systems for potentially extending gastric and urinary bladder residence times, dry granulation offers a relatively simple method for increasing the overall apparent density of the final dosage forms [9–12]. Moreover, roller compactor for dry granulation can be inserted in a continuous manufacturing process with easy in-line process control [13–15].

In dry granulation by roller compaction (RC), powder mixture is fed by a controlled device between two counter-rotating rolls to form ribbons, which subsequently are milled into granules for further processing. Friction between the powder blend and the roller surface drags the powder towards the narrow space separating the rotating rolls (roll gap) where materials are subjected to high pressure causing compaction. The feeding regularity of the roller compactor has a great influence on the final results of the granulation process [16]. The space between the two rolls needs to be continuously and uniformly filled to yield homogeneous compact materials [17]. Fine powders, typically exhibiting poor flowability due to cohesive properties, are usually fed by controlled loading devices equipped with rotating screws, while gravity hoppers tend to work best with non-cohesive and highly flowable powders.

Besides the parameters of the roller compaction process, the subsequent milling step has a critical effect on the granule properties [18]. Choosing the proper mill settings and screen size is fundamental in order to minimize the amount of fine particles generated during the crushing of the ribbons [19–24]. The selection of the type of milling system should consider the characteristics of the granules, but also the properties of the ribbons to be milled. These should be strong enough to be fractured in the form of granules and not to generate fines.

Among fillers used for roller compaction, the most widely studied and used are cellulose microcrystalline, lactose and calcium hydrogen phosphate [25–28] Each material is available on the market with various grades, differing in terms of particle size, bulk density and flowability. In particular, lactose is the water-soluble filler of choice for achieving balanced tableting properties of the powder blend, when high drug loading of a drug substance presenting plastic characteristics is concerned [29]. However, lactose can lead to instability issues due to the Maillard reaction, which occurs in the presence of primary and/or secondary amine compounds. Instability issues have been reported when lactose-based formulations were used for gelatin capsule filling: pellicle formation was observed due to the crosslinking of capsule shells, which caused slowed dissolution profiles [30,31]. In addition, lactose is also known for causing physiological intolerances in sensitive individuals. Mannitol is a polyol widely used in pharmaceutical formulations and particularly in orally dispersible and chewable tablets, where its high solubility and pleasant organoleptic properties, such as taste and mouth feel, make it the filler of choice [32]. It can also be used as a cryoprotector in freeze-drying and drug carrier in nasal and pulmonary delivery systems [33–35]. Mannitol is available in several grades with different technological characteristics for adapting to these various applications and, compared to other roller compaction fillers, it excels regarding its chemical inertness towards the drug ingredient, physiological tolerability, low hygroscopicity, and, for certain types, good flowability and ability to produce mechanically resistant tablets by direct compression. However, it should be noted that compared to conventional excipients for the formulation of powder blends intended for dry granulation, such

as lactose, microcrystalline cellulose and calcium hydrogen phosphate, mannitol has a relatively higher price [36,37].

With respect to unprocessed starting materials, roller compacted granules generally show a significant loss of ability to generate tablets with high mechanical resistance that is mostly exhibited by a reduction in tensile strength [38–41]. For materials having predominant plastic behavior this may be attributed to particle size enlargement or material hardening [2,42–45]. When brittle materials are concerned, such sensitivity of compaction properties to particle size and granules hardening is less evident, supporting the common practice of including brittle excipients as preferred fillers when granulating drug mixtures by roller compaction for tableting [46].

Based on these premises, the aim of the work was to evaluate different grades of mannitol in dry granulation by roller compaction in view of their use to formulate active ingredients with poor flow and compaction properties. Indeed, dry granulation was expected to allow for identification, among different grades of mannitol, the one which may best adapt to the characteristics of the specific drug substance to be formulated [47]. Therefore, among mannitol types available on the market, granular and spray-dried grades, typically proposed as fillers for capsule formulation, diluents in direct compression or drug carriers in inhalable formulations, have been considered along with unprocessed powder mannitol, which is the reference type for application in roller compaction. As this work was part of a broader screening study aimed at searching for different grades of mannitol characterized by a good roller compaction performance, it seemed useful to also include products specially indicated for direct compression or already available in granular form. As a matter of fact, in roller compaction a complete change in the morphology and density of the particles could be expected, which are known to highly impact the ability of the powder blend to generate high density ribbons and granules, and also to affect tableting properties. In this respect, characterization results of different types of mannitol as raw materials and roller compacted granules are reported in terms of inherent technological properties and characteristics of tablets prepared.

2. Materials and Methods

2.1. Materials

Mannitol powder (Mannogem Powder, PO, lot. 121808764), spray dried (Mannogem EZ lot. 121809019, and Mannogem XL lot. 121808686) and granular (Mannogem 2080 Granular, GR lot. 121707891) mannitol as well as sodium stearyl fumarate (Lubripharm, lot. 121708159) were kindly donated by SPI, USA. Prior to use, all materials were stored at 25 °C, 45% relative humidity.

2.2. Methods

2.2.1. Dry granulation process

Various mannitols were processed in a roller compactor (TFC220, Freund Vector, IA, USA) equipped with screw feeder rotating at 20 rpm, knurled rolls 200 mm diameter and 31 mm width operating at 2 rpm under 3 different roller compression forces (F_{RC}, 15, 30 and 45 kN), using gap values in the 3.38-3.78 mm range. Ribbons were milled using an oscillating mill (Oscillowit, Frewitt, CH) with screen size 1.0 mm, squared cross-section wire, operating at 150 rpm. Batch size was 1000 g for each processing condition.

2.2.2. Specific surface area analysis

Specific surface area (SSA) was measured by means of SA3100 Surface Area Analyzer (Beckman Coulter, UK) according to the BET method using N_2 as adsorbate gas (USP 32 Physical Test. Specific Surface Area. Volumetric Method). Prior to analysis, the samples (approximately 2 g) were degassed at 90 °C under vacuum (0.4 Pa) for 1 h. The measurements were carried out in triplicate.

2.2.3. Particle size analysis

The particle size distribution (PSD) of starting materials and granules was determined by dynamic image analysis method (Qicpic, Sympatec, DE) in the size range from 5 to 1705 μm. Approximately 5 g of materials was tested for each sample. Size was expressed as d_{10}, d_{50} and d_{90} (diameter of particles at 10, 50, and 90% of cumulative volume-based curve, respectively) and Span.

$$\text{Span} = (d10-d90)/d50 \quad (1)$$

2.2.4. Scanning Electron Microscope analysis

Morphology of powders and granules was analyzed by a scanning electron microscope (SEM; Sigma, Carl Zeiss, Germany). Samples were gold-sputtered using a plasma evaporator under vacuum, and photomicrographs were acquired at an accelerated voltage of 10 kV at differing magnifications.

2.2.5. Porosity of ribbons

Digital pictures of accurately weighed ribbons (n=20) were analyzed using IMAGE J software (version 1.53o, NIH, USA) to calculate the area. The thickness of the ribbons was measured using a digital caliper in different positions (Mod. CD -15CP, Mitutoyo, England). The volume was calculated by multiplying the area by the thickness of the ribbons. Starting from the mass of the ribbon, subsequently, the density was determined. The percent porosity was obtained as the ratio between the experimental density and the true density of mannitol (1.514 g/mL) [48].

2.2.6. Differential scanning calorimetry

Thermal behavior of mannitol starting materials and after dry granulation was assessed using differential scanning calorimeter (DSC 1 STARe System, Mettler Toledo, USA). Samples of approximately 5 mg were accurately weighed and sealed in aluminum pans. The samples were analyzed under a nitrogen atmosphere at a heating rate of 10 K/min over the temperature range from 20 to 200 °C.

2.2.7. Flowability testing

Compressibility index (CI) was calculated according to Ph.Eur. 10.7 by testing approximately 100 g of powders or granules using a jolting volumeter (STAV 2003, J. Engelsmann A., DE; 1250 taps) with 250 mL volumetric cylinder [49]. Values reported are the mean of 3 determinations. Flowability properties were classified according to the Ph.Eur. 10.7 ranking [50].

$$CI = 100 \cdot (\rho_{tapped} - \rho_{bulk}) / \rho_{tapped} \quad (2)$$

2.2.8. Compaction ability evaluation

Compaction ability (CA) of raw materials and granules was calculated by the slope of the regression line from the tensile strength (TS) vs pressure profiles (95% i.c., multiplied by factor 10^5) acquired from tablets prepared by a rotary tablet press (AMS8, Officine Meccaniche Ronchi, IT) equipped with a force detection system (FIT2008 software, B&D Italia, IT). A flat punch with a diameter of 11.28 mm was used and the die was filled manually. The tablets were produced rotating the turret at 20 rpm applying a force (Fa, force recorded by upper punch) in a range from 50-300 MPa. At least 5 replicates were tested for each setting. Prior to tableting powders and granules were mixed with 0.5% sodium stearyl fumarate in Turbula® (Willy A. Bachofen, CH) at 24 rpm for 5 min to prevent high ejection forces. Tablets with crushing strength below 20 N were considered unacceptable. Calculation of standard deviation of CA and statistics were performed according to Sonnergaard [51]. Tensile strength was calculated according to Fell and Newton [52].

Tensile strength=(2·Fc)/(π·D·h) (3)

where F_c is the crushing force measured by a diametric strength tester (TBH30, Erweka, DE) and D and h are the diameter and height of the cylindrical tablet measured by digital caliper (n=3).

3. Results

3.1. Technological characterization of raw materials

The different grades of mannitol showed remarkable differences in terms of morphology, bulk density, flow properties, PSD and SSA. In detail, SEM analysis showed powders with fine and plate-shaped particles for mannitol PO, spherical-shaped particles with clear hollow and porous structure for mannitol EZ and XL, while mannitol GR exhibited coarse, irregular and dense agglomerated particles (Fig. 1). To a closer look, EZ and XL particles showed the presence of inner small crystals, with needle shape morphology, surrounded by a thin layer of materials on the surface, while mannitol PO and GR, regardless of the great difference in particle size, when analyzed at high magnifications presented small crystals with similar morphology.

DSC analysis showed endothermic peak at 166 °C for all the types of mannitol, which consistently indicates the presence of polymorph β form (Fig. 2) [53,54].

Particle size of mannitol PO was found to be smaller than that of EZ and XL, and GR grades, this latter having the largest dimensions (d_{50}> 500 μm). According to Ph.Eur. classification, mannitol EZ, XL and GR exhibited good flow properties, while mannitol PO presented passable flowability characteristics. SSA analysis confirmed that materials having porous structure and lower tapped density, such as mannitol EZ and XL, developed the highest surface area, while mannitol GR grade presented the smallest SSA and highest density (Table 1).

Table 1. Results of technological characterization tests of powders and corresponding ribbons and granules obtained at different F_{RC}.

Material code	F_{RC} (kN)	ρ_{bulk} (g/mL)	ρ_{tapped} (g/mL)	CI (% ± sd) [*]	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	Span	SSA (m^2/g ± sd)	Ribbon porosity (% ± sd)
PO	-	0.55± 0.10	0.73± 0.21	25 ± 2 [passable]	94	160	231	0.85	0.766 ± 0.098	-
PO/RC15	15	0.68 ± 0.00	0.85 ± 0.01	20 ± 1 [fair]	659	983	1316	0.67	1.170 ± 0.190	24.39 ± 2.94
PO/RC30	30	0.70 ± 0.00	0.86 ± 0.01	19 ± 0 [fair]	731	1018	1323	0.58	1.274 ± 0.193	18.00 ± 4.34
PO/RC45	45	0.72 ± 0.00	0.87 ± 0.01	17 ± 0 [fair]	697	1039	1327	0.61	1.182 ± 0.233	19.48 ± 6.11
GR	-	0.63± 0.00	0.72± 0.00	12 ± 0 [good]	378	566	691	0.55	0.429 ± 0.028	-
GR/RC15	15	0.65 ± 0.00	0.81± 0.01	20 ± 0 [fair]	563	813	962	0.49	0.993 ± 0.173	29.31 ± 3.51
GR/RC30	30	0.66 ± 0.00	0.85 ± 0.01	22 ± 1 [passable]	715	1016	1323	0.60	1.023 ± 0.245	21.28 ± 4.03
GR/RC45	45	0.67 ± 0.00	0.84 ± 0.01	21 ± 0 [passable]	710	977	1314	0.62	0.957 ± 0.203	22.57 ± 2.64
EZ	-	0.46± 0.01	0.54± 0.02	15 ±1 [good]	131	202	331	0.99	0.903 ± 0.015	-
EZ/RC15	15	0.55 ± 0.00	0.69 ± 0.01	20 ± 1 [fair]	658	946	1303	0.68	1.585 ± 0.141	28.80 ± 7.04
EZ/RC30	30	0.63 ± 0.00	0.77 ± 0.00	18 ± 0 [fair]	727	1067	1333	0.57	2.129 ± 0.447	21.19 ± 4.95
EZ/RC45	45	0.65 ± 0.00	0.77 ± 0.01	15 ± 1 [good]	721	1031	1326.	0.59	2.093 ± 0.540	22.67 ± 4.33
XL	-	0.46± 0.02	0.53± 0.02	13 ± 1 [good]	135	213	319	0.86	0.830 ± 0.011	-
XL/RC15	15	0.60 ± 0.01	0.74 ± 0.02	18 ± 1 [fair]	651	907	1276	0.69	1.900 ± 0.233	30.81 ± 3.52
XL/RC30	30	0.63 ± 0.02	0.77 ± 0.02	19 ± 1 [fair]	626	908	1281	0.72	1.986 ± 0.482	24.88 ± 0.94
XL/RC45	45	0.63 ± 0.02	0.80 ± 0.02	21 ± 0 [passable]	724	995	1318	0.60	1.771 ± 0.228	28.14 ± 1.99

[*] classification according to the scale of flowability by Ph.Eur. 10.7

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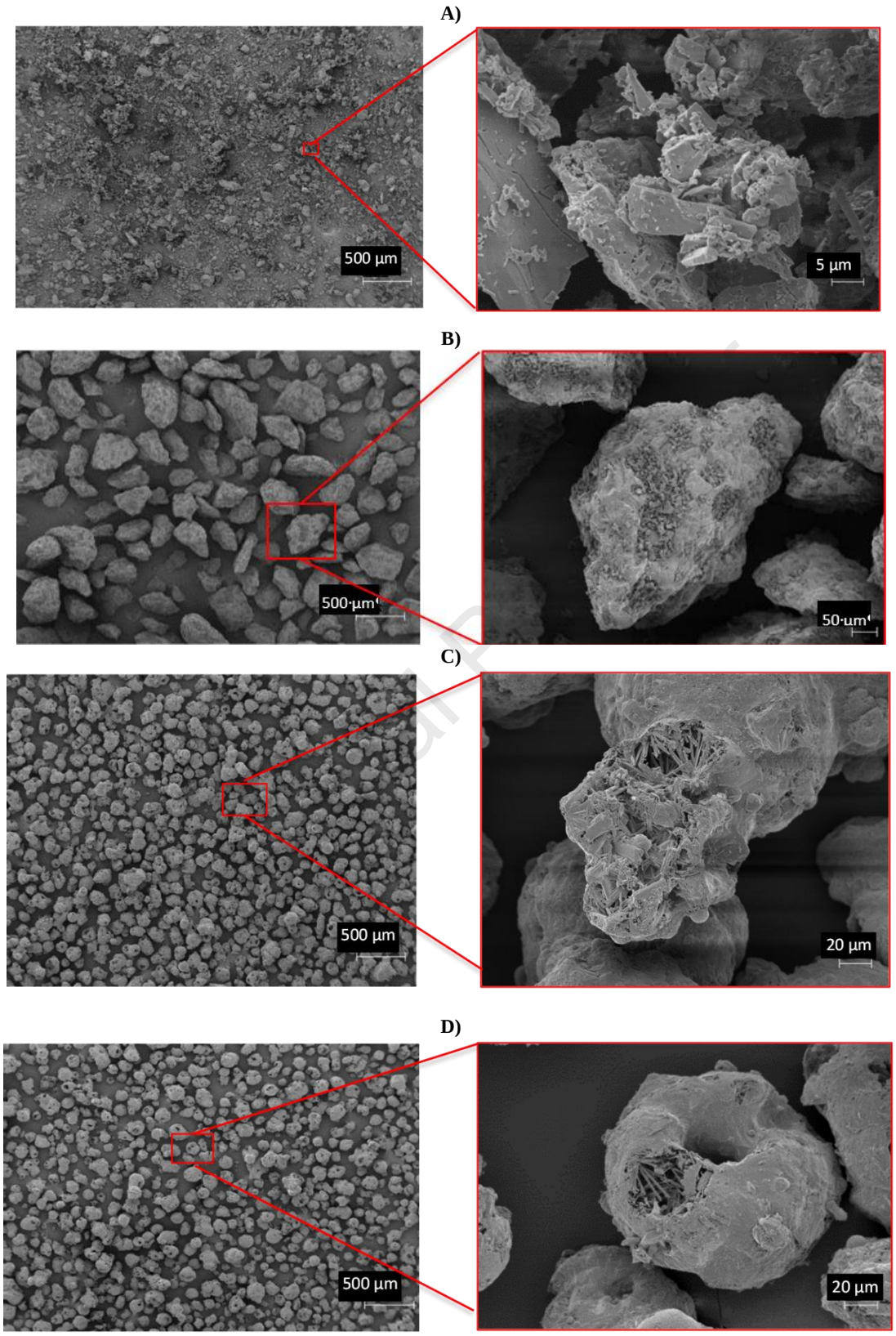

Fig. 1. SEM photomicrographs of mannitol raw materials PO (**A**), GR (**B**), EZ (**C**) and XL (**D**).

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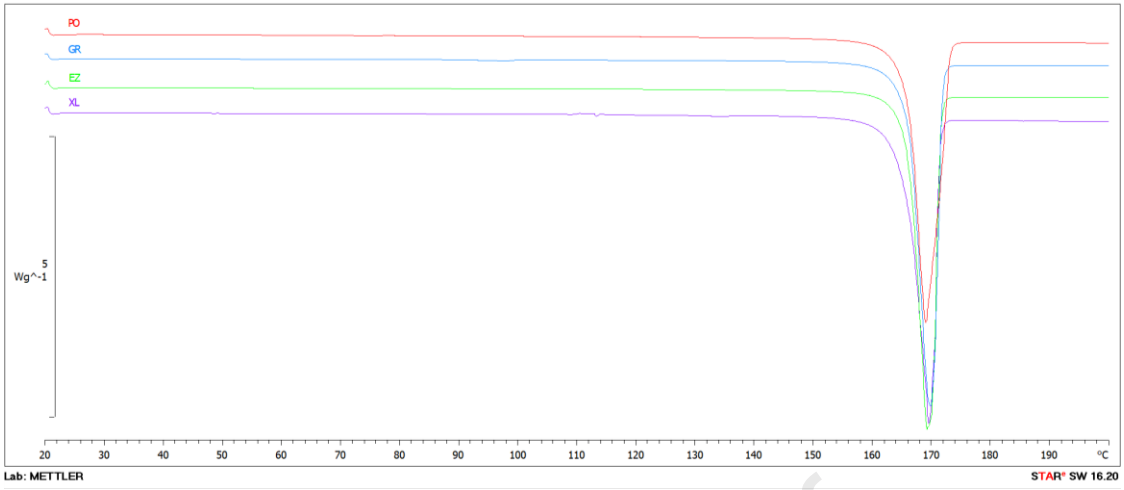

Fig. 2. DSC profiles of mannitol raw materials.

3.2. Dry granulation process

The four different types of mannitol were processed by a roller compactor using a pilot scale equipment operating at different compaction force (F_{RC}) by setting the hydraulic pressure of the floating roll. Compression force was fixed at 15, 30 and 45 kN, aiming at evaluating the behavior of materials at mild, intermediate and strong processing conditions. In preliminary trials 15 kN was found to be the minimum force for obtaining ribbons of sufficient consistency to be handled, while 45 kN was the maximum force that could be applied by the roller compactor. Rolls rotation speed and feeding screw rotation were maintained at fixed values (2 and 20 rpm respectively) with the aim of fixing the time for which the materials were subjected to the compaction force of the rolls. All the mannitols investigated could be successfully dry processed. Even the poor flowability of mannitol PO did not preclude consistent feeding of the rolls.

Ribbons with regular shape could be obtained from all the mannitol grades, porosity being included in the 18-31% range. In all cases, the lowest porosity was observed at 30 kN of F_{RC} (Table 1). With mannitol XL, porosity seemed to even increase at this F_{RC} value possibly due to lamination phenomena. The ribbons and by-pass powders collected under the rotating rolls were transferred into an oscillating mill granulator for grinding. Conditions of milling, such as squared cross-section wire screen with 1.0 mm opening and oscillating mode at 150 rpm, were set after preliminary trials, which provided satisfactory results in terms of material discharge rate, size of the granules and amount of fines generated. The mill was fed manually by loading the ribbons at approximately 200 g/min.

In Fig. 3, SEM photomicrographs of granules prepared at the highest roller compaction force are presented. Particle morphology, except for GR was modified compared to the starting materials, as expected. Particularly, the spherical geometry and porous network of spray-dried mannitols EZ and XL were lost. On the other hand, more regular particle agglomerates were generated from mannitol PO. In all cases, several very fine powder particles are visible at the surface of the granules, resulting from extensive fragmentation.

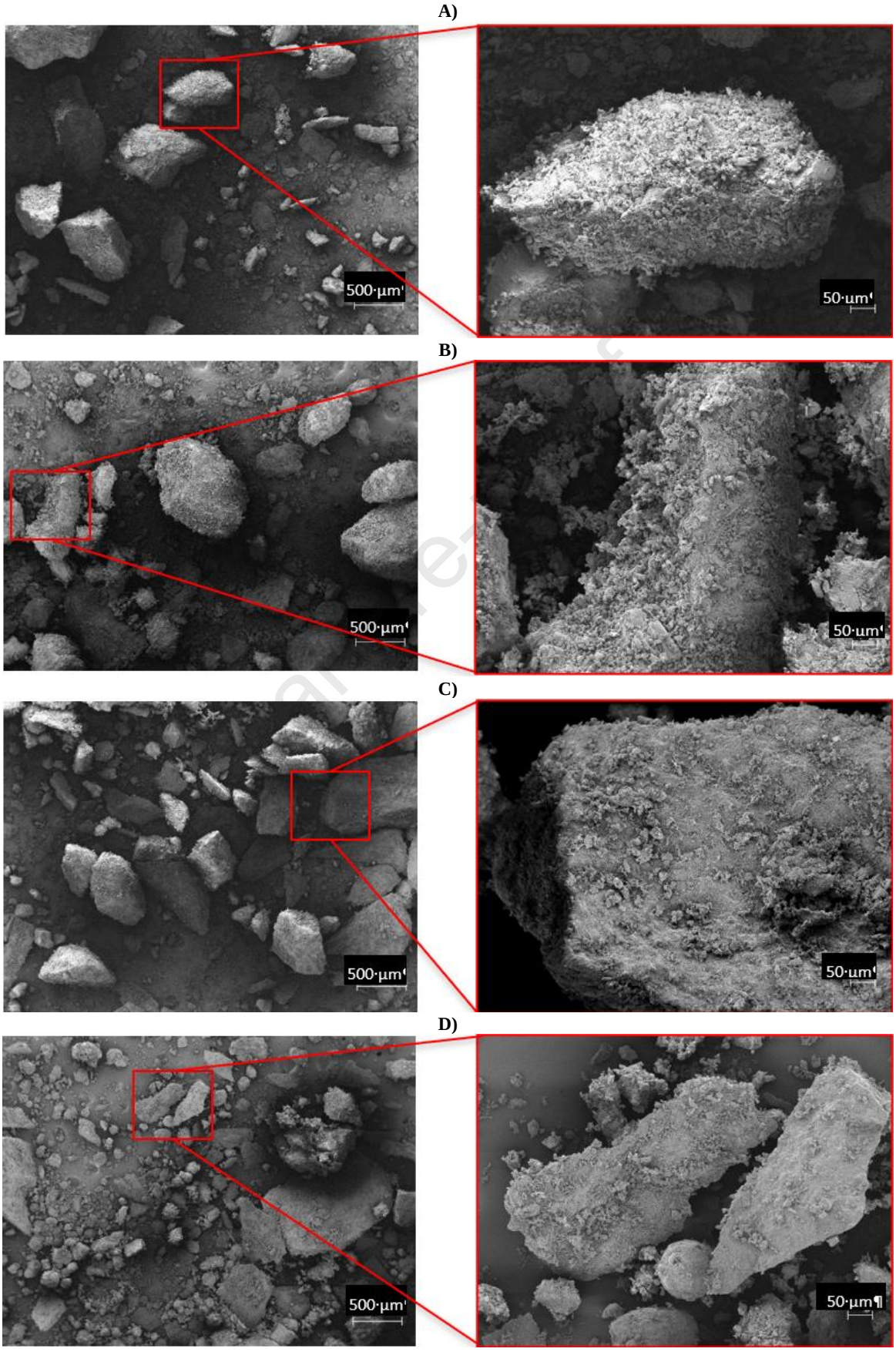

Fig. 3. SEM photomicrographs of granules obtained by roll compaction at F_{RC} 45 kN from mannitol PO (**A**), GR (**B**), EZ (**C**) e XL (**D**).

DSC studies performed on granules obtained at the highest F_{RC} (45 kN) showed the endothermic melting peak of mannitol at 166 °C for all tested materials, confirming that dry granulation did not affect the solid state of mannitol (Fig. 4).

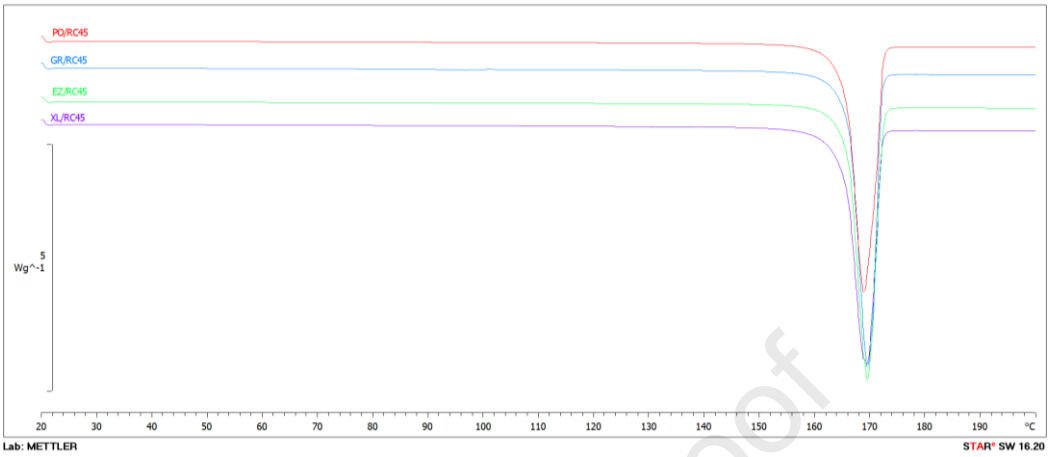

Fig. 4. DSC profiles of granules obtained at F_{RC} 45 kN from different mannitol grades.

Following dry granulation, an increase in particle size was pointed out by the shift to the right of the cumulative undersize curves (Fig. 5). For all types of mannitol, irrespective of their original size, dry granulation gave rise to particle size distributions with 80% of granules approximately ranging from 600 to 1300 µm (Table 1). While for mannitol PO, EZ and XL all the roller compaction forces yielded granules with roughly similar dimensions, in the case of GR, compaction at 15 kN resulted in slightly smaller granules as compared to higher forces, thus indicating lower compaction capacity of this mannitol type probably associated with larger size of the original particles.

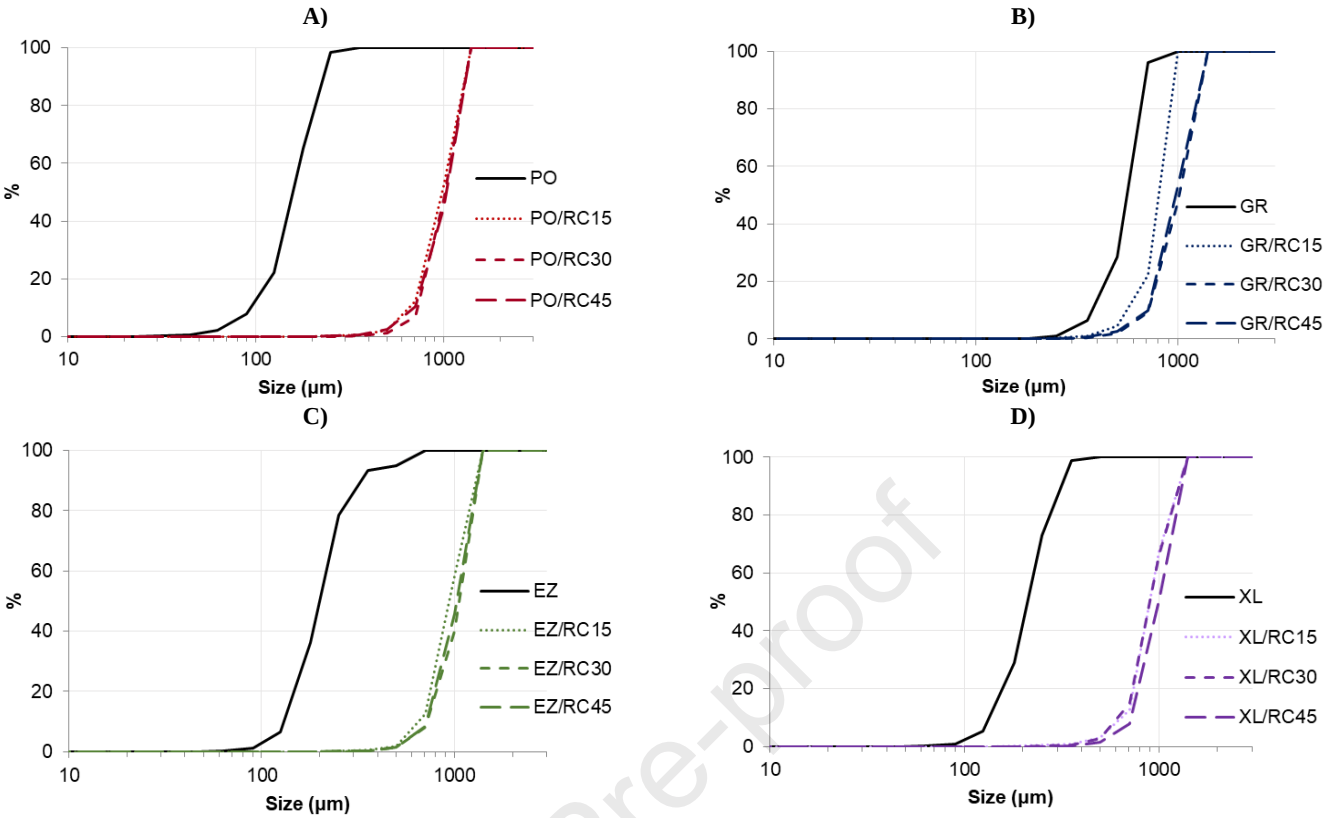

Fig. 5. Cumulative undersize distribution of different mannitol grades starting materials and granules obtained by roll compaction at increasing F_{RC}: PO (**A**), GR (**B**), EZ (**C**), XL (**D**).

Compared to the corresponding starting powders, granules showed higher specific surface area (SSA), thus indicating that particle fragmentation occurred under roller compaction, which is typical of brittle materials (Fig 6). In particular, SSA increased remarkably for granules obtained from granular and spray-dried grades of mannitol. Especially in the case of Mannitol EZ and XL a relatively high variability of SSA was observed, which may be due to inconsistent fragmentation of highly porous spray-dried products. Fragmentation was confirmed by SEM images, where very small particles were evident in the sectioned units and adhered to the surface of the granules. In particular, for mannitol EZ, a higher increase in SSA values was observed only when roller compaction pressures higher than 30 kN were applied.

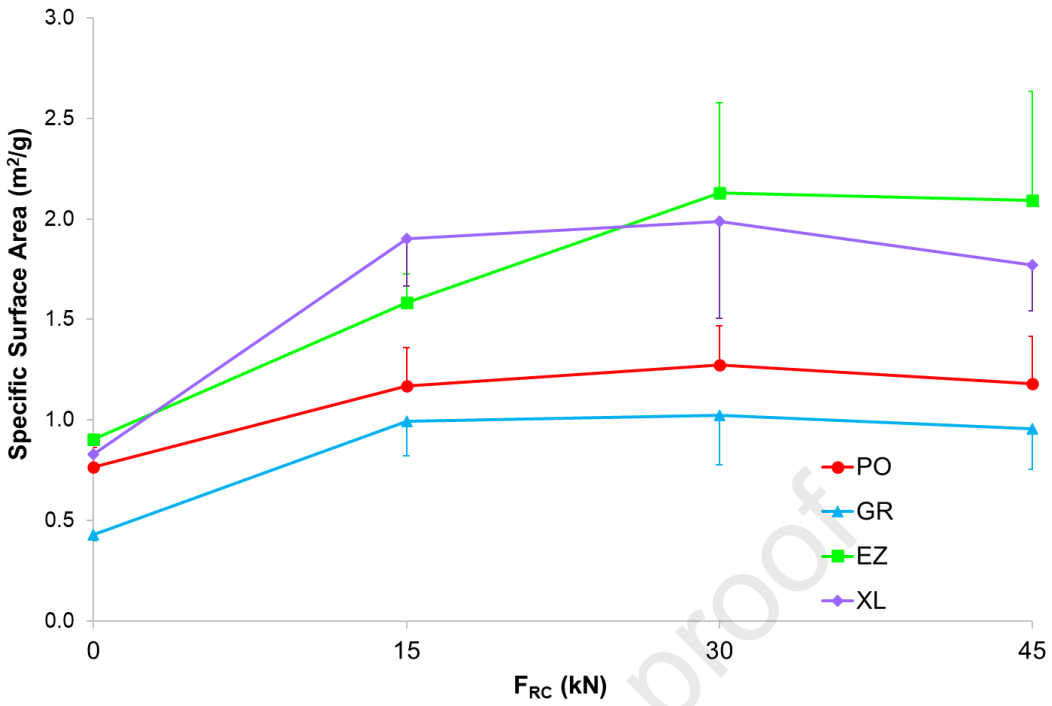

Fig. 6. Specific surface area of different mannitol grades and corresponding granules obtained at increasing F_{RC}. Vertical bars represent standard deviation (n=3).

Considering bulk density, with the exception of mannitol EZ at F_{RC} 15 kN, all granules presented values above 0.6 g/mL with a clear tendency to denser products when higher roller compaction force was applied. The bulk density of mannitol PO showed an increasing trend with respect to the other mannitol grades. Particularly, the highest bulk density value (0.72 g/mL) was achieved with this product at the maximum roller compaction force.

Flowability properties evaluated by compressibility index showed that granules obtained by mannitol GR, EZ and XL tended to be slightly less flowable: the starting products could be classified by Ph.Eur. as materials having good flowability that were worsened after granulation (Fig. 7). Only for mannitol EZ, granules processed at highest F_{RC} maintained the original flow characteristics. The flow characteristics of mannitol PO were remarkably improved by the dry granulation process at increasing force, as expected due to its powder form.

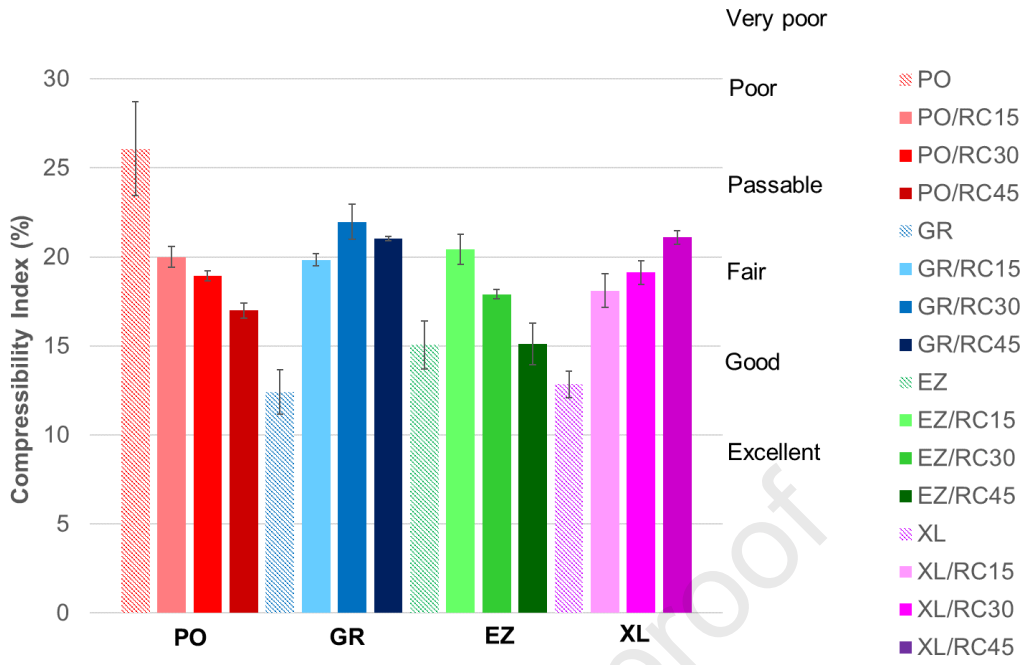

Fig. 7. Compressibility index of different mannitol grades and corresponding granules obtained at increasing F_{RC}. Vertical bars represent standard deviation (n=3). Scale of flowability according to Ph.Eur.10.7 [50].

The ability of raw materials and dry granules to be compacted was comparatively evaluated by preparing tablets at increasing compaction force using flat punches with 11.28 mm diameter. A lubricant was added prior to tableting to reduce ejection force and limit wearing of tooling. Both raw materials and the corresponding granules displayed overall good compaction properties. A linear relationship of tablet tensile strength versus tableting compaction pressure was found in all the cases (Fig. 8). Tablets mechanically strong enough to withstand further handling (tensile strength > 1.7 MPa) were obtained at tableting pressure > 200 MPa, even for dry granules of the mannitol grade showing the worst compaction properties (GR) [55]. The relationship between compaction ability of the granules and roller compaction force along with the values of starting materials is shown in Fig. 9. XL and EZ mannitol grades proved to be more sensitive than PO and GR in loosing ability to compaction after dry granulation. For these types of mannitol, which outperformed PO and GR grades in compaction, the higher the roller compaction force experienced in dry granulation, the lower was the compaction ability of the resulting granules. This drop-off could relate to the presence of amorphous material generated by spray drying process, which could increase sensitivity to compaction procedures prior to tableting as previously reported with respect to spray-dried [56–58]. This behavior can also be ascribed to the breakdown of porous structure during RC associated with particles enlargement and work-hardening phenomena, as extensively described in the literature [3,42,59]. On the other hand, PO and GR grades showed lesser compaction ability, which however seemed to be poorly affected by dry granulation. Although all types of mannitol considered were turned into granules of good quality, the findings of this study would suggest mannitol XL should be preferred in view of a possible application to active ingredients requiring high F_{RC} to prepare granules of high density [60].

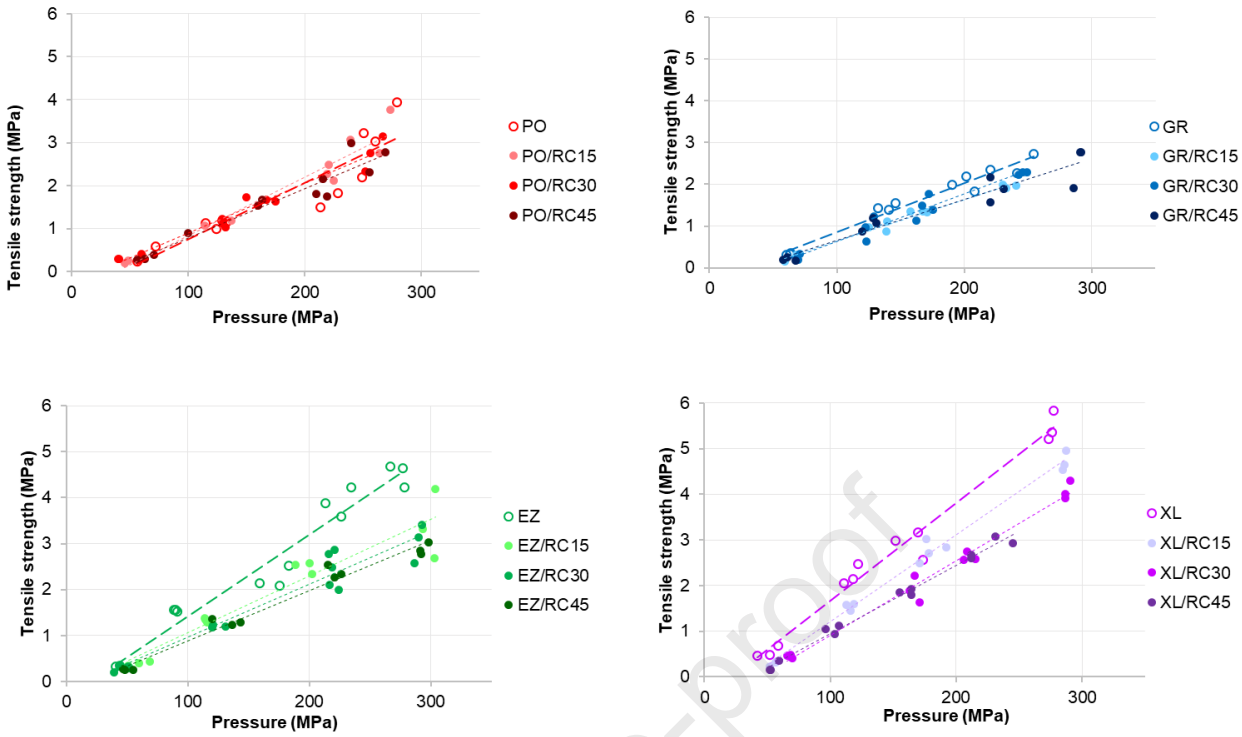

Fig. 8. Tensile strength vs pressure graphs of different mannitol grades and corresponding granules obtained at increasing F_{RC}. Lines represent linear regression.

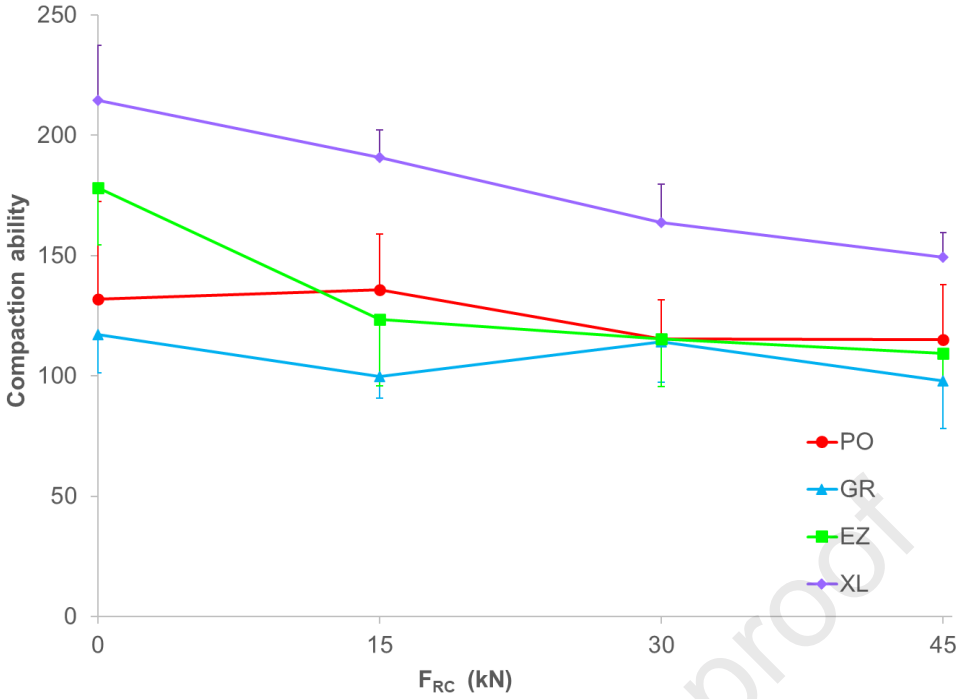

Fig. 9. Compaction ability of mannitol grades and corresponding granules as a function of F_{RC} applied for their production. Vertical bars represent standard deviation.

4. Conclusions

Various mannitol grades were evaluated for dry granulation by roller compaction in view of their use as main fillers to formulate active ingredients with poor flow and compaction properties. Although some of the products considered are mainly proposed for direct compression, the possibility of exploiting the excellent flow and compaction properties of processed mannitol to improve the ability to constantly feed the rolls and generate more resistant-to-crushing tablets was considered attractive when formulating active ingredients with problematic properties. All the tested materials proved able to yield granules with good technological properties in terms of flowability and bulk density, as well as satisfactory aptitude to tableting. However, the compaction ability of granules obtained from mannitol PO and GR was less affected by roller compaction force compared to that of mannitol XL and EZ grades. Overall, mannitol XL showed superior ability to compact even when processed at the highest roll compaction force. It should also be noted that processed materials may have higher purchase costs compared to powder/unprocessed mannitol, opening the evaluation of their use to economic considerations in addition to technological ones.

Therefore, all the considered mannitol grades can be proposed for the preparation of granules, allowing to select the most appropriate one depending on the specific characteristics of the drug to be formulated. In this regard, tableting properties of mannitol observed after dry granulation might help to compensate for possible loss of compaction ability of the drug under roller compaction, and eventually improve the drug loading capacity in the final tablet composition. In any case, to avoid mixing and segregation issues during the feeding of the rolls, the evaluation of particle size and bulk density of the drug will be useful to select the mannitol type with possibly matching characteristics.

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Author Contributions: Conceptualization: L.P., A.G., A.F., and M.C. (Matteo Cerea); Methodology: A. M. (Alessandra Maroni), A. M. (Alice Melocchi), M.C. (Micol Cirilli) and S.M.; Formal analysis: M.C. (Micol Cirilli), S.M and L.Z; Investigation: L.P., A.F., A.G., A. M. (Alessandra Maroni), A.M. (Alice Melocchi), M.C. (Micol Cirilli) and S.M.; Writing—original draft: M.C. (Micol Cirilli), S.M., L.Z., A.M. (Alessandra Maroni), A. M. (Alice Melocchi), M.C. (Matteo Cerea) and A.F.; Writing—review and editing: L.P., A.G., A.F. M.C. (Matteo Cerea), and A. M. (Alessandra Maroni); Supervision: A.G., L.Z. A.M. (Alice Melocchi), A.M. (Alessandra Maroni), M.C. (Matteo Cerea) and A.F; Project administration: L.P; Resources: M.C. (Matteo Cerea) and A.G.. All authors have read and agreed to the published version of the manuscript.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: