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ORIGINAL ARTICLE

PRODUCTION OF DIRECTLY COMPRESSIBLE EXCIPIENTS WITH MANNITOL BY WET GRANULATION: RHEOLOGICAL, COMPRESSIBILITY AND COMPACTIBILITY CHARACTERIZATION

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Abstract

The purpose of this research was to produce co-processed excipients using mannitol as base material with some of the most used binders: potato, maize pre-gelatinized starch, and K-25, K-29/32, K-90 povidone. Mannitol, one commercial based-mannitol product, and the produced materials were characterized by their particle size distribution, Carr's index, Hausner ratio, angle of repose, powder flow, and moisture content. Heckel analysis, compactibility profiles, and Ryshkewitch-Duckworth analysis were also evaluated. It is concluded that co-processing mannitol enhances flow, compressibility, and compactibility properties of the materials. Heckel analysis showed a decreased yield pressure (P_y) value for the co-processed materials; while a 10-times increment in mechanical resistance of co-processed materials was observed in compactibility profiles in comparison with mannitol tablets. Ryshkewitch-Duckworth analysis allowed the calculation of the bonding capacity, which in some cases was similar to ductile materials as microcrystalline cellulose.

Rezumat

Scopul acestei lucrări a fost obținerea de excipienți co-procesați pornind de la manitol, alături de lianți precum: cartof, poromb, amidon pre-gelatinizat și povidonă K-25, K-29/32, K-90. Manitolul și ceilalți excipienți au fost caracterizați prin distribuția mărimii particulelor, indexul Carr, raportul Hausner, capacitatea de curgere și umiditatea relativă. Analiza Heckel, pofilele de compactibilitate și analiza Ryshkewitch-Duckworth au fost, de asemenea, evaluate. Co-procesarea manitolului îmbunătățește profilele de curgere, compresibilitate și compactibilitate ale materialelor. Analiza Heckel a arătat o scădere a valorii presiuni (P_y) pentru materialele co-procesate; a fost observată o creștere de 10 ori a rezistenței mecanice pentru materialele co-procesate pe baza pofilelor de compactibilitate raportate la comprimatele cu manitol. Analiza Ryshkewitch-Duckworth a permis calcularea capacității de legare, care în unele cazuri a fost similară cu cea a celulozei microcristaline.

Keywords: co-processed excipients, mannitol, rheological characterization, compressibility and compactibility

Introduction

Historically, oral route has been the most often used route of prescription and administration of medicines; tablets are considered the pharmaceutical dosage form of choice for patients and pharmaceutical companies because they are cheap and easy to be administered [1]. There are three methods for their production: wet granulation (WG), dry granulation (DG) and direct compression (DC), their advantages and disadvantages are well documented for each one [2-4]. Granulation is a process of particle enlargement by means of agglomeration of individual particles, which at a certain point can be identified. The main difference between WG and DG is that the first requires the presence of a liquid to agglomerate the particles [5]. DC involves few processing steps, less equipment and time of production and therefore, permits economical and energy savings. However, DC is highly impacted by properties of the excipients used, e.g. flow, compressibility, compactibility, and dilution potential; which will allow good die filling, better content uniformity, and less weight variation.

About 80% of marketed tablets are produced by WG despite involving a larger number of operation stages, addition and removal of water, and stability related problems for thermolabile drugs and those that can be susceptible of hydrolysis [6]. It has been estimated that less of 20% of pharmaceutical materials can be directly compressed and that the rest of them lack good flow properties, cohesion, and lubrication to produce tablets by DC, which means that not always the excipients have the ideal performance properties to allow certain products to be developed or manufactured adequately [7, 8]. For such reasons, combinations of excipients are used and they are classified into two

broad groups: physical mixtures and co-processed excipients. The co-processing consists in the interaction of two or more excipients at sub-particle level; it produces an excipient with improved functionality and masking the undesirable properties when some of the components have them [9]. Co-processing is a cost-effective method of providing high functionality materials, and its principal advantage is the absence of rigorous toxicological and safety studies as those in new chemical entities designed to be used as excipients [10, 11]. At this respect, the most common co-processing strategies are spray-drying, granulation, melt extrusion and milling.

D-mannitol is a polyol and isomer carbohydrate of sorbitol. It is a crystalline odourless with sweet flavour powder which results refreshing for the mouth; therefore, is mainly used in pharmaceutical solid dosage forms as a diluent excipient (10 - 90% w/w) in chewing, paediatric and geriatric, and orally disintegrating tablets [12, 13]. Mannitol presents various polymorphs [14], but the commercial and more stable form (β polymorph) is characterized by having poor compressibility and compactibility properties, and insufficient disintegration [15-20]. Recently, the pharmaceutical industry has put great interest in mannitol due to its chemical stability, water-solubility, and low hygroscopicity [21]; however, crystalline mannitol is very friable, leading to the formation of fine particles that decrease its flow properties.

In addition, there are a few commercial co-processed (CP) excipients based on mannitol for DC e.g., Parteck® ODT (mannitol and croscarmellose sodium, produced by spray-drying) Pearlitol® Flash (mannitol and starch, produced by WG), Disintequick™ ODT (mannitol, lactose, crospovidone, and dextrose monohydrate, produced by freeze-drying), Compressol™ SM (mannitol and sorbitol, produced by WG), Ludiflash® (mannitol, crospovidone and polyvinyl acetate, produced by WG), F-MELT® Type C (mannitol, xylitol, microcrystalline cellulose, crospovidone, and dibasic calcium phosphate anhydrous, produced by spray-drying), and F-MELT® Type M (mannitol, xylitol, microcrystalline cellulose, crospovidone and magnesium aluminometasilicate, produced by spray-drying).

The aim of this study was to develop co-processed excipients using mannitol as a base excipient in combination with some of the most common polymers used at the pharmaceutical industry: starch (potato, corn and pregelatinized) and povidone (K-25, K-29/32 y K-90) by wet granulation in fluid bed dryer. Classify them according to their rheological characterization, compressibility and compactibility properties with mathematical models, compare the developed products with mannitol alone, their physical mixture (only for the best materials), and a commercial product (Pearlitol® Flash). According to the literature, there are few reports that deal with co-processing of mannitol and none of them has employed the proposed polymers and process treated by this research [8, 22-26].

Materials and Methods

Materials

The materials used were crystalline D-Mannitol (β polymorph, Merck Millipore, Germany), corn starch (Química Barsa, México), potato starch (Química Meyer, México), pregelatinized starch (Starch 1500®, Colorcon, USA), povidone K-25, K-29/32 and K-90 (Plasdone™, Ashland, USA), deionized water (Aguam, Mexico), Pearlitol® Flash (Roquette, France), and magnesium stearate (Merck Millipore, Germany).

Production of co-processed excipients

The co-processed materials were prepared using a fraction of mannitol's particle size between 40 - 100 µm. The dispersions of binding agents (starches and povidones) were prepared at 10% w/w by mixing 17.65 g of binder in deionized water (158.9 g) under constant stirring with an overhead stirrer (Caframo BDC 2002). The co-processing was performed in a fluid bed dryer (Aeromatic-Fielder Strea 1, Gea Pharma) by continuous spraying of the binder solutions to mannitol and drying at the same time, using a peristaltic pump (Watson-Marlow CSI-323), 100 g of mannitol were placed in the conical chamber. Mannitol was pre-heated for 5 minutes, once the chamber reached 50°C the spraying of the binder solutions started. Binder solutions were sprayed at a rate near to 4 - 6 g/min with an atomization pressure of 1.0 bar using a centred top-spray nozzle. The fluidizing air velocity was nearly to 0.95 m/s, inlet and outlet temperatures were 30 - 35 and 25°C respectively. The environmental conditions were 20 - 25°C and relative humidity of 40 - 55%. Corn starch (CS) and potato starch (PS) dispersions were prepared with hot water. Triplicate performed each batch; each one of them had a time of 40 - 50 min.

Preparation of physical mixtures

Physical mixtures were prepared using the same proportions of each excipient (85:15 % of Mannitol: Polymer respectively, it means 100 g of mannitol and 17.65 g of the polymers) in a V blender (0.5 L) coupled to an universal gear (Erweka® AR 402) during 5 min at 10 rpm in order to evaluate the influence of the co-processing in the materials' performance. Physical mixtures were produced only for the best co-processed excipients.

Particle size distribution

Particle size distribution was determined in a vibratory sieve shaker (Restch AS 200) with test sieves mesh 30, 40, 50, 60, 80, 100, 120, 140, 200, 250, 270 and 400, for 5 min each batch at 0.5 mm amplitude of oscillation [27]. The rheological properties of the selected fractions of particle size distribution were evaluated as described below.

Rheological characterization

Bulk and tapped density determination. Bulk density and tapped density (ρ_b and ρ_t) were manually determined by the measuring cylinder method (100 mL graduated cylinder) [28]. The ρ_b represents the quantity of powder necessary to fill the 100 mL cylinder without tapping the sample, whereas ρ_t represents the final volume registered once all particles stop the rearrangement caused by the mechanical compaction of the materials. Carr's index (CI) or compressibility percentage and Hauser's ratio (HR) were calculated using equation 1 and 2, respectively.

$$CI = \frac{\rho_t - \rho_b}{\rho_t} x\ 100 \quad , \qquad (1)$$

$$HR = \frac{\rho_t}{\rho_b} \quad , \qquad (2)$$

Angle of repose and flow rate. The angle of repose (AR) was determined by the funnel method; each material was poured into the funnel and then allowed the sample to flow through it and reach a flat surface. A powder cone was formed and measured relative to the horizontal, where *h* represents the height and *r* the ratio of the basis of the cone (equation 3). To calculate flow rate (F_r) a flowability tester (Erweka® SUM 22) with a stainless steel of 10 mm diameter outlet nozzle was used, this parameter represents the quantity of sample per unit of time (g/s) (equation 4).

$$AR = \tan^{-1}\left(\frac{h}{r}\right), \qquad (3)$$

$$F_r = \frac{g}{s}, \qquad (4)$$

Moisture content. Moisture content (% MC) was measured in a moisture analyser (Ohaus® MB45), with a heating ramp of 10ºC/min for 10 min until reaching a 100ºC final temperature.

Photographs of mannitol and co-processed materials. The photographs of the raw mannitol and co-processed materials were obtained using an Olympus SZ51 stereomicroscope (Olympus Corporation, PA, USA). The samples were placed and spread in the shade plate for microscope imaging.

Heckel analysis and tensile strength vs compaction pressure plots

Tablets were compressed in a hydraulic press (Carver 3012) using 13 mm diameter flat-faced punches, applying a compaction pressure of 7 to 282 MPa and a time of compression of 5 s. Quantity of 500 mg of each material were weighted for a single tablet. Relative density (ρ_{rel}) was determined by the ratio of bulk density of the tablet (ρ_b) and true density of powder (ρ_t); which was calculated from the measurement of tablets obtained at a compaction pressure of 650 MPa (equation 5). The material's deformation behaviour was evaluated through Heckel equation, where P_{compac} is the compaction pressure, *K* is the slope known as Heckel constant, and the inverse of *K* is the yield pressure (P_y). Additionally, the intercept *A* is related with ρ_{rel} (equations 6, 7 and 8, respectively). The slope was obtained from the linear portion of the plot, and it was selected with the minimum squares' method.

$$\rho_{rel} = \frac{\rho_b}{\rho_T} \quad , \qquad (5)$$

$$\ln\left(\frac{1}{1-\rho_{rel}}\right) = K\ P_{compac} + A \quad , \qquad (6)$$

$$K = \frac{1}{P_y} \quad , \qquad (7)$$

$$\rho_{rel} = 1 - e^{-A} \quad , \qquad (8)$$

Dimensions of tablets were measured 24 h after compression using an electronic Vernier and weighted with an accuracy of 0.1 mg (Mettler Toledo AB204-S). Three tablets were evaluated for each compaction pressure.

Such tablets were used to evaluate the diametrical crushing force (tablet hardness tester, Pharma Alliance PAH-01) and thus tensile strength (σ_T) *vs* compaction pressure (P_{compac}) plots were evaluated according to equation 9, where *F* is the breaking force, *d* is the diameter of the tablet, and *h* is the thickness of the tablet [29].

$$\sigma_T = \frac{2F}{\pi\ d\ h}, \qquad (9)$$

Ryshkewitch-Duckworth model

The tensile strength and porosity data of the compacts with different materials were fitted according to the Ryskewitch-Duckworth relation (Equation 10):

$$Ln\frac{\sigma_T}{\sigma_{T_0}} = -k\varepsilon \quad , \qquad (10)$$

in which σ_T is the tensile strength of the tablet, σ_{T0} the tensile strength at zero porosity, ε the compact porosity obtained with the relative density relation (equation 11), and *k* a constant of the model. The values of *k* and σ_{T0} were obtained by linear regression analysis.

$$\varepsilon = \left(1 - \frac{\rho_b}{\rho_T}\right), \qquad (11)$$

Statistical analysis

A normality test was performed for each parameter in Heckel and Ryshkewitch-Duckworth analyses in order to know the statistical test to be used for establishing whether it was statistically significant difference between our materials and the base excipient. All the comparisons used mannitol as control group.

For Heckel parameters (*K*, P_y and *A*; n = 3), Dunnett by multiple comparisons test was performed; while

multivariate analysis of variance (MANOVA; n = 30 for each material) was used to evaluate the behaviour during densification process.

Regarding to the Ryshkewitch-Duckworth analysis, its parameters were evaluated with a Kruskal-Wallis test for σ_{T0} and a Dunnett by multiple comparisons for k; furthermore, increasing σ_{T0} as function of porosity (ε) was evaluated with a MANOVA test.

Results and Discussion

Particle size distribution

Particle size is an important parameter that affects the properties related to a material's performance and therefore the final properties of a tablet such as hardness, friability, disintegration time, dissolution and content uniformity [30-32]. The last two are directly related to the quantity of pharmaceutical active ingredient in the pharmaceutical dosage form. Figure 1 shows the particle size distribution of mannitol, the co-processed excipients, and Pearlitol® Flash.

In the particle size distribution plot corresponding to mannitol, two populations (binomial and asymmetrical distribution) at 40 and 100 μm can be observed, both account for about 73% of the total distribution; they were recovered for co-processed production and for mannitol's rheological characterization.

According to the literature, it is considered that suitable particle size for DC must be between 200 - 400 μm [33]. In general terms, all co-processed presented a particle size into this range; materials with pregelatinized starch (PrS), potato starch (PS) and corn starch (CS) registered highest mean particle sizes (341, 315 and 314 μm, respectively); while the material with povidone K-25 (PVP) presented the smaller size (265 μm) (Table I). Pearlitol® Flash presented a mean particle size of 255 μm. In regarding to particle size curves, only the material with PVP K-29/32 presented a symmetrical distribution, while the others were asymmetrical as Pearlitol® Flash as well.

The f factor represents a measurement of the distribution's amplitude and it is defined by the ratio $d_{0.9}/d_{0.1}$; the lower value of f factor, the narrower the distribution, the higher homogeneity in particle size distribution will be revealed. Although the material with PVP K-25 presented the smaller mean particle sizes along with the PrS co-processed, both had the narrower distribution (f < 2.0) compared to materials with PS and CS which presented the wider, while Pearlitol® Flash presented an f value of 2.02. Table I summarizes the mean particle sizes, $d_{0.1}$, $d_{0.5}$, $d_{0.9}$, and f for the materials.

In order to avoid discrepancies and mistakes in the rheological characterization of the co-processed excipients influenced by the particle size differences, only the fractions of particle size distribution comprehended between 200 - 400 μm were taken to be evaluated. Fractions were collected after sieve analysis in each case.

Table I

Mean particle size of mannitol and co-processed excipients

Material	*MPS (μm)*	$d_{0.1}$	$d_{0.5}$	$d_{0.9}$	f
MAN	101	42.84	73.08	126.02	2.94
MAN-PS	315	98.70	246.96	396.90	4.02
MAN-CS	314	103.74	238.77	417.06	4.02
MAN-PrS	341	115.29	262.08	415.38	1.58
MAN-PVP K-25	265	138.82	213.05	273.42	1.97
MAN-PVP K-29/32	301	141.01	244.66	295.07	2.09
MAN-PVP K-90	312	107.10	251.68	351.66	3.28
Pearlitol® Flash (PF)	255	130.50	212.31	264.01	2.02

MPS = mean particle size; f = ratio $d_{0.9}/d_{0.1}$

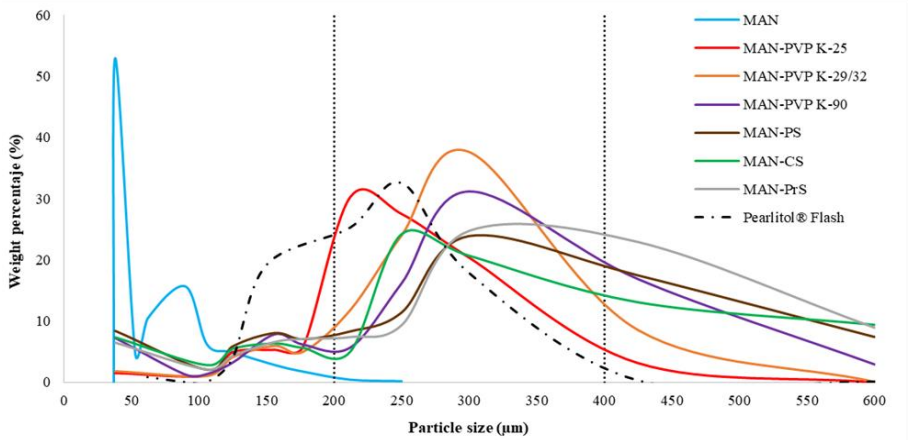

Figure 1.

Particle size distribution of mannitol, commercial product (Pearlitol® Flash, PF) and co-processed excipients

Rheological characterization

The rheological properties of the materials are summarized in Table II. Compressibility percentage or CI is a measurement of the material's ability to reduce its volume and along with Hausner´s ratio (HR), allows an assessment of inter-particulate interactions. In a free-flowing powder, the interactions are less significant and ρ_b and ρ_t will be present in similar values, on the contrary, in poor flowing powders inter-particulate interactions are present in a high percentage and so the difference between ρ_b and ρ_t [34]. At this respect, all co-processed excipients presented a ρ_b close to ρ_t; whereas mannitol had a difference of almost twice the value of the densities for co-processed materials. In accordance with the USP criteria [35], mannitol is classified as a poor flowing and compressible material; while the rest of the materials are acceptable, or in the case of co-processed with PVP K-25 it is excellent, which presented similar and even improved Carr and Hausner index than Pearlitol® Flash.

Table II

Rheological characterization of mannitol and co-processed excipients

Material	ρ_b (g/cm^3)	ρ_c (g/cm^3)	CI	HR	AR (°)	F_r (g/s)	% MC	Flow properties (*USP criteria*)
MAN	0.528 ± 0.002	0.733 ± 0.003	27.96 ± 0.02	1.38 ± 3.3 x 10^{-4}	45.86 ± 0.59	1.41 ± 0.38	0.06	Poor
MAN-PS (MAN-PS physical mixture)	0.317 ± 0.005 *(0.558)*	0.375 ± 0.004 *(0.734)*	15.46 ± 2.11 *(23.97)*	1.18 ± 0.014 *(1.31)*	32.76 ± 2.59 *(35.91)*	4.05 ± 0.19 *(2.17)*	1.56 *(ND)*	Good *(Passable)*
MAN-CS	0.312 ± 0.021	0.376 ± 0.012	17.02 ± 3.54	1.20 ± 0.019	31.93 ± 2.11	4.07 ± 0.22	1.80	Good
MAN-PrS	0.336 ± 0.010	0.396 ± 0.021	15.15 ± 1.38	1.18 ± 0.029	30.59 ± 3.81	3.96 ± 0.12	1.80	Excellent
MAN-PVP K-25 (MAN-PVP K-25 physical mixture)	0.290 ± 0.012 *(0.507)*	0.318 ± 0.024 *(0.689)*	8.80 ± 2.66 *26.41*	1.09 ± 0.038 *(1.35)*	34.23 ± 1.12 *(36.75)*	7.08 ± 0.09 *(2.85)*	1.93 *(ND)*	Excellent *(Poor)*
MAN-PVP K-29/32	0.294 ± 0.011	0.350 ± 0.022	16.00 ± 6.01	1.19 ± 1.0.09	34.95 ± 0.85	3.68 ± 0.37	2.21	Good
MAN-PVP K-90	0.307 ± 0.006	0.349 ± 0.010	12.03 ± 1.15	1.13 ± .014	33.27± 1.25	3.69 ± 0.42	0.93	Good
Pearlitol® Flash (PF)	0.478 ± 0.015	0.535 ± 0.007	10.65 ± 1.89	1.12 ± 0.02	23.38 ± 2.07	9.60 ± 0.29	1.78	Excellent

ND = non determined; ρ_b = bulk density; ρ_t = tapped density; CI = Carr's index; AR = angle of repose; HR = Hausner´s ratio; Fr = flow rate; %MC = percentage of moisture content

Angle of repose has been widely used for bulk powder characterization [36-38], it is also related with inter-particulate friction, and therefore with powder flowability. The higher angle value, the poorer will be the flow of the material and the greater its resistance to flow. For mannitol, an angle of repose of 45.86º was observed, according to the USP criteria [35] it is classified as a material with an acceptable flow, however, it just flowed after moving the sample with a spatula. For this reason, the correct classification would be a poor flowing material, while the rest of co-processed are classified as good flowing powders.

It is important to say that angle of repose is not considered a robust test to determine the material flow due to the dependence in test conditions [35, 39]; so that along with the angle it is evaluated F_r to have additional information and realistic data of how a material flows and how its performance is during die filling before compression. Mannitol presented a F_r of 1.41 g/s, while in the material with PVP K-25 it was observed a five-times increment compared with the base excipient. For the rest of co-processed materials, the increment was three times compared to mannitol. Pearlitol® Flash presented a minor angle in comparison with our products and a major, but nearer F_r to MAN-PVP K-25.

Moisture content (MC) is another property that has an impact on material's flow. Hiestand found that moisture could influence the interaction force between solid particles and as result, it affects cohesion and friction of the materials. Furthermore, this can cause stability problems in the final pharmaceutical dosage form [40]. In this research, it was important to determine such property due to the inherent characteristics of the co-processing method which involved wetting the materials with an aqueous dispersion. The results indicated that mannitol had moisture less than 0.1% that corresponded to the low hygroscopicity and low swelling ability of this material preventing the adsorption and absorption of water [21, 41]. On the other hand, the rest of co-processed presented a moisture content near to 2%. It has been suggested that as the moisture increases in a powder, the produced tablets could present less hardness due to the formation of multi-layered water, which avoids direct contact between particles [40]. Nevertheless, a dependence of tablet hardness with the moisture for certain materials has been reported; at this respect, Nokhodchi *et al*., [42] identified that HPMC K4M tablets increased their hardness as moisture was also increased from 0 to 14.9%.

The comparison with the physical mixtures was realized only for the best materials in each case; i.e. the PVP K-25 and Pre-gelatinized Starch mixes. The results are shown between parentheses in Table II, in which an improvement of the properties with the co-processing method can be seen due to the CI, HR, and AR decreasing, in addition to an improvement in flow rate for the co-processed materials.

Heckel analysis

Figure 2 shows Heckel plots for mannitol and its co-processed, we can observe from these plots a linear relation of $ln[1/(1-\rho_{rel})]$ as a function of P_{compac} between 21 - 211 MPa for all the tested materials. The linear region of such plots is where yielding of the materials

took place and densification occurred through particle's deformation, such regions were selected to analyse the model with the minimum squares regression; additionally, at low compaction pressures (0.1 - 21 MPa) a slight curvature is observed, attributable to the displacement and rearrangement of particles during compression [43]. Table III summarizes the parameters obtained with Heckel analysis. Figure 2 shows Heckel plots for a) starches and b) povidones co-processed excipients.

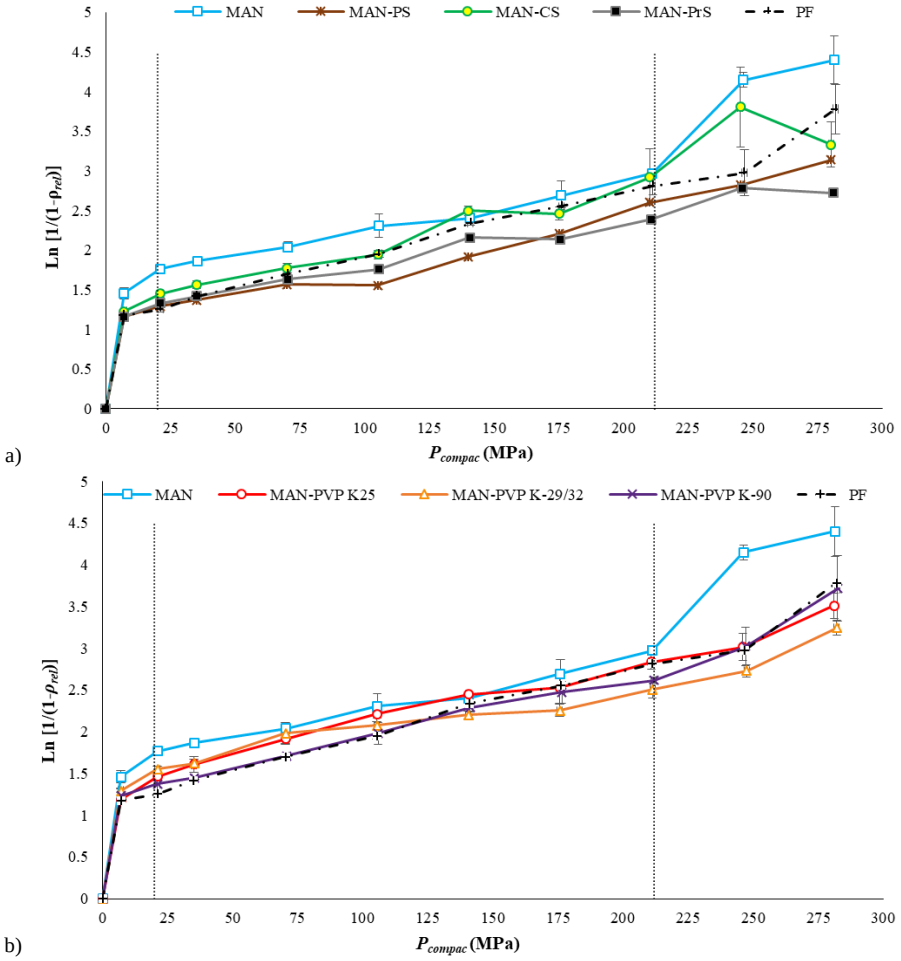

Figure 2.

Heckel plots of mannitol and co-processed excipients: a) starches and b) povidones

Even though some authors have reported deviations of Heckel modelling from linearity at lower compaction pressures (0 - 50 MPa) [44], in our data the linearity was observed with the range mentioned before; such region is shown between the dotted vertical lines in Heckel plots. The slope of the plots represents the Heckel constant (K), and its reciprocal, P_y gives information related with the plastic behaviour of a material; it represents the stress at which plastic deformation of a particle occurs [45]. The higher the P_y value, the greater compaction pressure a material will need to form a tablet. Mannitol presented a P_y of 180.80 MPa, a relatively high value that explains its poor compressibility properties, an increased resistance to deformation due to either a brittle deforming mechanism or a decreased plastic flow. However, the co-processing procedure decreased the P_y value in all the materials (except for MAN-PVP K-29/32), which means that co-processing allowed an increase in the plasticity of our materials compared with mannitol as the base excipient. MAN-CS presented the lower P_y value (123.84 MPa, Figure 2a), while the material with PVP K-25 that had the best rheological properties has a P_y of 142.63 MPa (Figure 2b). Since Heckel data exhibited a normal distribution, the statistical analysis (Dunnett by multiple comparisons followed by an ANOVA) showed a statistically significant difference in P_y (for all the co-processed materials with exception of MAN-PVP K-29/32) and A (only PVP K-29/32) which is related to the relative density. With respect to the densification process, a MANOVA analysis showed a statistically significant difference in all the materials in comparison with mannitol alone. Pearlitol® Flash showed a densification behaviour like MAN-CS and their P_y values were near one to another.

Table III

Parameters of Heckel equation for mannitol and co-processed excipients

Material	K (x 10^{-3})	P_y (MPa)	A	r^2	P^a	P^b	P^c	P^d
MAN	5.59 ± 2.52x10^{-4}	180.80 ± 6.67	1.2259 ± 0.04	0.9893	*Control*	*Control*	*Control*	*Control*
MAN-PS	7.26 ± 2.54 x 10^{-4}	139.08 ± 4.92	1.0859 ± 0.10	0.9548	0.012*	0.012*	0.078 (NS)	0.000*
MAN-CS	8.10 ± 1.5 x 10^{-3}	123.84 ± 22.56	1.2200 ± 0.11	0.9803	0.061 (NS)	0.001*	1.000 (NS)	0.000*
MAN-PrS	7.66 ± 7.11 x 10^{-4}	130.54 ± 24.93	1.2849 ± 0.05	0.9672	0.275 (NS)	0.002*	0.772 (NS)	0.000*
MAN-PVP K-25	7.18 ± 5.19 x 10^{-4}	142.63 ± 10.00	1.3661 ± 0.03	0.9833	0.264 (NS)	0.012*	0.077 (NS)	0.000*
MAN-PVP K-29/32	5.56 ± 2.10 x 10^{-4}	179.85 ± 8.89	1.4426 ± 0.01	0.9445	0.833 (NS)	1.000 (NS)	0.000*	0.000*
MAN-PVP K-90	7.10 ± 4.58 x 10^{-4}	140.81 ± 9.95	1.2173 ± 0.03	0.9921	0.549 (NS)	0.032*	1.000 (NS)	0.000*
Pearlitol® Flash (PF)	7.81 ± 5.97 x 10^{-4}	127.92 ± 9.68	1.1390 ± 0.05	0.9938	0.025*	0.001*	0.369 (NS)	0.000*

K = Heckel constant; P^a = P value for Heckel constant (K); P^b = P value for Yield pressure; P^c = P value for A ($\rho_{rel} = 1 - e^{-A}$); P^d = P value for densification process by MANOVA analysis; * = statistically different to mannitol alone when $\alpha \leq 0.05$; NS = not significant

Nordström *et al*. [46] reported that the mechanism of deformation for mannitol with a similar particle size to the used in this research, involved the fracture, but in such investigation the P_y value was 132 MPa, while other authors reported that mannitol is a plastic or ductile material as microcrystalline cellulose is [21]. This feature could be attributable to the existence of polymorphs; Burger *et al.* reported an induction of the polymorphic transition from β to δ mannitol, resulting in an enhancement of compressibility and compactibility of the material due to an increment in its density and a reduction of the elastic recovery during decompression [19]. In accordance with the classification of Roberts & Rowe [47], all the materials are classified in terms of their plasticity as moderately hard materials since their P_y values were between 80 and 200 MPa and we rank-ordered them as following: Mannitol-Corn Starch > Mannitol-Pregelatinized Starch > Mannitol-Potato starch > Mannitol-Povidone K-90 > Mannitol-Povidone K-25 >> Mannitol-Povidone K-29/32 >> Mannitol (base excipient).

An explanation for the P_y reduction in those materials with potato starch, corn starch, and pregelatinized starch could be the plasticity of starches in addition to their moisture content and even a synergistic effect. It is well known that water provides a plastic and lubricant effect [42, 48]; while in case of the materials with PVP K-25 and K-90, it has been reported for polymers like PVP and HPMC that moisture acts as a plasticizer by decreasing their T_g, then the material undergoes a transformation from a glassy to a rubbery state in which polymers have higher compression and compaction properties [49]. Additionally, water also fills the materials' pores and therefore helps to reduce the porosity [50]. Patel *et al.* found a strong dependence of P_y value on particle size of paracetamol, where increasing particle size resulted in higher yield pressure values, the increment in P_y for MAN-PVP K-29/32 could be influenced with size and shape of the particles in comparison with the PVP K-25 co-processed material [51].

Heckel model evaluates the effect of compaction pressure on densification or reduction of porosity during compression and has been used to assess the deformation mechanism of single compounds, and binary and ternary mixtures [52, 53]. This model is still widely used despite being questioned in the literature because of the obtained value parameters differ from one author to another depending on accuracy and robustness of the model [54, 55].

Tensile strength plots

Several investigations and models have been conducted and studied to gain knowledge about the mechanical properties of tablets [56-60]; however, the relationship of mechanical properties at different scale is not yet entirely understood [61]. During compaction process, measurements can be realized to ensure that compacts will have mechanical strength enough to avoid their abrasion and breaking when are being processed and handled; therefore, during manufacturing two tests are used to evaluate the mechanical strength of tablets: friability and resistance to crushing strength through diametrical tensile strength. The last one is the most used due to its easier implementation.

Figure 3 shows σ_T as a function of P_{compac} plots. It is noticed from these plots that tablets of mannitol did not increase their mechanical strength despite variations in compaction pressure, and even a decrease in tablet resistance is observed and attributable to an over-compaction, evidencing mannitol's poor compactibility reported by other authors [19, 41, 62]. For the co-processed materials containing starch (potato, corn and pregelatinized) it was observed a 3-6 times increment in the mechanical strength of the tablets compared to the base excipient in the range 7-175 MPa (Figure 3a).

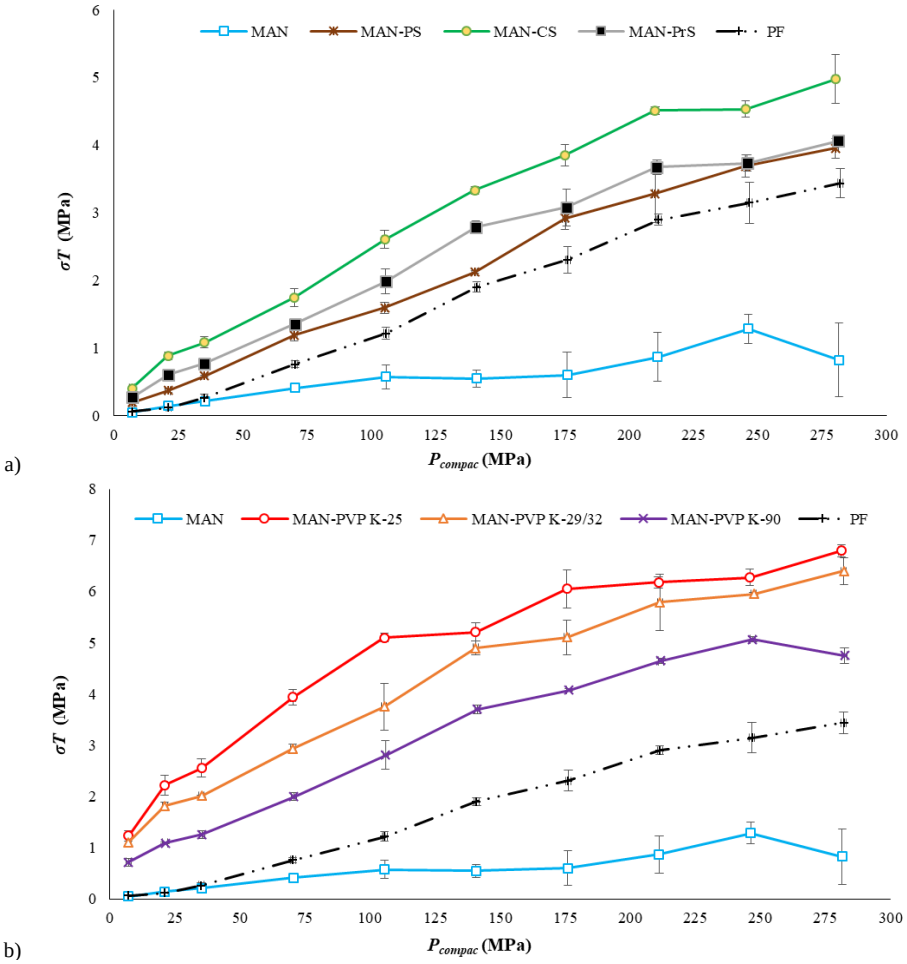

Figure 3.

Tensile strength as function on compaction pressure plots of mannitol, commercial product (Pearlitol® Flash, PF) co-processed excipients: a) starches and b) povidones

In the case of the co-processed containing PVP K-25 and K-29/32, a 10 times enhancement of mechanical strength of tablets was observed compared with mannitol alone for the same range of compaction pressures. The material with PVP K-90 was intermediate to the other materials (Figure 3b), while Pearlitol® Flash showed an inferior mechanical resistance in comparison with all our materials.

Powder consolidation in tablets is a process that involves pores reduction in the materials while inter-particulate bonds are created, which in turn implies different stages [63]. During compression process, there are two related events: compressibility, defined as the ability of a powder to reduce its volume under a pressure (represented by a porosity or densification *vs*. compaction pressure plot), and compactibility, defined as the ability of a powder to form a tablet with a mechanical hardness (represented by a tensile strength *vs*. compaction pressure plot) [64]. Some authors define compactability as the ability of a material to be transformed into tablets with certain hardness during the densification process and represent it by a tensile strength *vs*. solid fraction plot, considering such property as the most valuable. In addition, they consider a third property, the tablet ability represented by the definition of Leuenberger & Rohera to compactibility (tensile strength *vs*. compaction pressure plot) [64, 65].

Ryshkewitch-Duckworth model

The Ryshkewitch-Duckworth is an empiric model designed for the study of ceramic materials such as alumina and zirconia to study the relationship between mechanical strength and porosity and has been used to study several materials considering the porosity or the solid fraction [66]. It was found that the logarithm of the tensile strength is inversely proportional to the porosity and later, Duckworth made a correlation for a single compound tablets that resulted in equation 10 [67]. Such equation has been successfully applied to different systems with pharmaceutical applications and other science disciplines [68]. Since our materials were designed to be used as carriers in direct compression, we are considering these co-processed excipients as a single component excipient since they were granulated.

The effect of porosity on tensile strength is depicted in Figure 4 for mannitol and its co-processed excipients. Clearly can be seen that mannitol alone had a very

low mechanical strength independently of its porosity. For all the co-processed excipients (Figure 4a for starches' and Figure 4b for povidones' co-processed excipients), can be observed that with decreasing the porosity, the higher mechanical strength tablets are produced, being the best co-processed materials MAN-PrS and MAN-PVP K-25.

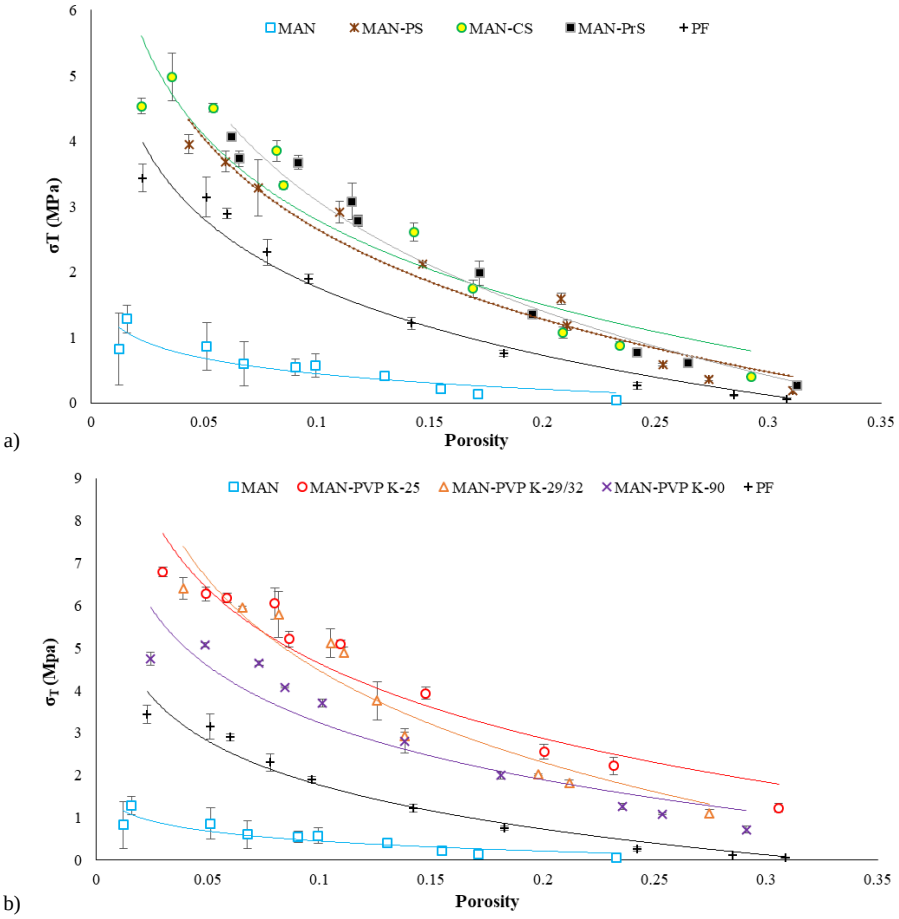

Figure 4.

Tensile strength plots as function of porosity of mannitol, commercial product (Pearlitol® Flash, PF) and co-processed excipients: a) starches and b) povidones

All the correlation coefficients obtained by linear regression are higher than 0.95, with exception of mannitol, which demonstrates that the relationship between the logarithm of the tensile strength and the porosity is linear and the experimental data can be fitted by Ryshkewitch-Duckworth equation. In the model, *k* represents the bonding capacity and σ_{T0} the tensile strength at zero porosity; the highest the *k* value, the stronger bonding of primary particles will be. The values of such parameters are presented in Table IV. Co-processed materials with PVP K-29/32 and PVP K-25 have the highest tensile strength at zero porosity, followed by that one with pre-gelatinized starch; however, mannitol alone had the highest bonding capacity and its value was close to the obtained by Pearlitol® flash and the reported value by Reynolds *et al.* (12.40 MPa), even though they used a mannitol for direct compression (Pearlitol® 200SD) [69]. This means that materials with PVP K-29/32, PVP K-25 and pregelatinized starch could produce strong tablets, and decreasing too much their porosity will increase the tensile strength; the bonding capacity for the materials with PVP K-25 and K-29/32 (6.04 and 6.92 MPa respectively) was near to the MCC value reported by Wu *et al*., (7.6) [70]. In contrast, tablets produced with mannitol alone will have very low tensile strength and decreasing the porosity could not increase significantly their mechanical resistance. Kruskall-Wallis test showed a statistically significant difference of tensile strength at zero porosity in our materials with respect to mannitol alone, while a Dunnett followed by an ANOVA test proved a statistically significant difference for Rhyshkewitch-Duckworth constant with exception of MAN-PS and MAN-PrS. Finally, a MANOVA test showed that the profiles (σ_{T0} *vs.* ε) of our materials were statistically significant different to mannitol (Table IV).

Table IV

Parameters of Ryshkewitch-Duckworth equation for mannitol and co-processed excipients

Material	k	σ_{T0}	r^2	P^a	P^b	P^c
MAN	13.21 ± 1.24	1.71 ± 0.36	0.9368	*Control*	*Control*	*Control*
MAN-PS	9.79 ± 0.40	7.87 ± 0.42	0.9879	0.474 (NS)	0.000	0.000*
MAN-CS	8.28 ± 0.36	6.79 ± 0.30	0.9725	0.001*	0.000	0.000*
MAN-PrS	9.68 ± 0.32	8.63 ± 0.16	0.9701	0.354 (NS)	0.000	0.000*
MAN-PVP K-25	6.04 ± 0.24	9.09 ± 0.35	0.9768	0.000*	0.000	0.000*
MAN-PVP K-29/32	6.92 ± 0.45	11.65 ± 0.74	0.9622	0.000*	0.000	0.000*
MAN-PVP K-90	7.73 ± 0.23	7.89 ± 0.26	0.9963	0.000*	0.000	0.000*
Pearlitol® Flash (PF)	13.62 ± 0.77	7.04 ± 0.49	0.9832	0.000*	0.000	0.000*

k = bonding capacity or Ryshkewitch-Duckworth constant; σ_{T0} = tensile strength at zero porosity; P^a = P value for Bonding capacity constant (k); P^b = P value for σ_{T0}; P^b = P value for porosity reduction by MANOVA analysis; * = statistically different to mannitol alone when $\alpha \leq 0.05$; NS = not significant

Despite that Ryshkewitch-Duckworth was an empirical model, according to Kundsen and Andersson there is a theoretical explanation related with the particle size, bond surface area between particles, pore shapes and even their orientation over the particles [71, 72]. Vromans *et al*., studied the correlation of the tensile strength with the surface area of lactose blends that was determined by mercury porosimetry. They found that the tensile strength was proportional to the surface area [73], while De Boer *et al*., also found a correlation of the tensile strength with the particle size at different compaction pressures, the smaller the particle size was, the higher the surface area in contact between particles and so the tensile strength [74]. On the other hand, some studies also considered the effect of the shape of the particles of some materials in their tensile strength and found that such property increased when more irregular the particles were, even in comparison with spherical particles [75, 76]. Is widely known that different grades of polymerization of PVP result in various molecular weights, conform they increase, the K value does as well and so their viscosity in aqueous solution resulting in harder granules. Wet granulations with PVP K-25/30/90 generally produces granules with better flow properties in comparison with other binders and gives higher binding strength when its concentration increases [77, 78]. In comparison, use of starches as binders produces granules that tend to adsorb and absorb water that does not allow them to establish strong interactions between particles leading to softer tablets with higher friability [77].

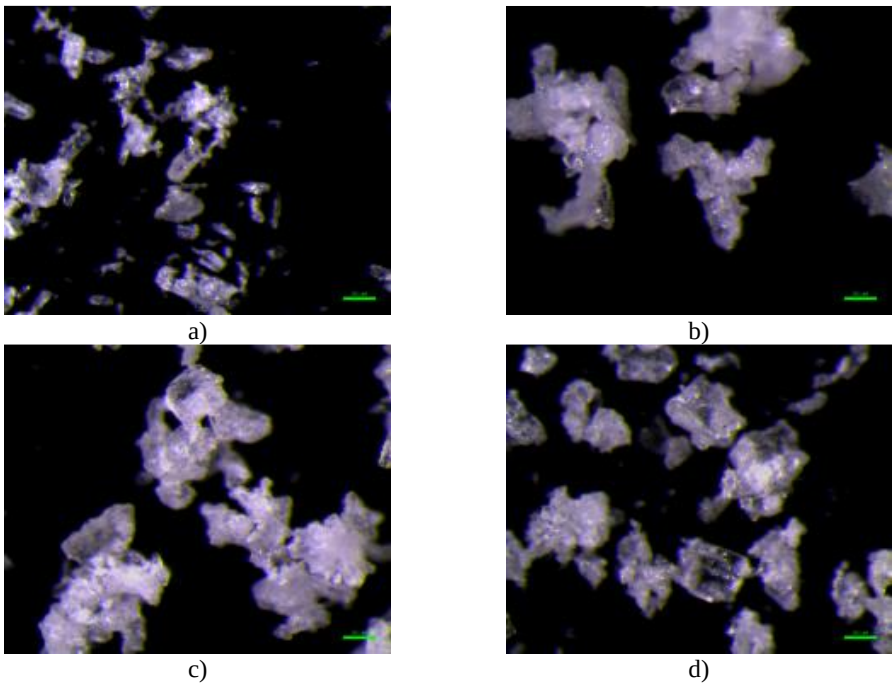

Figure 5.
Microphotographs at 56 X for: a) primary particles of mannitol, b) MAN-PVP K-25, c) PVP K-29/32 and d) MAN-PrS

The micrographics of mannitol and the co-processed excipients with PVP K-25, PVP K-29/32, and pre-gelatinized starch are presented in Figure 5, in which the primary particles of mannitol can be observed (5a) that seem to be crystalline structures; while in the co-processed excipients (5b-d), irregular particles are seen. Particle-particle bonding during compaction depends not only on factors like physical interactions related to the surface, size and shape of the particles, but also in molecular interactions (interfacial forces), and it has been proved that the magnitude of the attraction forces is highly influenced by the pressure applied and the surface energy [79]. The last one is closely related with the porosity of the materials, and in addition to the roughness of the particles in our co-processed excipients, could promote the mechanical interlocking among particles, resulting in the increase of the tensile strength of such materials.

Conclusions

This study shows how the wet granulation in a fluid bed drier as a co-processing methodology can improve the bad flow, compressibility and compactibility properties of crystalline mannitol in combination with different polymers. The rheological characterization of mannitol and the co-processed excipients exhibited an improvement in the flow and compressibility properties of our materials with respect to mannitol alone, showing that the best materials were those produced with povidone K-25 and pregelatinized starch. Compressibility characterization by Heckel modelling demonstrated an improvement in the densification process and decrease in yield pressure values for such materials too, which since a technological point of view is very important since it could represent either a lesser tooling weathering or producing tablets with lower compaction pressures. Tablet ability profiles and compactibility by Ryshkewitch-Duckworth modelling exhibited how the relationship between tensile strength with compaction pressure and solid fraction or porosity can be useful tools in order gain knowledge about the understanding of mechanical properties of materials when producing tablets; furthermore, they could provide support during tablet formulation, scale-up and technology transference, being the co-processed with povidone K-25 the material with better tensile strength independently of compaction pressure or porosity. Until now there are few reports about co-processing of mannitol and just a few of them provide a characterization that gives information about performance of the materials at an industrial scale; moreover, none of such reports used the polymers and process under study in the present research.

According to the characterization performed, we can conclude that the materials with the best properties were MAN-PVP K-25 and MAN-PrS, which could be widely recommended to be used in direct compression.

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