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Research Article

Importance of Wet Packability of Component Particles in Pellet Formation

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Abstract. This work explored the importance of packability of component particles in the different wet processing steps of extrusion–spheronization and investigated different processing and formulation approaches for enhancing packing of component particles during extrusion–spheronization to produce spherical pellets with high yield and narrow size distribution. Various cross-linked polyvinyl pyrrolidone (XPVP) and lactose grades with different particle sizes were used as pelletization aid and filler in 1:3 binary powder blends. Loosely packed extrudates obtained from coarse XPVP/lactose blends possessed low cohesive strength and produced irregular shaped pellets with low yield whereas tightly packed, rigid extrudates obtained from XPVP/fine lactose grades possessed high cohesive strength and produced elongated pellets. Adjustment of spheronization tip speed to provide sufficient forces generated by the rotating frictional base plate for facilitating packing by rearrangement of component particles improved pellet quality. Double extrusion, decreasing particle size of the formulation component(s), and/or widening particle size distribution of the powder blend are approaches applicable to improve cohesiveness of moistened mass by closer packing of component particles for production of good quality pellets.

KEY WORDS: cross-linked polyvinyl pyrrolidone; extrusion; packing; spheronization.

INTRODUCTION

The basic formulation for preparing drug-loaded pellets by extrusion–spheronization comprises the drug, pelletization aid, filler, and moistening liquid. Microcrystalline cellulose (MCC) is the most widely used pelletization aid whereas cross-linked polyvinyl pyrrolidone (XPVP) has been reported as a promising alternative to MCC (1–3).

The pelletization aid functionalities of several commercially available MCC and XPVP grades have been compared using MCC/XPVP and lactose (filler) binary blends (1,3). With XPVP–lactose blends, the resultant pellet quality was observed to be influenced by the particle size of XPVP in the formulation. Binary blends containing the fine particle size grades produced moistened masses with higher cohesive strength which upon extrusion–spheronization yielded highly spherical pellets with high yield and narrow size distribution. Extrudates produced from the coarse XPVP, polyplasdone XL (XL)–lactose binary blends shattered into small fragments during spheronization and produced irregular shaped agglomerates with low yield and wide size distribution. In contrast, the different particle size grades of MCC in MCC-lactose binary blends did not appear to have any effect on their moistened mass and pellet properties. MCC particles with different dry state particle sizes de-aggregated into smaller sub-units with more or less similar sizes whereas the particle sizes of the different XPVP grades remained relatively unchanged throughout the different wet processing steps of extrusion–spheronization (3). The study which focused on investigating the particle size of the pelletization aid in the wet state demonstrated that ideally a pelletization aid should have small in-process particle size. It was postulated that the XL–lactose binary blend did not give good quality pellets because the coarse particle size of the XL grade employed contributed to extrudates that were comparatively loosely packed and friable and unable to withstand the frictional forces generated by the rotating frictional base plate when spheronization was carried out at the investigated tip speed of 8 m/s or higher.

The packability of component particles during the different wet processing steps of extrusion–spheronization has significant impacts on the formation of the pellet structure. Extrusion–spheronization is a multi-step process involving several distinct wet processing phases, i.e., wet massing, extrusion, and spheronization, carried out sequentially to pack component particles in the moistened mass to form round pellets. Critical processing and formulation parameters must be suitably adjusted to promote good packing of component particles in the moistened mass for successful pellet formation. Using XPVP/lactose (1:3) powder blends as model formulations, this study was directed at investigating various processing and formulation approaches for enhancing packing of

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component particles in the moistened mass during the different wet processing steps of extrusion–spheronization. Based on the findings of the study, a guideline of possible strategies that may be introduced during extrusion–spheronization to improve the quality of resultant pellets by enhancing wet packability of the component particles was proposed.

MATERIALS AND METHODS

Materials

Two commercial coarse grades of XPVP were obtained from different sources, XL from International Specialty Products (Wayne, NJ, USA) and Kollidon CL (CL) from BASF (Ludwigshafen, Germany). Two milled XPVP grades, XLMB1 and XLMB2, were prepared from XL by cryo-ball milling (type S1, jar volume 500 mL, Retsch, Haan, Germany). Three commercial grades of lactose, Pharmatose 100M (100M), Pharmatose 200M (200M), and Pharmatose 450M (450M), were obtained from DMV International (Veghel, the Netherlands). Two milled lactose grades, MIC1 and MIC2, were prepared by jet milling (100AFG, Hosokawa Micron Ltd, Augsburg, Germany). All materials were equilibrated at 25°C and 50% relative humidity for at least 72 h before use. Isopropyl alcohol, filtered through 0.45 µm pore size filter, was used as the dispersion medium for particle size measurement. Distilled water was used as the moistening liquid to study torque rheological properties and for pellet preparation.

Preparation of Milled XPVP Grades

Milled XPVP grades were prepared from XL by cryo-ball milling (type S1, jar volume 500 mL, Retsch, Haan, Germany). Powder (50 g), pre-soaked with liquid nitrogen, was placed in the ball mill chamber with 100 steel balls of 10 mm diameter. The mill was then run for 7 min at 200 rpm. For the second stage of milling, the above procedure was repeated with the milled product from the first stage. The milled products after the first and second stages were assigned as XLMB1 and XLMB2, respectively.

Preparation of Micronized Lactose Grades

Micronized lactose grades were prepared from coarse lactose grade, 100M, by jet milling (100AFG, Hosokawa Micron Ltd, Augsburg, Germany) with a feeding screw rotation of 3 rpm. Micronized lactose was separated using a classifier rotating at 5,000 or 6,000 rpm. The micronized lactose batches obtained using 5,000 and 6,000 rpm classifier speeds were denoted as MIC1 and MIC2, respectively.

Characterization of Different XPVP and Lactose Grades

The different XPVP and lactose grades were characterized for their median particle size, size distribution, and specific surface area. Physical properties of the different XPVP and lactose grades are summarized in Table I.

Table I. Physical Properties of the Different XPVP and Lactose Grades

Material	Median particle size (µm)	Span	Specific surface area (m^2/g)
XL	183.5±5.7	2.03±0.03	0.720±0.041
CL	97.5±4.8	2.70±0.28	0.777±0.018
XLMB1	81.8±7.2	2.07±0.09	0.861±0.064
XLMB2	37.0±1.3	1.61±0.12	1.039±0.011
100M	158.5±7.2	1.26±0.02	0.174±0.004
200M	33.9±1.5	3.11±0.11	0.615±0.019
450M	23.9±0.8	1.98±0.04	0.775±0.094
MIC1	10.9±0.2	2.07±0.02	1.730±0.207
MIC2	5.1±0.1	2.15±0.01	2.489±0.309

Particle Size and Size Distribution

Particle size analysis of the different XPVP and lactose grades was carried out by laser diffraction (LS230, Coulter Corporation, Brea, CA, USA) using the dry and wet powder modules, respectively. In the dry powder module, dry powder sample, pre-sieved through a 1-mm aperture size sieve, was steadily delivered to achieve an obscuration of 4–11%. In the wet powder module, wet powder sample (approximately 0.2 g of powder dispersed in isopropyl alcohol) was added dropwise until polarization intensity differential scattering reached 45–55%.

For both dry and wet powder modules, median particle size was calculated from the cumulative percent undersize plot. Span, derived using the following equation, was used for characterizing particle size distribution (1).

$$Span = \frac{x_{90} - x_{10}}{x_{50}} \tag{1}$$

where x_{10}, x_{50}, and x_{90} were diameters of particles at the 10, 50, and 90 percentiles of the cumulative percentage undersize plot, respectively. Three measurements were carried out for each XPVP or lactose grade and the average median particle size and span calculated.

Specific Surface Area

Determination of specific surface area of the different XPVP and lactose grades was carried out using the Brunauer–Emmett–Teller adsorption method (SA3100, Coulter, Miami, FL, USA) with nitrogen as the adsorbate gas. The powder samples were degassed for 12 h under nitrogen at 80°C to remove any pre-adsorbed gases and moisture from the powder surfaces. For each XPVP or lactose grade, the experiment was carried out in triplicate, and the results were averaged.

Characterization of Powder Blends

Different powder blends consisting of XPVP and lactose in a weight ratio of 1:3 were mixed by geometric dilution prior to blending in a double cone blender (Erweka, Heusenstam, Germany) at 10 rpm for 20 min. The powder blend containing

XPVP/lactose (1:3) were coded by the XPVP grade–lactose grade. The powder blends were then characterized for their particle size, size distribution, and torque rheological properties.

Particle Size and Size Distribution

Determination of particle size and particle size distribution of the powder blend was carried out by laser diffraction (LS230, Coulter Corporation, Brea, CA, USA) using the wet powder module with isopropyl alcohol as the dispersion medium. The median particle diameter (X_{50}) was calculated from the cumulative percent undersize plot. Span (SP_{ble}), derived using the following equation, was used for characterizing particle size distribution (1).

$$SP_{ble} = \frac{X_{90} - X_{10}}{X_{50}} \tag{2}$$

where X_{10}, X_{50}, and X_{90} are diameters of particles at the 10, 50, and 90 percentiles of the cumulative percent undersize plot, respectively. Averages were calculated from three repeats.

Torque Rheological Properties

Torque rheological properties of the various powder blends were determined using a mixer torque rheometer (Caleva Process Solutions Limited, Dorset. UK). Twenty-four grams of a powder blend was added into the mixer bowl and mean torque generated by the dry powder recorded. Distilled water was added to the powder blend at increments of 5% (*v/w*) and mixed. Mean torque values generated for the 19 water additions were recorded. For each formulation, the studies were carried out in triplicates. Maximum torque (T_{max}) and water required to achieve maximum torque (W_{Tmax}) were determined from the mean torque against water addition plot of the corresponding powder blend. High T_{max} indicates high cohesive strength of the wet mass.

Pellet Preparation

A 1:3 ratio (800 g) powder blend of XPVP/lactose was transferred to a planetary mixer (Kenwood Major, Havant, UK) and moistened over 5 min with distilled water amounting to 90% of its W_{Tmax} obtained from the mixer torque rheometry studies (3). The resultant wetted mass was extruded through a radial screw extruder (E140, Niro, Eastleigh, UK) fitted with a screen of 1 mm aperture diameter and thickness. For double extrusion (DE) formulations, the extrudates collected immediately after extrusion were reprocessed through the same extruder. Extrudates (750 g) were transferred to the spheronizer (S320, Niro, Eastleigh, UK) fitted with a 30-cm-diameter cross-hatch patterned frictional base plate and spheronized at the specified spheronization tip speed (2, 4, 6, or 8 m/s) for 5 min. Pellets produced were then collected and oven-dried at 60°C for at least 12 h. The amount of moistened material adhering on the spheronizer wall and frictional base plate after spheronization was denoted as material adhesion and expressed as a percentage of the total weight of extrudates used for spheronization. At least two repeat batches were carried out for each formulation. Formulations were coded by the blend components and spheronization tip speed used. The inclusion of "DE" in the formulation code referred to the double extrusion formulations.

Characterization of Extrudate Cohesive Strength

The bowl of the mixer torque rheometer (Caleva Process Solutions Limited, Dorset, UK) was operated without load to set the baseline. An amount of freshly prepared extrudates, corresponding to a dry weight of 24 g powder blend, was added into the mixer bowl and the generated torque measured for characterizing the cohesive strength of the extrudates. For each formulation, at least four replicates were conducted and the average extrudate cohesive strength value calculated.

Pellet Characterization

The dried pellets were characterized for their yield, size (i.e., median diameter), size distribution, shape (i.e., aspect ratio and circularity), micromeritic properties (i.e., porosity and median pore diameter), and crushing strength. Good quality pellets should have a high yield, median diameter close to extrusion screen aperture size, narrow size distribution, spherical shape, low porosity and median pore diameter, and high crushing strength.

Yield, Size, and Size Distribution

For pellet size analysis, a nest of sieves (Endecotts, England, UK) with aperture sizes in a √2 progression from 250–2,800 μm was used on a sieve shaker (VS 1000, Retsch, Haan, Germany) at 1 mm amplitude for 10 min. The pellet fraction between 710 and 1,400 μm was denoted as pellet yield expressed as a percentage of the total dry weight of extrudates used for spheronization. Median diameter (D_{50}) was defined as the pellet size corresponding to the 50 percentile mark on the cumulative percent undersize plot. Span (SP_{pel}), derived using the following equation, was used for characterizing particle size distribution of pellets (3).

$$SP_{pel} = \frac{D_{90} - D_{10}}{D_{50}} \tag{3}$$

where D_{10}, D_{50}, and D_{90} were diameters of pellets at the 10, 50, and 90 percentiles of the cumulative percent undersize plot, respectively. SP_{pel} reflects the degree of size homogeneity of the pellet batch. A smaller SP_{pel} value indicates a narrower pellet size distribution.

Shape Characteristics

An image analyzer consisting of a computer system connected to a digital camera (DSP 3CCD, Sony, Tokyo, Japan) mounted on a stereomicroscope (SZH, Olympus, Tokyo, Japan) was used to determine the shape characteristics of pellets. The images of at least 200 randomly selected pellets from the 710–1,400-μm fraction of each pellet batch were captured (magnification *X* 7.98 μm/pixel; *Y* 7.98 μm/pixel) and analyzed (Image-Pro, Version 6.3, Media Cybernetics, Bethesda, MD, USA) for aspect ratio and circularity. Aspect ratio is related to elongation while sphericity is described by the circularity value (4). For a perfect sphere, both shape descriptors should be 1.

$$Aspect\ ratio = \frac{l}{b} \tag{4}$$

$$Circularity = \frac{4\pi A}{P^2} \tag{5}$$

where l, b, A, and P are the length, breadth, area, and perimeter of the two-dimensional particle outline, respectively.

Micromeritic Properties

Mercury intrusion porosimetry (AutoPore IV 9500, Micromeritics, Norcross, GA, USA) was used to determine the micromeritic properties of pellets at a pressure range of 2–60,000 psia. Mercury contact angle (φ), surface tension (γ), and density were taken as 130°, 485 dynes/cm, and 13.53 g/mL, respectively (5). Approximately 75% of the penetrometer volume was filled with pellets from the 850–1,000-μm size fraction of each batch. The low-pressure experiment was performed at a pressure range of 2–30 psia followed by the high-pressure experiment at a pressure range of 30–60,000 psia. The pore diameter (PD) at each experimental pressure (Pr) point was calculated according to equation proposed by Washburn (6).

$$Pore\ diameter\ (PD) = -\left({}^{1}/_{Pr}\right) 4\gamma cos\varphi \tag{6}$$

The cumulative intruded mercury volume after high-pressure experiment included both intra- and inter-particulate void volumes. Median pore diameter (PD_m) is defined as the pore diameter corresponding to 50% of the maximum cumulative intruded volume of mercury. Porosity of the pellet sample was calculated using the following Eq. (5)**.**

$$Porosity\ = \left(1 - \frac{\rho_e}{\rho_a}\right) \times 100 \tag{7}$$

where effective particle density of the pellet sample, ρ_e, is $W_s/(V_p - V_{Hg})$; apparent density of the pellet sample, ρ_a, is $W_s/((V_p - V_{Hg}) - V_i)$; W_s is the weight of the pellet sample; V_p is the volume of the empty penetrometer; and V_{Hg} is the volume of mercury filled into the penetrometer at 50 μm Hg vacuum. V_i represented specific intruded mercury volume in the entire pressure range of 2–60,000 psia. Two repeats were conducted for each pellet batch.

Crushing Strength

Pellet crushing strength was determined using a compression tester (EZ-Tester-100N, Shimadzu Corporation, Kyoto, Japan) with a mobile upper compression platen fitted with a 100-N load cell. The lower compression platen was fixed to a jig mounting plate. Twenty-five 1,000-μm pellets from each pellet batch were selected and crushed at a loading rate of 1 mm/min. The maximum force required to crush a pellet was termed as the crushing force (F). Pellet crushing strength was calculated using Eq. (8) as proposed by Dyer *et al.* (7).

$$Crushing\ strength = \frac{4F}{\pi d^2} \tag{8}$$

where d is pellet diameter.

Multivariate Data Analysis

Unscrambler 9.8 (Camo Inc., Bangalore, India) was used for multivariate data analysis. Principal component analysis (PCA) was carried out to detect interrelationships between the physical properties of the binary blends and the resultant extrudate and pellet properties. All the data were normalized by weights (1/standard deviation) to fit them to approximately the same scaling.

RESULTS AND DISCUSSION

Processing Approaches

The influence of processing parameters, i.e., double extrusion and spheronization tip speed, on pellet properties of XL/CL-200M formulations were investigated to elucidate how pelletization potential of these coarse XPVP–lactose binary blends could be improved.

Double Extrusion

The quality of both the XL- and CL-based pellets was improved with double extrusion of the extrudates prior to the spheronization step (Table II). Pellets produced from double extrusion extrudates had comparatively higher yield, lower SP_{pel}, lower aspect ratio, higher circularity, and higher crushing strength. In addition, the resultant pellets had lower PD_m and porosity.

Physical properties of the XL/CL-200M binary blends are given in Table III. Their moistened masses had low cohesive strength as indicated by their low T_{max} values.

The single extrusion XL-200M and CL-200M extrudates had low cohesive strength and were comparatively loosely packed (Fig. 1). The cohesive strength of the extrudates increased when double extrusion was carried out (t test, $p < 0.05$). The higher cohesive strength of the extrudates with double extrusion indicated that another round of extrusion assisted in densifying the comparatively loosely packed XL-200M or CL-200M extrudates by reducing the inter-particulate void spaces. This improved cohesive strength reduced the likelihood of extrudates shattering during the spheronization step. It was also noted that increasing the number of times the material was extruded beyond double extrusion did not give rise to remarkable improvement in the pellet properties for both the XL- and CL-based formulations.

Table II. Properties of Pellets Prepared from XL-200M and CL-200M Formulations Spheronized at Different Spheronization Tip Speeds (2–8 m/s)

Formulation	Material adhesion (%, *w/w*)	Yield (%, *w/w*)	D_{50} (μm)	SP_{pel}	Aspect ratio	Circularity	Crushing strength (N/mm^2)	PD_m (μm)	Porosity (%)
XL-200M-8	21±17	13±4	403±95	1.72±0.02	1.230±0.159	0.819±0.076	1.48±0.29	9.4±0.9	56.8±1.9
XL-200M-8-DE	13±2	57±6	1,005±78	0.98±0.12	1.165±0.096	0.846±0.046	2.21±0.34	7.4±0.7	48.7±2.5
CL-200M-8	52±10	17±5	1,055±78	1.75±0.01	1.286±0.187	0.776±0.079	1.06±0.17	7.3±0.3	50.8±0.7
CL-200M-8-DE	50±3	28±6	1,078±67	1.16±0.14	1.253±0.164	0.795±0.075	1.18±0.20	6.0±0.2	48.6±0.3
XL-200M-6	5±0	61±5	873±53	1.15±0.07	1.169±0.096	0.858±0.026	1.53±0.35	8.4±0.1	50.7±0.6
XL-200M-4	1±0	79±2	845±7	0.94±0.06	1.339±0.199	0.826±0.045	1.29±0.23	9.9±0.1	52.2±1.5
XL-200M-2	1±0	82±2	833±11	0.75±0.11	1.475±0.242	0.794±0.043	1.15±0.17	9.7±0.1	52.8±0.4
CL-200M-6	15±1	31±5	1,373±117	1.04±0.17	1.108±0.073	0.858±0.026	1.16±0.29	5.9±0.7	45.3±1.0
CL-200M-4	2±0	88±0	975±78	0.56±0.01	1.157±0.102	0.868±0.025	0.80±0.22	6.4±0.3	46.1±0.4
CL-200M-2	1±1	84±3	848±11	0.46±0.00	1.379±0.225	0.835±0.044	0.63±0.14	7.1±0.1	45.0±2.1

D_{50} median diameter, SP_{pel} span, PD_m median pore diameter of pellets

Spheronization Tip Speed

It was observed that spheronization tip speed (2–8 m/s) affected the various pellet properties differently (Table II). Decreasing tip speed from 8 to 4 m/s generally led to a decrease in the SP_{pel} values of the resultant XL-200M and CL-200M pellets. However, no significant differences in the SP_{pel} values were observed with further decrease in tip speed (ANOVA, $p>0.05$). Pellet yields above 75% were obtained when spheronization was conducted at or below a tip speed of 4 m/s. The highest D_{50} values were obtained with a tip speed of 6 m/s. D_{50} values decreased with tip speeds above and below 6 m/s. These findings were consistent with those reported by Wan *et al.* (8) which concluded that the size of resultant pellets prepared from MCC–lactose formulations generally followed an increasing trend with increasing tip speed up to an optimum and thereafter decreased with further increase in tip speed. Aspect ratio values decreased when tip speed was reduced, reaching a minimum at about 6 m/s tip speed before starting to increase with further decrease in tip speed. Similarly, circularity values increased when tip speed was reduced, reaching a maximum at about 6 m/s tip speed before starting to decrease with further decrease in tip speed. XL-200M and CL-200M pellet batches that were spheronized at 8 m/s tip speed had significantly higher pellet porosity compared to the corresponding pellet batches that were spheronized at the other tip speeds investigated. No significant difference in pellet porosity was observed between pellet batches that were spheronized at the other tip speeds (ANOVA, $p>0.05$). For both the XL- and CL-based formulations, the crushing strengths of the resultant pellets were not significantly changed when tip speed was decreased from 8 to 6 m/s. However, further decrease in tip speed significantly decreased pellet crushing strength.

Use of a comparatively wide range of tip speeds (2–8 m/s) allowed for investigation of the effect of frictional forces generated by the rotating frictional base plate during the spheronization step on the pelletization potential of coarse XL/CL-200M binary blends and their resultant pellet quality. The comparatively high frictional forces generated at the high end (8 m/s) of the investigated tip speed range caused some of the extrudates to shatter. Decreasing the tip speed reduced the shattering tendency of the extrudates and facilitated packing by particle rearrangement, improving yield, and tightening the size distribution of the resultant pellets. Nevertheless, at the low end (2 m/s) of the investigated tip speed range, the frictional forces generated by the frictional base plate were sufficient for breaking up the extrudates into small cylindrical fragments but inadequate for particle rearrangement to round the cylindrical extrudates into spherical pellets. As such, elongated pellets were produced as indicated by the higher aspect ratio values.

Formulation Approaches

With regard to formulation approaches, particle size reduction of pelletization component particles, i.e., via substitution of the coarse XL grade in the XPVP-200M powder blends with milled XPVP and substitution of lactose 200M in XL/CL–lactose powder blends with fine particle size grades of lactose, was investigated for improving pellet properties.

Table III. Physical Properties of XPVP–Lactose Powder Blends Containing XPVP and Lactose of Different Particle Size Grades

			Rheological properties	
Powder blend	X_{50} (μm)	SP_{ble}	W_{Tmax} (%, v/w)	T_{max} (Nm)
XL-200M	109.5±7.7	3.45±0.12	60.0±1.2	0.180±0.002
CL-200M	65.3±1.4	2.97±0.05	50.0±2.9	0.141±0.012
XLMB1-200M	58.5±1.9	2.83±0.05	55.0±2.9	0.226±0.014
XLMB2-200M	36.6±2.9	1.60±0.03	50.0±1.3	0.234±0.010
XL-450M	77.4±3.8	4.86±0.27	65.0±1.0	0.256±0.026
XL-MIC1	55.5±2.8	6.56±0.34	57.5±2.5	0.387±0.028
XL-MIC2	45.0±3.5	7.08±0.36	55.0±0.6	0.561±0.069
CL-450M	48.0±0.8	3.97±0.01	45.0±1.4	0.186±0.016
CL-MIC1	26.5±0.3	6.62±0.22	40.0±1.4	0.204±0.013
CL-MIC2	20.3±0.7	7.88±0.77	37.5±1.4	0.260±0.040

X_{50} median diameter, SP_{ble} span of powder blends, T_{max} maximum torque, W_{Tmax} amount of water required to reach maximum torque in rheological profile

Particle Size Reduction of Pelletization Aid or Filler Component

Pellet quality was improved by reducing the particle size of either the pelletization aid or filler component in the binary blend employed for extrusion–spheronization. For the XPVP–lactose formulations, this was demonstrated in particular by the XPVP-200M binary blend containing XLMB2 which produced pellets with high yield, low SP_{pel}, low material adhesion, high crushing strength, low aspect ratio, and high circularity values. In addition, pellet porosity decreased with a decrease in the particle size of XPVP used in the formulation (Table IV).

Pellet properties were significantly (ANOVA, $p<0.05$) influenced by particle size of the lactose grade used as filler in combination with the coarse XL or CL XPVP grades (Table IV). Replacement of 200M with smaller particle size lactose grades affected the different pellet properties to different extent. Formulations containing XL or CL in combination with 200M had significantly higher material adhesion than the other XL/CL–lactose formulations. No significant differences in material adhesion were observed for formulations containing XL or CL with the smaller size lactose grades. Pellet crushing strength followed an increasing trend with a decrease in particle size of the lactose in the formulation. For both XL- and CL-based pellets, PD_m, pellet porosity, and SP_{pel} values decreased for batches using smaller size lactose particles from 200M to MIC1. However, no further significant changes in PD_m, pellet porosity and SP_{pel} values were observed when MIC1 was replaced with MIC2 in the formulation. Similarly, aspect ratio values decreased reaching minima with the formulations containing MIC1 but increased subsequently with finer lactose employed. For XL-based pellets, yield increased with a decrease in the lactose particle size although no significant difference in yield was observed when MIC1 was replaced with MIC2. A similar trend in the yield was found for CL-based pellets, but no significant difference was observed when 200M was replaced with 450M.

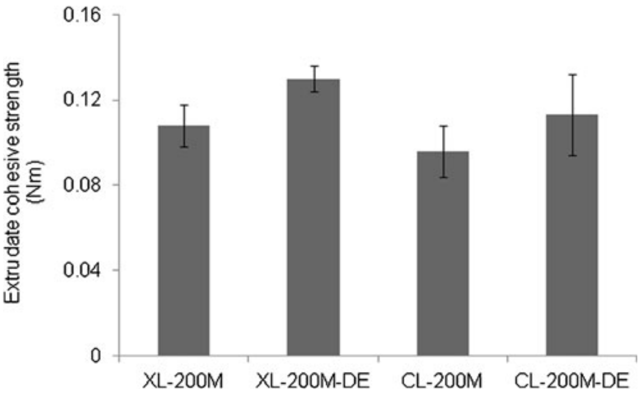

Fig. 1. Cohesive strength of single and double extrusion extrudates prepared from XL/CL-200M powder blends moistened with water corresponding to 90% of W_{Tmax} of the respective powder blend. *Error bars* represent standard deviations

Influence of Powder Blend Particle Size and Size Distribution on Pellet Formation by Extrusion–Spheronization

The XPVP-200M binary blends containing finer XPVP particles obtained from cryo-ball milling of the coarse XL grade, i.e., XLMB1 and XLMB2, had smaller X_{50}, lower W_{Tmax}, and higher T_{max} than the corresponding binary blend containing the coarse XL grade (Table III). When blended with finer lactose grades, both coarse XPVP grades, XL and CL, yielded binary blends with higher SP_{ble} and smaller X_{50} as particle size of the lactose component in the blend decreased (Table III). Particle size of the lactose grades in binary blends containing coarse XL and CL grades significantly influenced the rheological properties of their moistened masses. For the same XPVP grade, moistened masses with smaller particle size lactose generally exhibited higher T_{max} (ANOVA, $p<0.05$; Table III).

XPVP-200M binary blends containing the finer XPVP grades (XLMB1-200M and XLMB2-200M) produced extrudates with higher cohesive strength and pellets with higher crushing strength than those of the coarse XL-200M binary blend (Fig. 2). Similarly, the extrudate cohesive strength and pellet crushing strength increased progressively with decreasing particle size of the lactose grade employed in the XL/CL–lactose formulations (ANOVA, $p<0.05$, Fig. 2).

Unlike XPVP, lactose is water soluble and may undergo dissolution from the particle surfaces during the wet processing stages of extrusion–spheronization. The dissolved lactose could serve as a binder in the liquid bridges at the inter-

Table IV. Properties of Pellets Prepared from XPVP–Lactose Powder Blends Containing Different Particle Size Grades of XPVP and Lactose

Formulation	Material adhesion (%, *w*/*w*)	Yield (%, *w*/*w*)	D_{50} (μm)	SP_{pel}	Aspect ratio	Circularity	Crushing strength (N/mm^2)	PD_m (μm)	Porosity (%)
XL-200M-8	21±17	13±4	403±95	1.72±0.02	1.230±0.159	0.819±0.076	1.48±0.29	9.4±0.9	56.8±1.9
XLMB1-200M-8	18±0	39±5	935±92	1.18±0.12	1.175±0.115	0.848±0.039	1.80±0.29	8.0±0.4	49.9±2.9
XLMB2-200M-8	4±1	91±1	1,163±11	0.31±0.04	1.148±0.079	0.885±0.017	3.63±0.43	5.1±0.1	43.4±0.5
XL-450M-8	10±5	68±5	980±57	0.92±0.10	1.171±0.096	0.856±0.041	2.17±0.35	5.3±0.0	49.3±0.9
XL-MIC1-8	1±0	89±2	885±7	0.57±0.07	1.149±0.091	0.881±0.024	3.42±0.56	2.7±0.0	45.2±0.5
XL-MIC2-8	1±1	90±3	878±11	0.50±0.07	1.210±0.123	0.869±0.026	4.28±0.63	2.2±0.0	43.2±0.5
CL-200M-8	52±10	17±5	1,055±78	1.75±0.01	1.286±0.187	0.776±0.079	1.06±0.17	7.3±0.3	50.8±0.7
CL-450M-8	23±7	26±6	800±127	1.63±0.04	1.166±0.107	0.859±0.042	1.53±0.24	5.8±0.6	45.2±0.5
CL-MIC1-8	5±4	83±4	988±18	0.61±0.01	1.122±0.066	0.892±0.027	2.62±0.38	2.0±0.4	39.4±0.9
CL-MIC2-8	4±1	84±4	970±14	0.60±0.02	1.145±0.083	0.879±0.025	3.44±0.43	1.7±0.1	37.0±1.6

D_{50} median diameter, SP_{pel} span, PD_m median pore diameter of pellets

particulate contact areas and subsequently form solid bridges on drying, increasing the cohesive strength of the wet mass and extrudates and crushing strength of pellets, respectively. In theory, the amount of dissolved lactose may increase with greater specific surface area of lactose and greater amount of water. Although specific surface area was increased with finer grades of lactose (Table I) in the XL/CL–lactose formulations, lesser amounts of water were used for pellet production. Therefore, the influence of differences in the amount of dissolved lactose between the different formulations on differences in the cohesive strength of the wet mass and extrudates and crushing strength of pellets may not be remarkable. Similarly, the water requirement for pellet production decreased with a decrease in the particle size of the milled XPVP grade in the XPVP-200M formulations. Although the amount of dissolved lactose was likely to decrease, wet mass and extrudate cohesive strength as well as pellet crushing strength were observed to increase when finer grades of XPVP were used in the XPVP-200M formulations. Therefore, increased cohesive strength of the wet mass and extrudates and crushing strength of pellets were mainly attributed to increased inter-particulate contact due to greater specific surface area with decreased particle size.

The correlation loading plot (Fig. 3) from PCA showed that T_{max}, extrudate cohesive strength, yield, circularity, and crushing strength correlated positively with SP_{ble} and negatively with X_{50} of the binary blends used. On the other hand, SP_{pel}, aspect ratio, porosity, and PD_m of pellets correlated positively with X_{50} and negatively with SP_{ble} of the binary blends. Multivariate data analysis indicated that good quality pellets were mainly produced from the powder blends with smaller X_{50} and/or higher SP_{ble}, identifying powder blend particle size and size distribution as powder blend properties critical to successful pellet formation by extrusion–spheronization.

The ability of a moistened powder mass to pack well during extrusion–spheronization is influenced by the particle size and size distribution of its component particles. In general, small particles can potentially pack closer together than coarse particles and powders with a wider size distribution tend to pack better by smaller particles filling voids between larger ones. With sufficient forces during spheronization, the higher cohesive strength extrudates prepared from binary blends with smaller X_{50} and/or higher SP_{ble} were more amenable to reshaping without breakage and densification which in turn improved pellet sphericity. However, as exemplified by the XPVP-MIC2 binary blends (XL-MIC2-8 and CL-MIC2-8), formulations with small X_{50} and very high SP_{ble} may have produced extrudates that were not only strongly binding but also more rigid such that the frictional forces generated during spheronization at a tip speed of 8 m/s may not provide sufficient shear for rearranging the component particles in the extrudates to reshape the extrudates into round pellets. Consequently, less spherical, elongated pellets were produced (Table IV).

Influence of the Different Wet Processing Steps of Extrusion–Spheronization on Packability of Component Particles for Pellet Formation

Importance of component particle wet packability for successful pellet formation by extrusion–spheronization is schematically presented in Fig. 4. Mechanism of pellet

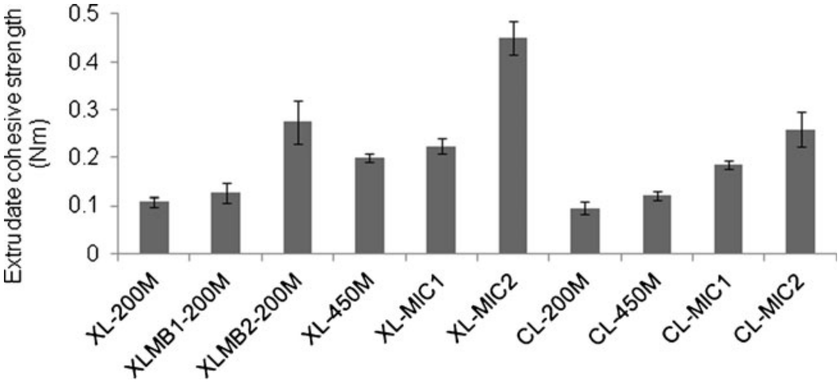

Fig. 2. Cohesive strength of extrudates prepared from milled-PVP–lactose and XL/CL–lactose powder blends moistened with water corresponding to 90% of W_{Tmax} of the respective powder blend. *Error bars* represent standard deviations

formation based on the packability of component particles in the wet agglomerates during the different steps of extrusion–spheronization will be discussed under the respective processing steps.

Wet Massing

The wet massing step in extrusion–spheronization involves the addition of a moistening liquid, almost always water, to the powder mass. Therefore, for ease of wetting by the moistening liquid, the components in the formulation for extrusion–spheronization should be hydrophilic. Due to the hydrophilicity of formulation components, a small portion of the liquid may be entrapped inside the crevices, if any; the rest of the liquid becomes surface liquid films available for forming liquid bridges between solid particles. However, successful liquid bridge formation between particles requires a minimum inter-particulate distance. When the force of gravity is negligible, subject only to surface tension of the moistening liquid, the maximum inter-particulate distance for liquid bridge formation is equal to the circumference of the cylindrical liquid bridges, Plateau–Rayleigh limit (9,10). At a distance longer than the circumference, the liquid bridge becomes unstable and breaks up into two droplets. If the force of gravity is not negligible, the break up occurs at even shorter lengths (11).

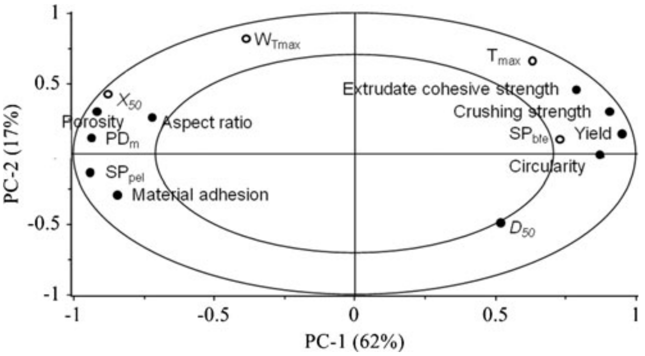

Fig. 3. PCA correlation loading plot for the physical properties of binary powder blends (*unfilled circles*) and resultant extrudate and pellet properties (*filled circles*); X_{50} and $\mathrm{SP}_{\mathrm{ble}}$—median particle size and span of powder blend, respectively; D_{50}, $\mathrm{SP}_{\mathrm{pel}}$, and PD_{m}—median diameter, span, and median pore diameter of pellets, respectively

In addition, the strength and stability of the liquid bridge increases with a decrease in the length of the liquid bridge (12). Particles with smaller size and/or a wider size distribution pack well, decreasing inter-particulate distances and increasing the opportunities for more stable and stronger liquid bridges to form. Theoretically, at a zero separation distance, the strength of the liquid bridge would be at its maximum with the smallest liquid bridge volume. However, this condition is not practically possible since surface roughness and rugosity would cause particles to have some small separation distances when they come in contact (12).

Liquid bridge formation between particles helps to form moist agglomerates of particles and contribute to the cohesive strength of the moistened material (13,14). The strength of the moistened material depends on the strength of liquid bridges as well as the numerical abundance of the liquid bridges. The numerical abundance of the liquid bridges increases with an increase in particle surface area. Due to their greater specific surface area, smaller particles of a given material would have greater opportunity for formation of larger number of liquid bridges.

Apart from liquid bridge formation, the moistening liquid also acts as a lubricant. Surface lubrication by the liquid facilitates rearrangement and packing by decreasing the inter-particulate friction and reducing the chances of electrostatic force generation.

Extrusion

During the extrusion step, shear-assisted consolidation enables particle–particle rearrangement and reduces the void spaces within the moistened material to further densify and strengthen the wet mass. Due to densification, excess liquid is squeezed out to the extrudate surfaces and aids in surface smoothing as well as in lubricating the extrusion process. The degree of densification depends on the physical properties of the formulation components and the amount of force applied during extrusion. Usually, a wet mass with better packability undergoes greater densification, as indicated by the higher T_{max} values with the formulations containing smaller particle size lactose or XPVP grades. A wet mass which on extrusion produces loosely packed, brittle extrudates, may be further densified by a second round of extrusion, as shown by XL/CL-200M-8-DE formulations.

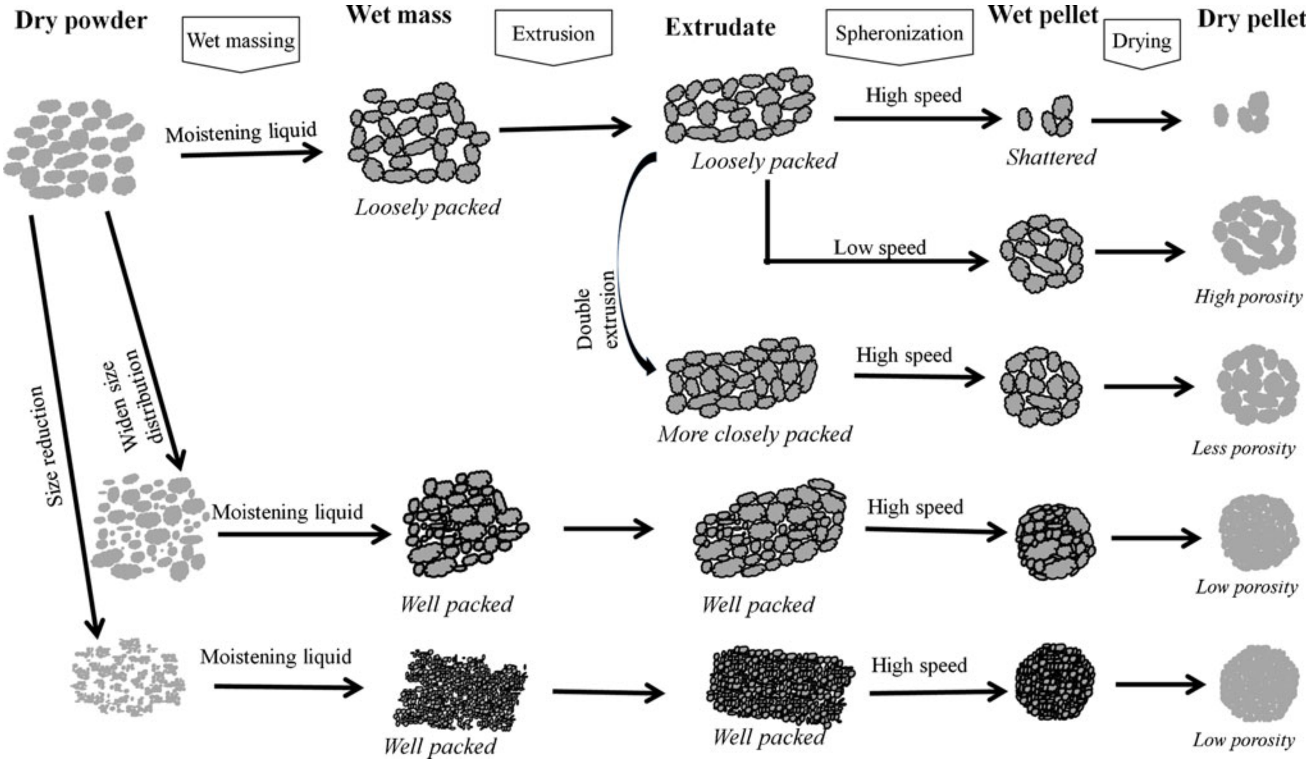

Fig. 4. Schematic diagram showing importance of component particle wet packability for successful pellet formation by extrusion spheronization

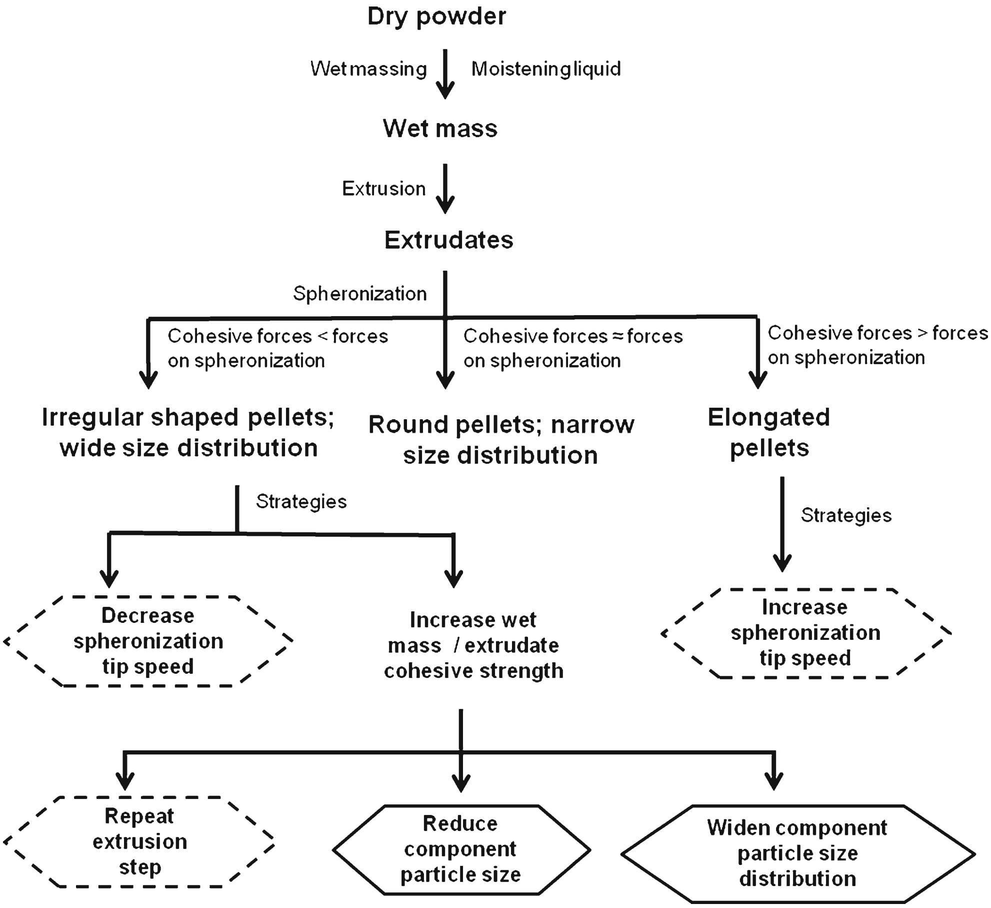

Fig. 5. Schematic showing different processing (*dotted line*) and formulation (*solid line*) strategies to improve pellet quality by enhancing wet packability of component particles during extrusion–spheronization

Spheronization

Spheronization is the most critical step in pelletization by extrusion–spheronization as it is during this step that the moist extrudates are rounded into pellets. During spheronization, the extrudates are mainly subjected to two types of forces, i.e., cohesive forces largely contributed by the liquid bridges between the component particles that are dependent on the close packing of the component particles in the moistened mass and forces on spheronization, comprising centrifugal and frictional forces, resulting from the rotation of the spheronizer frictional base plate (spheronization tip speed). The extrudates are initially broken up by the forces on spheronization into short cylindrical fragments, with lengths dependent on extrudate diameter (15), texture of the extrudate surface (16), the groove width (17), and tip speed (18) of the spheronizer frictional base plate. Owing to the centrifugal forces generated during spheronization, moistening liquid from the interior may be squeezed out to the surfaces of the agglomerates. The excess liquid on the agglomerate surface imparts plasticity, facilitating growth and reshaping of the agglomerates by frictional forces generated by friction between the tumbling agglomerates, between agglomerates and the frictional base plate, and between agglomerates and the spheronizer wall. The cohesive forces and forces on spheronization work in opposition and the quality of produced pellets are dependent on the comparative magnitude of these forces. Maintenance of the sequential packing of component particles and formation of spherical pellets with narrow size distribution requires a balance between the forces on spheronization and the cohesive forces. The forces on spheronization generated by the rotation of the frictional base plate should provide sufficient shear to break up and then reshape the extrudates while the cohesive liquid bridges ensure structural integrity of the moistened material. This provides the component particles, especially those on the surfaces, a “jogging” motion to re-orientate them, improving packing of the component particles and continuous reshaping of the agglomerates to form spherical pellets.

Strategies to Improve Product Quality

Possible processing and formulation strategies that could be employed during extrusion–spheronization to produce good quality pellets are schematically presented in Fig. 5. During spheronization, if the cohesive forces are comparatively higher than the forces on spheronization, as observed with XL/CL-MIC2-8 formulations, the component particles of the extrudates would resist rearrangement, appearing finally as elongated entities. Increasing the forces on spheronization by increasing spheronization tip speed could be a possible processing strategy to round the agglomerates. On the contrary, if the forces on spheronization are high compared to the cohesive forces as observed in the case of the XL/CL-200M-8 formulations, the extrudates may shatter due to abrasion of the extrudate surfaces leading to “unpacking” of the component particles which disrupts the liquid bridges, increasing fines production and decreasing the mean particle size of the resultant agglomerates. In such cases, reducing forces on spheronization by decreasing spheronization tip speed (processing strategy) to sufficient for rearrangement of the component particles in the extrudates during the spheronization step or increasing cohesive strength of the wet mass/extrudates (formulation/processing strategy) to resist shattering and enable controlled breaks along the extrudates into short, regular size fragments at the employed tip speed are possible strategies that could be used to produce better quality pellets. Nevertheless, for pellet production employing wet masses with low cohesive strength, decreasing the tip speed employed during spheronization may not be a suitable option when strong and dense pellets are required. This is because the low tip speed may just be sufficient for rounding the wet agglomerates but not adequate to further consolidate them, as exemplified by the high and similar porosity of the XL/CL-200M formulations spheronized at different tip speeds (Table II). The cohesive strength of extrudates could be increased with closer packing of component particles by repeating the extrusion step (processing strategy) or by substitution of the formulation component(s) with finer particle size grades (formulation strategy). Extrusion consolidates moistened mass mainly by particle–particle rearrangement. Hence, by repeating the extrusion step, depending on the material, cohesive strength of extrudates and subsequently pellet properties could be improved (formulations XL/CL-200M-8-DE, Table II) but only up to a certain limit. In comparison, the formulation strategy by substitution of the formulation component(s) with finer particle size grades could afford better packing of components with low inter-particulate voids providing much more flexibility for improving the cohesive strength of extrudates and finally spherical pellets could be produced with high crushing strength and low porosity (Table IV).

CONCLUSION

Using XPVP–lactose (1:3) binary blends as model formulations, this study demonstrated that the arrangement of component particles or packability during wet processing is a critical factor to produce spherical pellets with high yield and narrow size distribution by extrusion–spheronization. The packability of a formulation is dependent on the suitable particle size and size distribution of its component particles and the forces exerted on the particles during the wet processing steps. Packing of component particles in the formulation during wet processing is responsible for its inter-particulate contacts and consequently the overall cohesive strength of the agglomerates which determines the integrity and reshaping ability of the coalesced particles in response to shear forces and ultimately the successful formation of pellets.

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