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Research Article

Roller Compaction, Granulation and Capsule Product Dissolution of Drug Formulations Containing a Lactose or Mannitol Filler, Starch, and Talc

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Abstract. This study investigated the influence of excipient composition to the roller compaction and granulation characteristics of pharmaceutical formulations that were comprised of a spray-dried filler (lactose monohydrate or mannitol), pregelatinized starch, talc, magnesium stearate (1% *w/w*) and a ductile active pharmaceutical ingredient (25% *w/w*) using a mixed-level factorial design. The main and interaction effects of formulation variables (i.e., filler type, starch content, and talc content) to the response factors (i.e., solid fraction and tensile strength of ribbons, particle size, compressibility and flow of granules) were analyzed using multi-linear stepwise regression analysis. Experimental results indicated that roller compacted ribbons of both lactose and mannitol formulations had similar tensile strength. However, resulting lactose-based granules were finer than the mannitol-based granules because of the brittleness of lactose compared to mannitol. Due to the poor compressiblility of starch, increasing starch content in the formulation from 0% to 20% *w/w* led to reduction in ribbon solid fraction by 10%, ribbon tensile strength by 60%, and granule size by 30%. Granules containing lactose or more starch showed less cohesive flow than granules containing mannitol and less starch. Increasing talc content from 0% to 5% *w/w* had little effect to most physical properties of ribbons and granules while the flow of mannitol-based granules was found improved. Finally, it was observed that stored at 40 °C/75% RH over 12 weeks, gelatin capsules containing lactose-based granules had reduced dissolution rates due to pellicle formation inside capsule shells, while capsules containing mannitol-based granules remained immediate dissolution without noticeable pellicle formation.

KEY WORDS: compaction; flowability; granulation; particle size; ribbon; starch.

INTRODUCTION

Roller compaction is a dry granulation process used in the pharmaceutical industry to create drug granules with suitable densification, drug content uniformity and powder flowability for manufacturing solid dosage forms such as tablets and capsules. During the roller compaction operation, uniformly mixed powder blends are passed continuously through the gap between a pair of counter rotating compression rolls to form solid ribbons or sheets which are then passed through a mill or granulator with a suitable sized screen to form dry granules. Compared to wet granulation processes, dry granulation by roller compaction has various advantages such as simpler manufacturing procedure, easier scale up and higher production throughput. Dry granulation is also energy efficient and suitable for processing pharmaceutical agents that are sensitive to moisture and heat.

Numerous experimental studies on the effects of dry granulation processing parameters to different kinds of formulated powder blends have been reported (1–4). It was found that dry granulation processing parameters, such as compression force, gap width, roll speed, feeding screw speed, granulating screen size, played different roles to the properties of ribbon and granule products (5–8). Modern roller compactors that are capable of independently controlling roll compaction force and gap width as well as controlling other processing variables could produce ribbons with uniform densification at the target solid fraction consistently (9,10). Ribbons with suitable solid fraction are usually preferred since barely compacted ribbons can disintegrates back to original primary particles of individual ingredients while overly compacted ribbons lead to hard brittle granules with poor reworkability (i.e., poor recompressibility). The most frequently used excipient used for dry granulation applications is the directly compressible microscrystalline cellulose (MCC) which unique fibrous structure offers excellent compressibility and high capacity to accommodate co-processed ingredients (11,14). Other directly compressible excipients such as lactose, mannitol, di-basic calcium phosphate are also

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commonly used, particularly in conjunction with MCC, to produce dry granules with suitable mechanical properties for tablets (13,12). Spray-dried mannitol seems to have compressibility properties comparable with spray-dried lactose for making tablets by direct compression. Direct compressible pregelatinized starch seemed to be less frequently used in dry granulation. Pregelatinized starch can be deformed plastically under high compression pressures to produce tablets with adequate hardness. However, at lower compression pressures, pregelatinized starch appears less compressible and compactable, which lead to tablets with low hardness (15). Similar poor compactability of pregelatinized starch may also occur on roller compaction; however, systematic investigation about this subject is still yet established. Other excipients such as cellulose-based polymers were also used in dry granulation as dry binders or modified release agents (16,17).

The goal of this formulation study was to investigate the roller compaction and granulation characteristics of pharmaceutical formulations that contain a ductile active pharmaceutical ingredient (API), a directly compressible filler (either lactose monohydrate or mannitol), pregelatinized starch (as a filler), talc (as a glidant) and Mg stearate (as a lubricant). Since the API used here has rather high ductility (i.e., high plasticity), spray-dried lactose monohydrate and mannitol were used as the main filler without MCC. Twelve dry granulation formulations were generated by a mixed level factorial design. The effect of three independent variables, main filler type (lactose or mannitol), starch content level, and talc content level, to the ribbon and granule properties of these formulations were investigated using the multi-linear regression and variance analysis. In addition, hard gelatin capsules containing dry granules of different formulations were manufactured and stored under the accelerated stability condition, 40 °C/75% RH, over 12 weeks. The dissolution rates of these capsules were then examined using a USP 2 apparatus in conjunction with offline high performance liquid chromatography (HPLC) assay.

EXPERIMENTAL

Materials

The developmental API bulk used in the formulations was fixed at 25% *w*/*w*. This API was found to be platy-shaped crystals with high ductility. The bulk and tapped densities of this API lot were 0.439 and 0.665 g/mL, respectively. Excipients used in the study included spray-dried lactose monohydrate (Fast Flo 316, Foremost Farms, Rothschild, WI, USA), spray-dried mannitol (Mannogem EZ, SPI Pharma, New Castle, DE, USA), pregelatinized starch (Starch 1500, Colorcon, Inc., West Point, PA, USA), Talc (140 Grade, IMI Fabi, LLC (USA), NC, USA) and magnesium stearate (vegetable-derived, Malinkrodt, St. Louis, MO, USA). The particle size of the all ingredients are shown later in Fig. 4.

Formulation Design and Statistical Analysis

Table I lists the 12 dry granulation formulations created from the mixed-level factorial design that covers two types of filler (lactose or mannitol), three levels of starch content (0%, 5%, and 20% *w*/*w*), and two levels of talc content (0% and 5% *w*/*w*). The amounts of API and magnesium stearate in all samples were kept constant at 25% *w*/*w* (active) and 1% *w*/*w*, respectively. Multi-linear stepwise regression analysis was used to analyze the dependence of response variables (Y) of DG samples on the three independent variables: filler type (F), starch content (S) and talc content (T). The response variables (Y) include the following physical properties: ribbon solid fraction, ribbon tensile strength, granule particle size, and granule flow properties.

Statistical software, Fusion Pro Version 7.3.20, was used to perform the regression analysis. Quadratic regression modeling with backward elimination (i.e., successive removal of model terms until all remaining terms in the final model have F values above a set target F value) was employed for calculating the main effects and significant interactions for the three independent variables. The target F value for backward elimination was 4 which is equivalent to a probability P-Value of 0.05 used in a t test. The resulting models can be presented as follows

$$Y = \beta_0 + \beta_1 F + \beta_2 S + \beta_3 T + \beta_4 FS + \beta_5 FT + \beta_6 ST + \beta_7 S^2 \quad (1)$$

where F is the filler type that is categorized as 0 and 1 for lactose and mannitol, respectively. S and T are the normalized weight of starch (i.e., 0, 0.25, 1) and talc (i.e., 0, 1) in their respective range. The coefficients of regression terms include a constant β_0 and parameters from β_1 to β_7. The significance of model terms can also be ranked (pareto ranking) on a relative scale from 0 to 1, where 1 is the rank of the term with the strongest effect across its experiment range.

Sample Manufacturing

The dry granules of each formulation were manufactured via delumping, blending, lubrication, roller compaction and milling. Then, the prepared granules were lubricated and encapsulated into hard gelatin capsules.

Delumping and Blending

API and all excipient bulk lots were passed individually through a Comil (Comil 197S, Quadro Engineering Inc., Waterloo, ON, Canada) equipped with a 0.045-in. screen and a round-armed impeller rotating at 1,100 rpm. API and excipients were dispensed from the delumped bulk lots and

Table I. Formulations Generated From Factorial Design

Dry granulation ingredients	% *w*/*w*
Active ingredient	25.3
Starch 1,500	0, 5 or 20
Talc 140	0 or 5
Magnesium Stearate[a]	1
Lactose or mannitol	Remaining
Total	100

[a] Evenly divided for blend and granule lubrications

blended on a PK blender (Patterson-Kelley, East Stroudsburg, PA, USA) for 300 rotations. The prepared blend was subsequently lubricated with 0.5% *w/w* Mg stearate for 100 rotations. The quantity of each prepared blend was about 600 g.

Roller Compaction

Powder blends were compacted into ribbons by a roller compactor (Mini-Pactor, Gerteis Maschinen+Processengineering AG, Jona, Switzerland). A pair of smooth compaction rolls with 25 cm in diameter and 2.5 cm in width was used. The roll pair consists of a normal roll and a rimmed roll that effectively reduce the bypass (leakage) of granules during compaction. Gap control was used during the roller compaction operation. The press force, gap width, and press roller speed were set at 7 kN/cm, 2 mm and 2 rpm, respectively. Due to small quantity, each blend sample was charged directly into the tamp agar assembly rather than the main feed hopper.

Milling and Lubrication

Each ribbon sample was passed through a mill (Fitzmill Model L1A, Fitzpatrick Company, Chicago, IL, USA) equipped with a 0.065-in. screen and a set of knives moving forward at 2,500 rpm. Afterwards, the prepared granules were lubricated with 0.5% *w/w* Mg stearate in a PK blender (Patterson-Kelley, East Stroudsburg, PA, USA) for 100 rotations.

Encapsulation

Each dry granulation sample was hand filled in Size 3 grey/grey Coni-Snap capsules to the target weight of 200 mg using an encapsulator (Minicap T-50, Scientific Instruments and Technology). The capsules were polished and contained in the induction sealed high-density polyethylene bottles that were subsequently stored at 40 °C/75% RH for accelerated stability tests.

Physical Property Measurements

Ribbon Solid Fraction, Envelope, and True Densities

The solid fraction of ribbons was calculated according to the following relationship:

$$SF = \frac{\rho_e}{\rho_o} \tag{2}$$

where SF is the solid fraction (i.e., relative density) of ribbons; ρ_e is the envelope density of ribbons; ρ_o is the true density of the granules milled from ribbons (18). The true density of granulated materials was determined using a helium pycnometer (UltraPycnometer® 1000, Quantachrome Corporation, Boynton Beach, FL, USA). The envelope density of each ribbon sample was measured by a GeoPyc® 1360 envelope density analyzer (Micromeritics Instrument Co., Norcross, GA, USA). Both true and envelope densities of each sample were performed in triplicate, and the average and the relative standard deviation of measured values were calculated.

Ribbon Tensile Strength

The tensile strength of the ribbons was quantified by a three-point beam bending test using a texture analyzer (TA. XT Plus, Texture Technologies Corp, Scarsdale, NY, USA) via the following equation (18–20).

$$\sigma_T = \frac{3}{2}\frac{F \times L}{W \times t^2} \tag{3}$$

where σ_T is the tensile strength at fracture; F is the force applied at fracture; W and t are the width and thickness of flat-faced rectangular compacts fabricated from ribbons, respectively; L is the gap distance between two supporting beams underneath the compact. The third beam moves downwards to bend the compact right at the middle of the two supporting beams. The speed of applied force was fixed at 0.1 mm/s.

Granule Particle Size Distribution

The particle size distributions of the powder samples were measured using a Sympatec HELOS particle size analyzer (Sympatec GmbH, Clausthal-Zellerfeld, Germany) equipped with a VIBRI/RODOS dry dispersion module. The quantity of sample used in each measurement was about 1 g. The laser diffraction patterns of the powder samples were converted to the volume-based particle size distribution using the supplied Fraunhofer diffraction calculation that assumes sample powders are spherical particles. Each sample was measured in triplicate and the average particle size distribution was calculated.

Granule Bulk and Tapped Density

The bulk density, ρ_b, of granules was determined by the weight of granules filled into a 25 mL graduated cylinder. The tapped density, ρ_t, of granules was determined by tapping the filled graduated cylinder for 2,000 taps using a tap density tester (Vanderkamp, VanKel Industries, Edison, NJ, USA). Carr compressibility index (CI) of ribbons was then calculated.

Granule Flow Evaluation

Flow properties of granules were assessed using an avalanche tester (Aero-Flow™ Model 325000, TSI Inc., St. Paul, MN, USA) that measured the avalanche time distribution of tested powders tumbling inside a slowly rotating drum over a time period. The flow cohesivity and variability of powders were assessed based on the mean value and the coefficient of variation of measured avalanche time distribution, respectively. In this study, each sample was tested in duplicate using 50 mL of materials per run. The speed and duration of drum rotation were set at 145 s per rotation and 20 min, respectively. These selected operational parameter values were demonstrated to reproducibly rank the flow properties of a series of common pharmaceutical excipient powders (21).

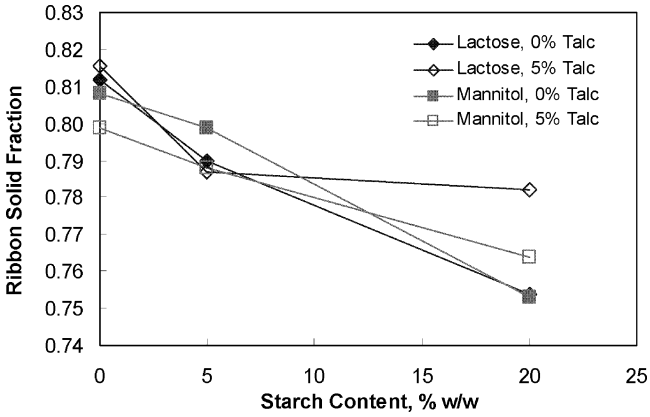

Fig. 1. Ribbon solid fraction with respect to the starch content

Capsule Dissolution

The dissolution of capsules containing dry granules was performed on a USP 2 dissolution apparatus with the paddle rotating at 50 rpm and the dissolution medium of 900 mL USP water at 37 °C. For each dissolution test, six capsules per sample were used. The dissolution rates of API from capsules were measured by an HPLC system (Agilent 1100, Agilent Technologies, CA, USA) equipped with a C18 chromatographic column (Phenomenex Luna C-18(2), 3 μm, 4.6 mm× 5 cm) and an ultraviolet detector with the wavelength set at 210 nm.

RESULTS AND DISCUSSION

Solid Fraction of Ribbons

Figure 1 illustrates the solid fraction of ribbons made by roller compaction with respect to the starch content. The solid fraction of ribbon samples was found in the range of 0.75–0.81. By stepwise omitting the least significant coefficients of the quadratic model, the following model was obtained

$$SF = 0.8115 - 0.0549S - 0.0113T + 0.0227ST \qquad (4)$$

where the coefficient of determination R^2=0.88 and the significance of model terms follows the order: S=1, ST= 0.26. These results indicate that the starch content is the dominating main effect to the ribbon solid fraction while the filler type and the talc content are insignificant to the ribbon solid fraction. As shown in Fig. 1, for all lactose and mannitol-based ribbons, increasing in starch content from 0, 5% to 20% *w/w* leads to steady reduction of the solid fraction of ribbons from 0.81, 0.79 to 0.76.

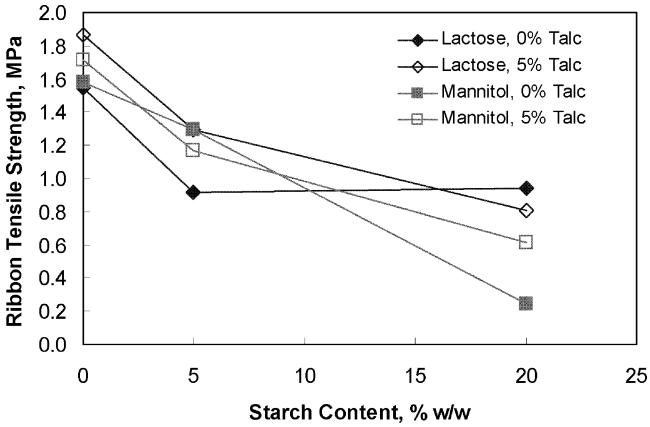

Fig. 2. Ribbon tensile strength with respect to the starch content

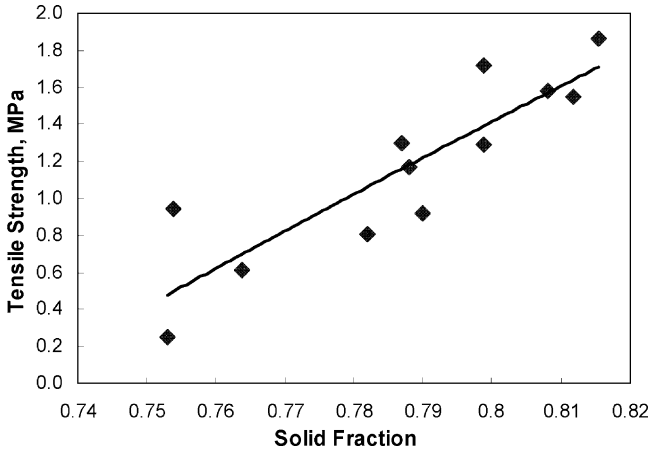

Fig. 3. Ribbon tensile strength with respect to solid fraction

Tensile Strength of Ribbons

Figure 2 shows the tensile strength at fracture, σ_T, of ribbons with respect to the starch content. The tensile strength of ribbons was found ranging from 0.25 to 1.86 MPa. The tensile strength of each ribbon in Fig. 2 is the average of at least three replicate measurements. However, for the softest ribbon samples (two, three, and nine), only one to two replicates were measured due to difficulties in obtaining sizable compacts. The relative standard deviation of tested compact specimens falls in the range of 11–33%. Multi-linear regression analysis leads to the following model

$$\sigma_T(MPa) = 1.5605 - 0.9468S \qquad (5)$$

where R^2=0.768. It is clear that starch is the only statistically significant factor to ribbon tensile strength. As shown in Fig. 3, for both lactose and mannitol samples, increase in starch content from 0% to 5% *w/w* results in the significant reduction in tensile strength from around 1.7 MPa to less than 1 MPa. The variation in filler type and talc content does not affect the tensile strength of ribbons noticeably.

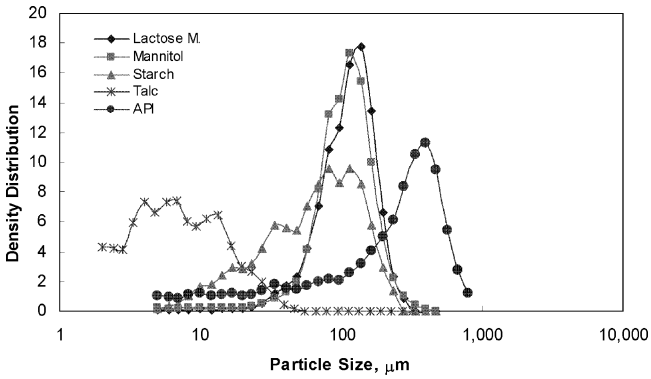

Fig. 4. Particle size distribution of API and excipients

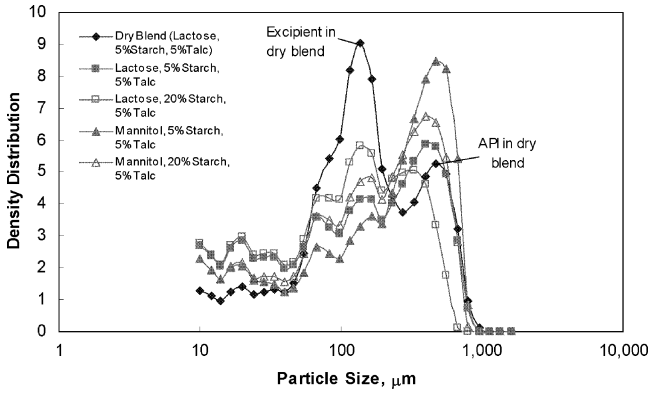

Fig. 5. Particle size distribution of selected dry granulation samples and a dry blend (as reference)

Figure 3 illustrates the tensile strength of ribbon samples with respect to their solid fraction. The tensile strength displays a positive correlation to the solid fraction with the coefficient of determination R^2=0.77. This trend suggests that ribbons with higher densification have more inter-particle bonding inside ribbon matrix and hence have stronger ribbon integrity.

Particle Size Distribution of Dry Granules

Figure 4 illustrates particle size distribution of API and individual excipients used in this study. The API has a fairly wide particle size distribution with the maximum peak located around 400 μm. Both spray-dried lactose monohydrate and mannitol have similar particle size distributions with the maximum peak located around 120 μm. The particle size distribution of pregelatinized starch, peaked at around 80 μm, is slightly smaller and partially overlaps with those of lactose and mannitol. Compared to other excipients, talc has a much smaller particle size distribution peaked at 10 μm.

The particle size distributions of selected dry granule samples are illustrated in Fig. 5. The particle size distribution of a dry blend sample is also illustrated as a reference. This dry blend sample displays two apparent particle size peaks located at around 450 and 120 μm that correspond to API and lactose/mannitol/starch excipients, respectively. Note that the existence of starch is evident with a shoulder on the left side of the 120 μm peak. It is notable that the particle size distribution of each dry granulation sample also looks somewhat bi-modal with a large size peak located between 300 and 700 μm and a pair of small size peaks located around 80 and 120 μm.

The large size peak of granule samples consists of dry granules of broad size range and the maximum of the peak varies with the composition of formulations. The small size peaks of granule samples match the particle sizes of lactose/mannitol/starch ingredients, suggesting they may consist of those excipient primary particles fragmented from milled ribbons. The appearance of fine particles is evidenced by D10 less than 10 μm, indicating that ribbons were relatively fragile or severe milling conditions were used.

Figure 5 reveals that lactose samples have smaller granules and larger quantity of particles than the corresponding mannitol samples. Similarly, samples with 20% *w*/*w* starch have smaller sized granules and large quantity of particles compared to the corresponding samples with 5% *w*/*w* starch. In brief, smaller granules and more particles occur in the presence of lactose (instead of mannitol) and starch.

Table II illustrates the particle size and densities of dry granules made form roller compacted ribbons. Figure 6 illustrates the volume-averaged mean diameter (VMD) of granule samples varies from 140 to 240 μm. Multi-linear regression analysis leads to the following model

$$\mathrm{VMD}(\mu\mathrm{m}) = 193.190 + 43.220F - 49.483S \qquad (6)$$

where R^2=0.835 and the significance of model terms follows the order: S=1.0, F=0.873. The effect of filler type and starch content to VMD appeared comparably significant while talc effect appeared insignificant. Starch effectively reduces the VMD, and mannitol leads to the higher VMD as compared to lactose.

Powder Densities of Dry Granules

As illustrated in Table II, the lactose granules have higher bulk and tapped densities than the mannitol granules. Starch reduced the density of lactose granules while it does not for mannitol granules. These trends could be attributable to the fact that lactose is significantly denser than both mannitol and starch. The CI of all samples falls in the range

Table II. Particle Sizes, Densities, and Carr Compressibility Index of Powder Samples in This Study

	Cumulative particle size			Powder density		
Sample	D10 (μm)	D50 (μm)	D90 (μm)	Bulk density (g/mL)	Tapped density (g/mL)	Carr index (CI)
1	6.51	114.06	556.43	0.597	0.847	29.6
2	6.45	101.48	481.30	0.611	0.821	25.6
3	6.86	91.76	375.93	0.584	0.793	26.4
4	6.14	99.04	505.71	0.610	0.867	29.6
5	6.47	103.71	492.16	0.603	0.842	28.4
6	6.42	89.79	358.37	0.598	0.812	26.4
7	5.74	141.64	512.82	0.564	0.762	26.0
8	6.45	181.59	593.06	0.559	0.752	25.6
9	6.61	118.17	448.62	0.559	0.759	26.4
10	6.45	172.15	552.87	0.573	0.778	26.4
11	6.96	186.73	562.35	0.556	0.764	27.2
12	7.36	135.84	491.11	0.558	0.783	28.8

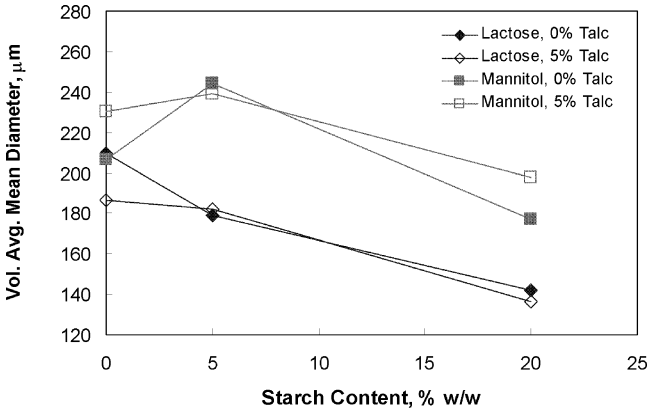

Fig. 6. Volume averaged mean diameter of dry granules with respect to the starch content

between 24.4 and 29.6. Overall, the CI values suggest that virtually all granule samples have moderate flowability that is acceptable for encapsulation.

Flow Property of Dry Granules

The flow property of dry granulation samples was measured using a powder avalanche tester. Most samples exhibits cascading with occasional slumping or pure cascading flow in the rotating cylinder. The mean time to avalanches (MTA) and the coefficient of variation of avalanche time (COV) of samples are indications of their flow cohesivity and variability, respectively. As shown in Fig. 7, the MTA values of granule samples fall in the ranges of 3.04 to 5.12 s while the COV values of samples are between 35% to 42%. The regression result is shown below

$$\mathrm{MTA(s)} = 3.8255 + 1.1042F - 0.7633S - 0.5583FT \qquad (7)$$

where R^2=0.920 and the significance of model terms follows the order: F=1; S=0.925; FT=0.677. The regression results clearly indicate that increasing the starch content and use of lactose reduce the flow cohesivity of granules. Talc also reduces the flow cohesivity of mannitol granules but not lactose granules. The regression result is shown below

$$COV(\%) = 36.228 + 3.743F + 8.187S - 8.187S^2 \qquad (8)$$

where R^2=0.822 and the significance of model terms follows the order: F=1, S^2=0.41. The regression results indicate that the filler type is the most significant factor to COV. Lactose granules have significantly less flow variability than mannitol granules. In addition, the first and second orders of starch content also play a minor role to the variability of granular flow.

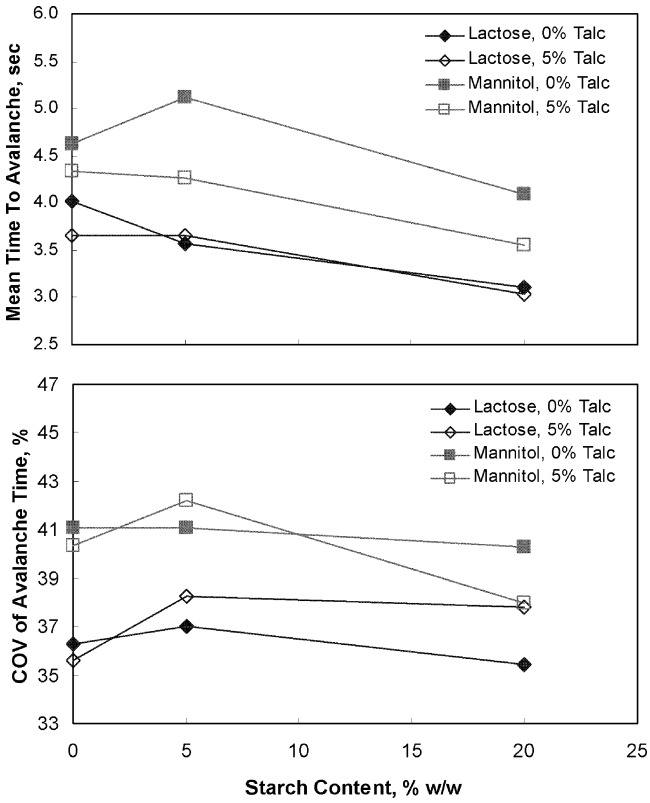

Fig. 7. Mean value (MTA) and coefficient of variation (COV) of avalanche time of dry granules with respect to the starch content

Discussion of Physical Properties of Ribbons and Granules

In this study, pregelatinized starch exhibits the most significant effect to the ribbon and granule properties. For both lactose and mannitol granules, an increase in starch content from 0% to 20% *w/w* reduces ribbon solid fraction by 10%, ribbon tensile strength by 60%, and granule size by 30%. These trends could be attributed to the poor compress-

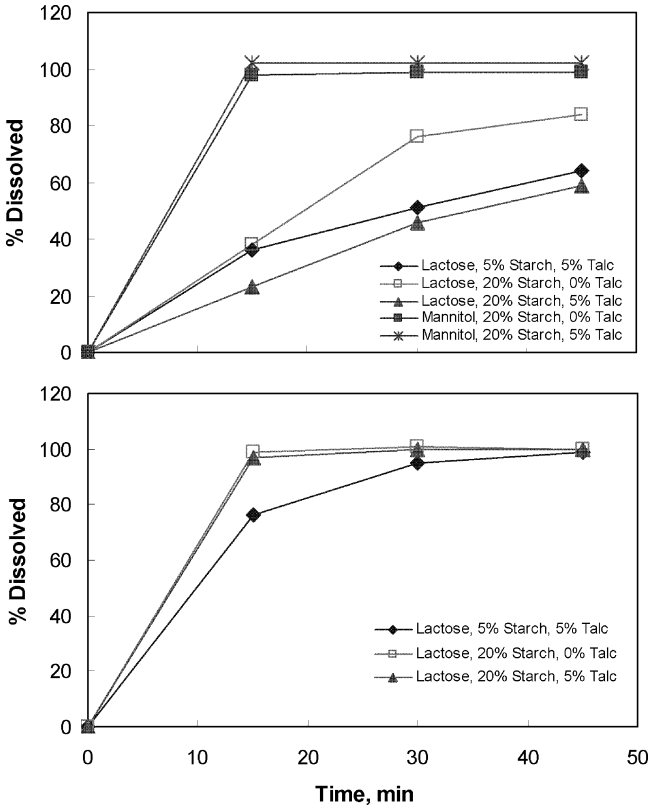

Fig. 8. Percent dissolved (arithmetic averages, n=6) for the tested formulations at 12 weeks 40 °C/75% (*upper plot*) and 24 weeks refrigerated (*lower plot*)

ibility of starch. Previous studies observed that pregelatinized starch exhibited extensive yet slow plastic deformation during compaction (15). Under the typical force and rate of roller compaction, the plastic deformation of pregelatinized starch could be too slow; hence, it also underwent significant elastic deformation which subsequent recovery caused the reduction of solid fraction and tensile strength of ribbons. Discrete primary particles of pregelatinized starch with approximately the same size before and after the compaction have been observed under microscope (15). Since the elastically deformed starch particles cannot form strong inter-particle bonding with other ingredients, starch-based ribbons upon milling are prone to fragmentation into smaller granules along with starch and other primary particles.

With regard to the filler type used in this study, both lactose and mannitol ribbons show similar tensile strengths while the lactose granules have significantly smaller particle sizes than the mannitol granules. This opposite trend could be attributed to the fact that lactose is more brittle than mannitol. Consequently, lactose ribbons are prone to fractured into smaller granules than mannitol ribbons under a given milling condition.

Comparison of the particle size distribution and flow properties of granules reveals that smaller lactose granules have less flow cohesivity (i.e., better flow) than larger mannitol granules. Smaller granules with higher starch content also have better flow than larger granules with lower starch content. The effect of talc on the ribbon solid fraction, ribbon strength, and granule size is insignificant perhaps due to the small quantity of talc (5% *w*/*w*) used as well as due to its lack of elastic deformation. Nevertheless, it seems that talc acts as a glidant to facilitate the flow of mannitol granules as evidenced by the lower MTA values of samples containing 5% *w*/*w*. On the other hand, talc appears not modifying the flow of lactose granules noticeably.

Dissolution of Dry Granulation Capsules

Dissolution test was performed for selected dry granulation capsule samples that were stored at 40 °C/75% RH for 12 weeks and 5 °C for about 24 weeks. The dissolution profiles of these capsules are illustrated in Fig. 8. For capsules stored at 40 °C/75% RH, it was notable that capsules containing mannitol dissolved significantly faster than those containing lactose. Lactose-containing capsules stored at 40 °C/75% RH for 12 weeks have noticeably slower dissolution rates than those refrigerated at 5 °C. On the other hand, mannitol-containing capsules remain similarly fast dissolution at different stability conditions.

The negative effect of accelerated stability condition to the dissolution of lactose-containing capsules is likely due to the crosslinking of the gelatin capsule shells since noticeable pellicle formation (a palpable gel-like colorless film) inside capsules was also observed from lactose-containing capsules stored at 40 °C/75% RH for 12 weeks. It was found that larger degrees of pellicle formation correlated well with the slower rates of capsule dissolution, and granular materials trapped inside the pellicles could not be dissolved easily by the dissolution medium. Pellicle formation also causes large variation in the rate of dissolution of lactose-containing capsules.

Pellicle formation by the crosslinking of capsule shells could result from a variety of chemical sources such as aldehyde (22–24). In this study, pellicle formation in lactose-containing capsules could be due to the reaction between the aldehyde group of lactose and the free ε-amino group of gelatin molecules. This reaction leads to an imine intermediate which, through an amadori rearrangement, produces a ketose sugar. The carbonyl functionality of the formed ketose sugar is then free to react with other amine groups of gelatin molecules to form the cross-linked gelatin (25).

CONCLUSIONS

Both spray-dried lactose and mannitol fillers formed roller compacted ribbons with similar solid fraction and tensile strength; however, resulting lactose-based granules were smaller than mannitol-based granules due to the brittleness of lactose. Presence of pregelatinized starch caused the noticeable reduction in ribbon solid fraction, tensile strength and granule size due to the poor compressibility of starch. A minor content (e.g., 5% *w*/*w*) of talc had little effect to the physical properties of ribbons and granules. Stored at 40 °C/75% RH over 12 weeks, gelatin capsules containing lactose-based granules formed pellicles and had slowed dissolution while capsules containing mannitol-based granules did not.

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