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Research Article

Influence of Starting Material Particle Size on Pellet Surface Roughness

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Abstract. The purpose of this study was to investigate the effect of pelletization aids, i.e., microcrystalline cellulose (MCC) and cross-linked polyvinyl pyrrolidone (XPVP), and filler, i.e., lactose, particle size on the surface roughness of pellets. Pellets were prepared from powder blends containing pelletization aid/lactose in 1:3 ratio by extrusion–spheronization. Surface roughness of pellets was assessed quantitatively and qualitatively using optical interferometry and scanning electron microscopy, respectively. Both quantitative and qualitative surface studies showed that surface roughness of pellets depended on the particle size of XPVP and lactose used in the formulation. Increase in XPVP or lactose particle size resulted in rougher pellets. Formulations containing MCC produced pellets with smoother surfaces than those containing XPVP. Furthermore, surface roughness of the resultant pellets did not appear to depend on MCC particle size. Starting material particle size was found to be a critical factor for determining the surface roughness of pellets produced by extrusion–spheronization. Smaller particles can pack well with lower peaks and valleys, resulting in pellets with smoother surfaces. Similar surface roughness of pellets containing different MCC grades could be due to the deaggregation of MCC particles into smaller subunits with more or less similar sizes during wet processing. Hence, for starting materials that deaggregate during the wet processing, pellet surface roughness is influenced by the particle size of the material upon deaggregation.

KEY WORDS: extrusion–spheronization; filler; particle size; pelletization aid; surface roughness.

INTRODUCTION

Extrusion–spheronization is a multistep pelletization process that could be used to produce highly spherical, dense pellets with narrow size distribution. The pellets are usually filled into capsules and used as multiple unit solid dosage forms. Pellet flow rate, thereby capsule fill uniformity, is dependent on the gravitational and frictional forces acting on the pellets. Frictional forces were observed to be increased with increased pellet surface roughness (1). Furthermore, since pellet surface roughness indirectly determines the specific surface area, it could have an impact on important benefits related to the drug release from pellets (2). In addition, the surface roughness of pellets used as cores for coating could contribute to variability in the thickness of the applied coat layer and could influence the amount of coating agent required to achieve the desired coat characteristics in modified-release pellets (2,3). Coat thickness variability due to core pellet surface roughness could lead to variation in drug release from the coated pellets (2,4). Therefore, knowledge regarding factors affecting the surface roughness of pellets could be of importance. Pellet surface roughness was found to be dependent on the shape of the pellets (5–7). Process variables that were reported to influence pellet surface roughness were methods of pellet preparation and spheronization time (5). Pellets prepared from formulations that were subjected to extrusion prior to spheronization had relatively smoother surfaces than those prepared by granulation followed by spheronization or by direct spheronization. Longer spheronization times produced pellets with smoother surfaces. The influence of amount of water as moistening liquid on the surface roughness of microcrystalline cellulose (MCC)-based pellets was investigated qualitatively using scanning electron microscopy (8) and quantitatively using laser profilometry (5). The qualitative analysis study revealed that the formulations with larger amounts of water produced pellets with smoother surfaces. However, the quantitative analysis study did not demonstrate significant influence of amount of water on pellet surface roughness. As pellets are formed by aggregation of starting materials, particle size of the starting materials could be an important factor in determining the surface roughness of the resultant pellets. Understanding the influence of starting material particle size on the resultant pellet surface roughness could be useful to formulation scientists in the selection of component materials to prepare pellets with the desired surface roughness. However, the influence of starting material particle size on the surface roughness of pellets has not been investigated.

The basic starting materials for the production of pellets by extrusion–spheronization consist of drug (active component), pelletization aid (to fulfill the requirement of moistened mass for extrusion and spheronization), and filler (to provide the required bulk). The materials investigated for their application as pelletization aid include MCC (9–11), cross-linked polyvinyl

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pyrrolidone (XPVP) (12–14), carrageenan (15,16), chitosan (17,18), hydroxypropyl methylcellulose (19,20), and powdered cellulose (21,22). Among the pelletization aids, MCC is considered as the gold standard (23) and XPVP is a promising alternative to MCC as pelletization aid (12). The materials employed in pelletization as fillers include lactose (24–27), dicalcium phosphate (10), sorbitol (28), and mannitol (29). Among the investigated fillers, lactose is the most commonly used filler for pharmaceutical pelletization. The influence of MCC and lactose proportions in the formulation on the surface roughness of pellets was investigated (30). It was observed that the pellet surface roughness increased with increasing lactose fraction in the formulation. A number of studies have been carried out to investigate the influence of pelletization aid [MCC (10,14) and XPVP (12,14)] and filler [lactose (24–27)] particle size on pellet size, size distribution, and shape. While particle size of XPVP (12,14) and lactose (24–27) had significant effect on pellet size, size distribution, and shape, different particle size grades of MCC (10,14) did not appear to have any significant effect and could be used interchangeably to produce pellets with similar quality in terms of pellet size, size distribution, and shape.

Therefore, the purpose of this study was to investigate and compare the effect of starting materials of different particle size on the surface roughness of pellets produced by extrusion–spheronization. The influence of particle size of pelletization aid was investigated using several grades of two commonly used pelletization aids, MCC and XPVP, whereas the influence of particle size of filler was investigated using several grades of lactose.

MATERIALS AND METHODS

Materials

Three grades of XPVP, polyplasdone XL (XL), polyplasdone XL-10 (XL10), and polyplasdone INF-10 (INF10) from International Specialty Products (ISP; Wayne, NJ, USA), and three grades of MCC, Avicel PH 102 (PH102), Avicel PH 101 (PH101), and Avicel PH 105 (PH105) from FMC Biopolymer (Cork, Ireland) were used as pelletization aids. Three grades of lactose α-monohydrate, Pharmatose 125M (125M), Pharmatose 200M (200M), and Pharmatose 450M (450M) from DMV International (Veghel, The Netherlands), were used as filler for preparation of pellets. All the materials were equilibrated at 50% relative humidity and 25°C prior to experimentation. Distilled water was used as the moistening liquid.

Characterization of Starting Materials

Starting materials were characterized for their size, size distribution and specific surface area. For each powder grade, measurement of particle size, size distribution, and specific surface area were carried out in triplicate and results shown in Table I.

Size and Size Distribution

Particle size and size distribution of starting materials were measured by laser diffraction (LS230, Coulter Corporation, Brea, CA, USA) with a sampling time of 100 s. The dry powder module was used for the pelletization aids, i.e., the different grades of MCC and XPVP, whereas the wet powder module with isopropyl alcohol, filtered through 0.45-μm pore size filter, as the dispersion medium was used for the lactose grades.

Table I. Physical Properties of the Different MCC, XPVP and Lactose Grades Used as Starting Materials for Pellet Production

Material	Grade	x_{50} (μm) (n=3)	Span (n=3)	Specific surface area (m^2/g) (n=3)
MCC	PH102	131.3±3.9	1.78±0.09	1.080±0.022
	PH 101	74.4±3.9	1.82±0.04	1.145±0.031
	PH105	32.2±1.8	1.57±0.37	1.769±0.021
XPVP	XL	183.5±5.7	2.03±0.03	0.720±0.041
	XL10	30.0±1.0	1.60±0.02	0.902±0.051
	INF10	19.5±0.3	1.55±0.03	1.273±0.039
Lactose	125M	65.9±3.3	1.65±0.04	0.330±0.026
	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

x_{50} median particle size of starting material

In the dry powder module, powder sample, presieved through a 1-mm aperture size sieve, was steadily delivered to achieve an obscuration of 4–11%. In the wet powder module, approximately 0.2 g of the powder sample was dispersed in 50 mL isopropyl alcohol. The dispersed sample was then added dropwise until polarization intensity differential scattering reached 45–55%.

For both dry and wet powder modules, median particle diameter (x_{50}) was calculated from the cumulative percent undersize plot. Span was derived using Eq. (1).

$$\text{Span} = \frac{x_{90} - x_{10}}{x_{50}} \quad (1)$$

where x_{10}, x_{50}, and x_{90} were diameters of particles at the 10, 50, and 90 percentiles of the cumulative percent undersize plot, respectively.

Specific Surface Area

Specific surface areas of powders were determined using the Brunauer–Emmett–Teller adsorption method (SA3100, Coulter, Miami, FL, USA) using nitrogen as the adsorbate gas. The powder samples were degassed for 12 h under nitrogen at 80°C to remove any preadsorbed gases and vapors from the powder surfaces.

Preparation of (MCC/XPVP)/lactose (1:3) Powder Blends

MCC/XPVP and lactose powders were mixed in a double cone blender (AR400E, Erweka, Heusenstamm, Germany) rotated at 40 rpm for 20 min. The powder blends were coded by pelletization aid grade–lactose grade.

Characterization of Powder Blends

The powder blends were characterized for their size, size distribution, and rheological properties. For each powder blend, measurement of particle size, size distribution, and rheological properties were carried out in triplicate.

Particle Size and Size Distribution

Particle size and particle size distribution of the powder blends were determined by laser diffraction (LS230, Coulter Corporation, Brea, CA, USA). For MCC-lactose powder blends and XPVP-lactose powder blends, the dry powder module and the wet powder module with isopropyl alcohol as dispersion medium were used, respectively. The median particle diameter, denoted as X_{50}, was calculated from the cumulative percent undersize plot. Span values were derived using Eq. (1). The X_{50} and span values of different MCC/XPVP-lactose powder blends are summarized in Table II.

Rheological Properties

The dry powder blend (24 g) was added to the mixer bowl of a mixer torque rheometer (Caleva Process Solutions Limited, Dorset, England) and subsequently mixed for 30 s. The mean torque generated by the dry powder blend was recorded. Distilled water, corresponding to 5% *w*/*w* of the dry powder mass, was added and mixed for 30 s during the first 10 additions. The mean torque generated by the wetted mass was recorded after each addition. For the remaining nine additions, distilled water was added at an interval of 60 s after which the mean torque generated was again recorded. From the "mean torque (Nm) *versus* liquid added (%, *w*/*w*)" plot of each formulation, the respective maximum torque ($T_{\max}$) and amount of water required to reach the maximum torque ($W_{T_{\max}}$) were determined.

Preparation of Pellets by Extrusion–Spheronization

(MCC/XPVP)/lactose powder blend (800 g) was transferred to a planetary mixer (Kenwood Major 250, Kenwood Ltd, Havant, UK) and moistened over 5 min with distilled water. Water was added over the initial 2 min, and wet massing was then carried out for another 3 min. For optimum quality pellets, the amount of distilled water employed amounted to 80% (MCC/lactose powder blends) or 90% (XPVP/lactose powder blends) of the $W_{T_{\max}}$ obtained from rheology studies on the corresponding powder blend (14). The wetted mass was subsequently transferred to a radial screw extruder (E140, Niro, Eastleigh, UK) and extruded through a screen of 1-mm aperture diameter and thickness. Extrudates (750 g) were transferred to the spheronizer (S320, Niro, Eastleigh, UK) fitted with a cross-hatched 30-cm diameter frictional base plate and spheronized at 500 rpm (471 m/min tip speed) for 5 min. After spheronization, pellets were collected and dried using a fluid bed dryer (STREA-1 Pro, GEA, Bubendorf, Switzerland) at inlet temperature of 80°C and air flow rate of 80 m^3/h until the product temperature reached 40°C. Dried pellets were equilibrated overnight at 50% relative humidity and 25°C. Three repeat batches were carried out for each formulation. Formulations containing pelletization aids were coded by "F" followed by the powder blend.

Morphology of Extrudates

Photographs of the freshly prepared extrudates were taken using a stereomicroscope (SZ61, Olympus, Tokyo, Japan).

Characterization of Pellets

Size Analysis

The pellets (approximately 80 g) were sieved through a series of sieves with aperture sizes decreasing in a $\sqrt{2}$ progression from 2,800 to 250 μm. Sieving was carried out at an amplitude of 1 mm, using a mechanical sieve shaker (VS 1000, Retsch, Haan, Germany), for 10 min. The fraction of pellets >2,800 μm was defined as the oversize fraction (%, *w*/*w*), whereas the fraction of pellets between 710 and 1,400 μm was defined as the yield (%, *w*/*w*). D_{10}, D_{50}, and D_{90}, the diameters of pellets at 10, 50, and 90 percentiles, respectively, were determined from the cumulative percent undersize plot. SP_{pel} value was calculated using Eq. (2).

$$SP_{pel} = \frac{D_{90} - D_{10}}{D_{50}} \quad (2)$$

Shape Analysis

Shape analysis was carried out using an image analyzer, comprised of a computer system connected to a video camera (DSP 3CCD, Sony, Tokyo, Japan) mounted on a stereomicroscope (SZH, Olympus, Tokyo, Japan). For each pellet batch, 100 pellets (i.e., in total 300 pellets per formulation) were randomly selected from the 710 to 1,000 μm size fraction and used for shape analysis. Aspect ratio and roundness values were calculated using imaging software (Image-Pro, Version

Table II. Particle Size, Size Distribution, and Rheological Properties of (MCC/XPVP)/Lactose (1:3) Powder Blends Used for Pellet Production

Powder blend	X_{50} (μm) (n=3)	Span (n=3)	$W_{T_{\max}}$ (%, *v*/*w*) (n=3)	$T_{\max}$ (Nm) (n=3)
PH102-450M	62.9±8.3	5.73±0.50	55.0±2.9	0.597±0.045
PH101-450M	45.3±3.1	4.98±1.14	55.0±1.7	0.653±0.029
PH105-450M	30.1±0.8	1.99±0.16	55.0±0.0	0.638±0.048
XL-450M	77.4±3.8	4.86±0.27	65.0±1.0	0.256±0.026
XL10-450M	31.5±2.1	1.77±0.08	60.0±0.0	0.335±0.017
INF10-450M	27.4±7.9	1.97±0.18	50.0±0.0	0.323±0.011
XL10-125M	46.0±1.6	2.73±0.02	52.5±2.9	0.235±0.017
XL10-200M	35.4±0.3	2.04±0.04	55.0±1.5	0.248±0.025

X_{50} median particle size of powder blend

6.3, Media Cybernetics, Bethesda, MD, USA) from images of the pellets captured by the video camera. Roundness values emphasize the sphericity of pellets while the elongation of pellets is described by the aspect ratio.

$$\text{Aspect ratio} = \frac{l}{b} \tag{3}$$

$$\text{Roundness} = \frac{P^2}{4\pi A} \tag{4}$$

where b, l, A, and P are the breadth, length, area, and perimeter of the two-dimensional particle outline, respectively. For a perfect sphere, these two shape descriptors bear values of 1.

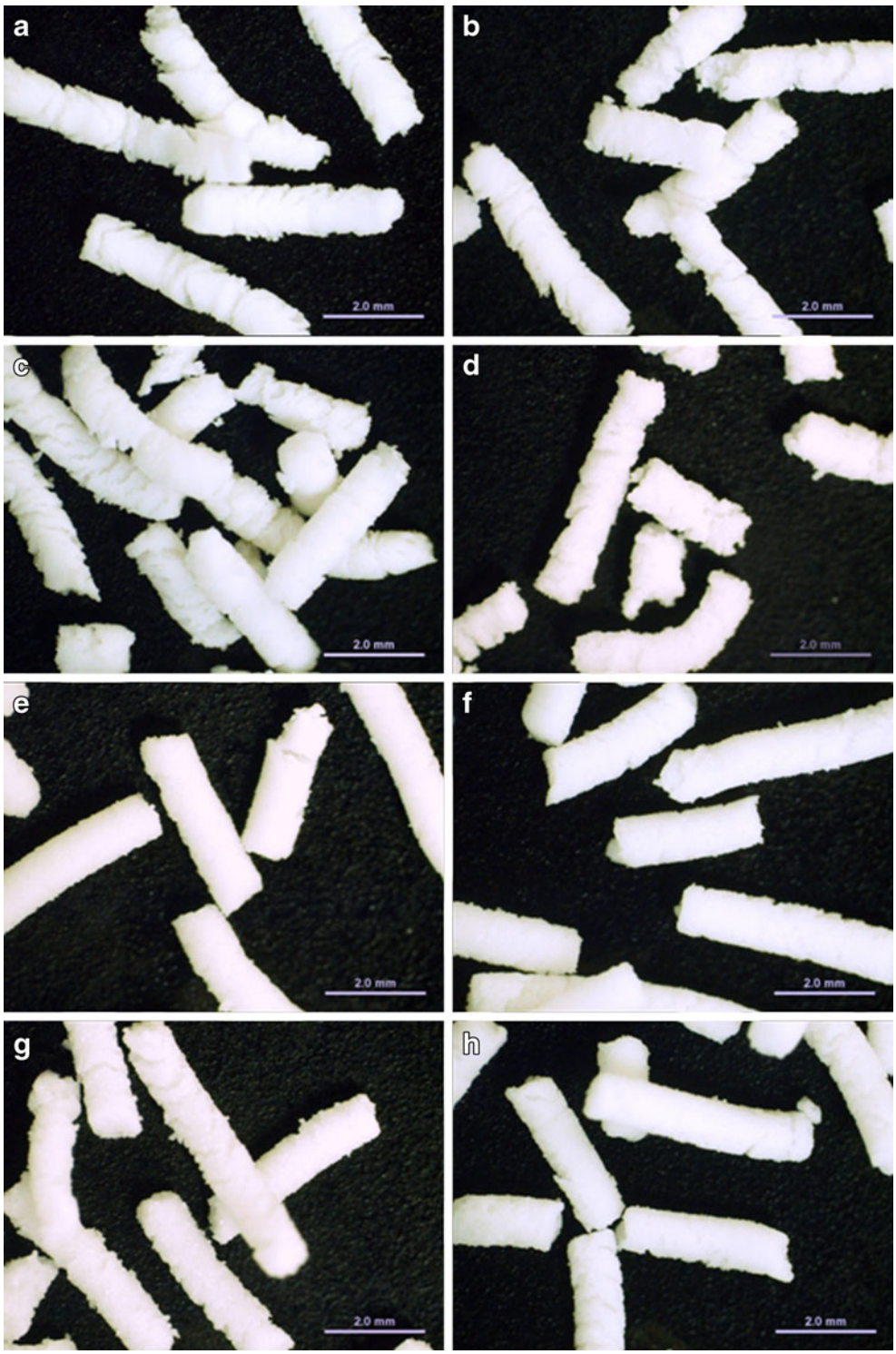

Fig. 1. Photographs depicting the surface of MCC/XPVP-lactose extrudates: **a** F-PH102-450M, **b** F-PH101-450M, **c** F-PH105-450M, **d** F-XL-450M, **e** F-XL10-450M, **f** F-INF10-450M, **g** F-XL10-125M, and **h** F-XL10-200M

Quantitative Analysis of Surface Roughness by Optical Interferometry

Pellet surface roughness analysis was conducted using the vertical scanning interferometry mode of the optical profiler (Wyko NT1100, Veeco, Tucson, AZ, USA). A combination of ×2 field of view lens and ×20 objective lens was employed to attain a magnification of ×42.9 and a scan size of 109.7×144.1 μm. This magnification provided lateral and vertical resolutions of 195.85 and 1 nm, respectively. For each pellet batch, 100 pellets (in total 300 pellets per formulation), randomly selected from the 710 to 1,000 μm size fraction, were scanned and the images obtained were analyzed using the computer software (Vision 3.0, Vecco, Tucson, AZ, USA). The arithmetic mean roughness (R_a) and root mean square roughness (R_q) values were digitally approximated as shown in Eqs. (5) and (6), respectively.

$$R_a = \frac{1}{MN}\sum_{i=1}^{m}\sum_{i=1}^{n}\left|Z_{ji}\right| \tag{5}$$

$$R_q = \sqrt{\frac{1}{MN}\sum_{i=1}^{M}\sum_{i=1}^{N}Z^2\left(x_i, y_j\right)} \tag{6}$$

where M and N referred to the number of data points in the x and y directions, respectively, and Z referred to the height of the surface relative to the reference mean plane. The number of data points in x (M) and y (N) directions were 736 and 480, respectively. R_a, defined as the arithmetic mean of the absolute values of surface departures from the mean plane, is a useful indicator of the overall variation in the pellet surface without being adversely affected by small numbers of sharp peaks or valleys. R_q obtained by squaring each height value in the dataset, then taking the square root of the mean, represents the standard deviation of the surface heights. An increase in either R_a or R_q values could be interpreted as an increase in the roughness of the pellet surface being analyzed.

Qualitative Analysis of Surface Roughness by Scanning Electron Microscopy

Pellets, randomly selected from the 710 to 1,000 μm size fraction, were attached to a stud using carbon tape before being gold coated using a fine coat ion sputter (JFC-1100, JEOL, Tokyo, Japan). Photomicrographs of the pellet surfaces were obtained using a scanning electron microscope (SEM, JSM-5200, JEOL, Tokyo, Japan).

Statistical Analysis

Statistical analysis was performed using Graph Pad Instat (Version 3, GraphPad Software, Inc., San Diego, CA, USA). Unscrambler 9.8 (Camo Inc., Bangalore, India) was used for principal component analysis (PCA).

RESULTS AND DISCUSSION

Rheological Properties of Powder Blends

Rheological properties, i.e., T_{max} and $W_{T_{max}}$, of the different MCC/XPVP-lactose powder blends are presented in Table II. The influence of MCC particle size on T_{max} was found to be insignificant (ANOVA, $p>0.05$). Likewise, no significant difference (ANOVA, $p>0.05$) between the $W_{T_{max}}$ values was observed despite the variation in MCC particle size.

In contrast, the particle sizes of XPVP and lactose were observed to have an impact on the T_{max} values of the binary mixtures. The T_{max} values increased and $W_{T_{max}}$ values decreased with decreasing particle size of XPVP or lactose. Compared to MCC-lactose powder blends, powder blends containing XPVP-lactose exhibited lower T_{max} values.

Extrudate Properties

The photographs of extrudates obtained from the different MCC/XPVP-lactose formulations are shown in Fig. 1. All the MCC-lactose formulations produced similar quality extrudates with sharkskinning and irregular surfaces. The extrudates prepared from XL-450M formulation was similar to those produced from MCC-lactose formulations. However, extrudates with relatively smoother surfaces were produced from the remaining XPVP-lactose formulations. Visual observation of the extrudate photographs did not reveal any remarkable effect of lactose particle size in the XPVP-lactose formulations on the extrudate surface morphology.

Table III. Physical Properties of Pellets Prepared From Powder Blends Containing (MCC/XPVP)/Lactose in 1:3 ratio

Formulation	Oversize fraction (%, *w*/*w*) (*n*=3)	Yield (%, *w*/*w*) (*n*=3)	D_{50} (μm) (*n*=3)	SP_{pel} (*n*=3)	Aspect ratio (*n*=300)	Roundness (*n*=300)
F-PH102-450M	0.0±0.1	85.8±2.5	850±9	0.47±0.02	1.148±0.084	1.123±0.011
F-PH101-450M	0.0±0.0	83.3±4.0	843±15	0.48±0.01	1.129±0.065	1.120±0.009
F-PH105-450M	0.0±0.1	82.4±2.3	838±8	0.46±0.04	1.137±0.070	1.125±0.011
F-XL-450M	3.8±0.5	55.4±4.2	900±40	1.12±0.05	1.140±0.075	1.144±0.016
F-XL10-450M	0.2±0.2	95.9±0.9	1,140±10	0.37±0.03	1.135±0.077	1.128±0.012
F-INF10-450M	0.0±0.1	96.9±0.3	1,113±6	0.43±0.01	1.128±0.072	1.130±0.014
F-XL10-125M	0.1±0.1	96.4±0.2	1,153±6	0.33±0.02	1.131±0.064	1.146±0.012
F-XL10-200M	0.0±0.1	97.1±0.1	1,130±5	0.39±0.01	1.140±0.068	1.132±0.010

D_{50} mass median diameter of pellets, SP_{pel} span value of pellets

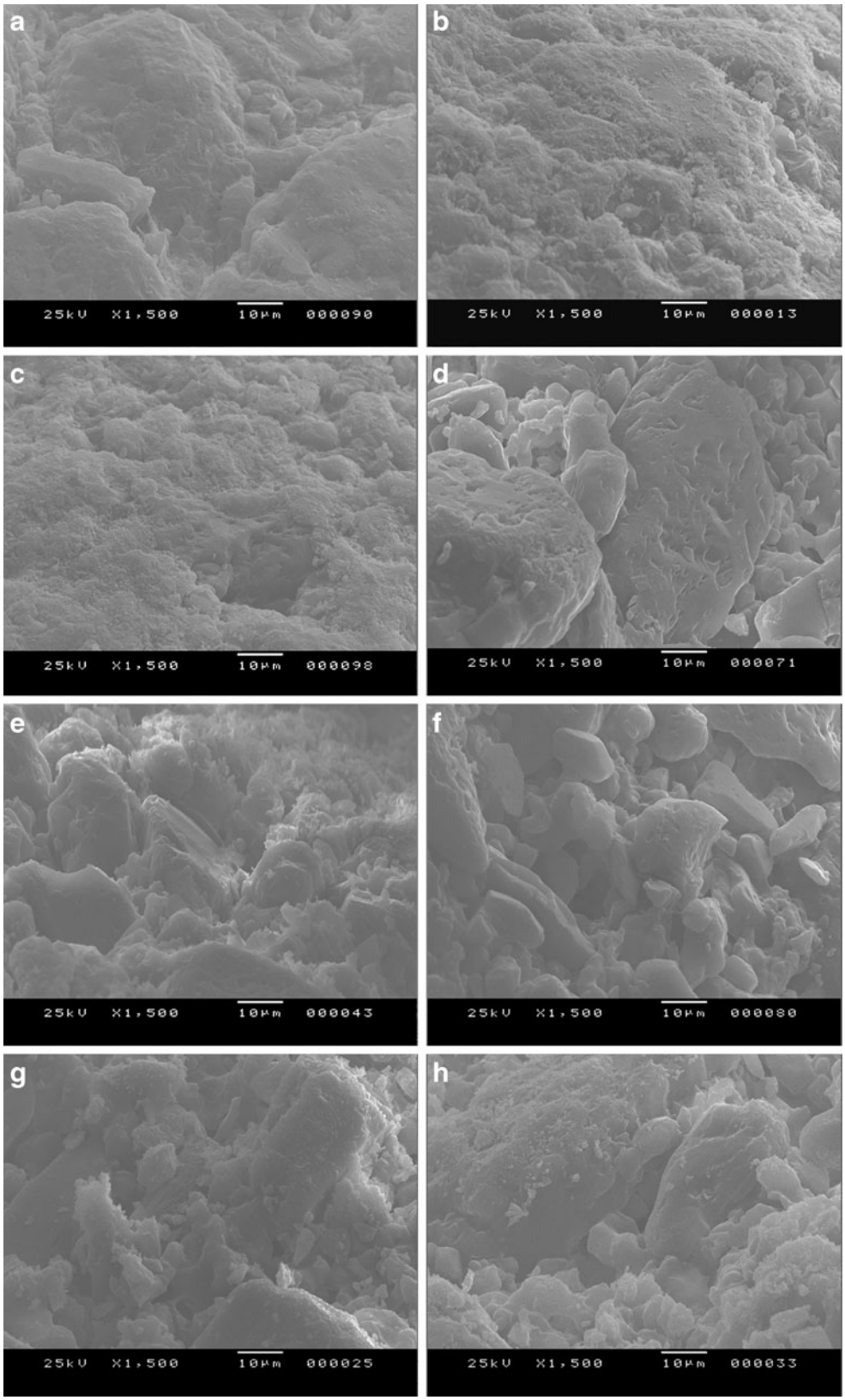

Fig. 2. SEM photomicrographs depicting the surface of MCC/XPVP-lactose pellets: **a** F-PH102-450M, **b** F-PH101-450M, **c** F-PH105-450M, **d** F-XL-450M, **e** F-XL10-450M, **f** F-INF10-450M, **g** F-XL10-125M, and **h** F-XL10-200M

Pellet Properties

Yield, Size, Size Distribution, and Shape

Physical properties of MCC/XPVP-lactose pellets are presented in Table III. All the investigated MCC grades produced pellets with similar oversize fraction, yield, D_{50}, SP_{pel}, aspect ratio, and roundness. These findings were consistent with those reported in earlier studies (10,14).

In general, XPVP-lactose formulations produced pellets with comparable D_{50}, aspect ratio, and roundness values, although F-XL-450M pellets exhibited lower yield and higher SP_{pel} (Table III). With the exception of F-XL-450M, pellets prepared from the formulations containing the remaining XPVP grades had higher yield, larger D_{50} and lower SP_{pel} values. As mentioned earlier, MCC-lactose and XL-450M powder blends produced extrudates with irregular surfaces. At beginning of the spheronization process, these extrudates could have undergone more extensive fragmentation, yielding fragments with wider size distribution and in turn resultant pellets with smaller D_{50}, lower yield and higher SP_{pel}. Nevertheless, the fragments from all the formulations were observed to be rounded successfully, yielding pellets with similar aspect ratio and roundness.

Surface Roughness

The SEM photomicrographs of the investigated pellet formulations are given in Fig. 2 while their quantitative surface roughness data, as represented by R_a and R_q, are shown in Table IV. Both qualitative and quantitative surface roughness assessments showed that the surfaces of MCC-lactose pellets were smooth and similar irrespective of the MCC grades used. All the MCC-based formulations were found to have similar R_a and R_q values (ANOVA, $p>0.05$) and formed a group in the PCA score plot (Fig. 3), indicating similar degree of surface roughness irrespective of the particle size grade of MCC employed in the starting MCC-450M powder blends. These findings were congruent with observations made from the SEM photomicrographs, which showed MCC-450M pellets with similar smooth surfaces (Fig. 2).

Table IV. Quantitative Surface Roughness Parameters of Pellets Prepared from Powder Blends Containing (MCC/XPVP)/Lactose in 1:3 Ratio

Formulation	R_a (μm) (n=300)	R_q (μm) (n=300)
F-PH102-450M	3.82±0.65	5.91±0.99
F-PH101-450M	3.69±0.69	5.48±1.36
F-PH105-450M	3.66±0.69	5.68±0.90
F-XL-450M	6.62±1.32	9.33±1.83
F-XL10-450M	5.04±0.78	7.37±1.27
F-INF10-450M	4.87±0.70	7.27±1.18
F-XL10-125M	7.73±2.06	10.57±2.59
F-XL10-200M	5.61±0.70	7.90±0.98

R_a arithmetic mean roughness, R_q root mean square roughness

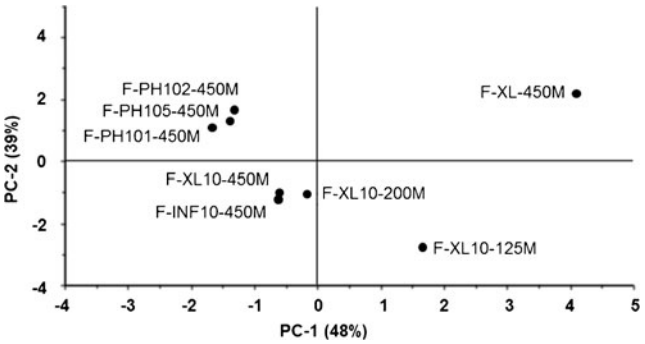

Fig. 3. PCA score plot of MCC/XPVP-lactose pellet formulations containing different grades of MCC/XPVP and lactose

Both quantitative and qualitative surface roughness analyses indicated that all the investigated XPVP-lactose pellets had rougher surfaces than MCC-lactose pellets. The ability of MCC to produce pellets with smoother surfaces has also been reported in another study (21) where it was observed that MCC-based pellets had relatively smoother surfaces than powdered cellulose-based pellets. The surfaces of the investigated XPVP-lactose pellets did not appear to be similar (Fig. 2), and their R_a and R_q values were found to be dependent on the particle size grade of XPVP employed in the starting XPVP-450M powder blend (Table IV). In general, XPVP-450M pellets containing larger particle size grades of XPVP had rougher surfaces as reflected by their higher R_a and R_q values (ANOVA, $p<0.05$). A similar trend was seen with starting powder blends containing XL10 and different particle size grades of lactose. Among the XPVP-lactose pellet formulations, the F-XL-450M and F-XL10-125M pellet formulations exhibited higher R_a and R_q values (Table IV) and were located far from the other XPVP-lactose formulations in the score plot (Fig. 3).

Influence of Starting Material Particle Size on Pellet Properties

The packing ability of the component particles during the different wet processing steps of extrusion and spheronization was found to be important for pellet formation. The packing ability of component particles was reported to be dependent on the particle size and size distribution of the components (31). As observed in a previous study on in-process particle sizes of different MCC and XPVP grades (14), MCC grades with different dry state particle sizes had more or less similar in-process particle sizes during wet processing whereas the in-process particle sizes of the different XPVP grades investigated were not remarkably different from their respective dry state particle sizes. Although lactose is soluble in water, the amount of water used as moistening liquid in extrusion–spheronization was sufficient for pellet production but not enough for causing significant dissolution of the lactose particles. Hence, the particle size of lactose was likely to approximate their particle size in the dry state.

In-process deaggregation of MCC grades with different dry state particle sizes into small, more or less similar sizes during wet processing ensured similar interactions between the MCC and lactose particles across the investigated MCC-lactose formulations. Therefore, MCC-lactose moistened masses containing different MCC grades behaved in a similar fashion during the different wet processing steps of extrusion–spheronization, yielding moistened mass, extrudates, and pellets with similar quality. It was postulated that pellet surface roughness is determined by the packing of the component particles on the pellet surface, which in turn is largely influenced by their particle size. Hence, all the MCC-lactose pellets exhibited similar surface roughness. Unlike MCC, the commercially available XPVP grades and lactose grades are not agglomerates of smaller subunits that are susceptible to deaggregation with application of forces during wet processing. With the relatively large XL or 125M particles in the blend composition, the particles in the resultant blends may not pack as closely together as those particles in powder blends containing small particle size XPVP and lactose grades. It was reported that looser packing of particle in the pellets produced pellets with rougher surfaces (1). Hence, the F-XL-450M and F-XL10-125M pellets had an overall more uneven and undulating surface appearance with greater variation in peak heights on the pellet surfaces (Fig. 2) and exhibited higher R_a and R_q values (Table IV).

The in-process particle sizes of the investigated MCC (11–22 μm) and INF10 (17–19 μm) grades were comparable (14). However, as indicated by their lower R_a and R_q values, pellets produced from the MCC-lactose formulations were found to have smoother surfaces than those produced from INF10-lactose formulations. Deaggregation of MCC particles during wet processing may have exposed some amorphous ends, which could form hydrogen bonds with water molecules to give a gel-network (32). It is plausible that due to this gel network, the pellets containing MCC undergo shrinkage on drying (32,33), which could have conferred additional effect of increasing the smoothness of the MCC-based pellet surfaces.

CONCLUSION

Starting material particle size is an important determinant of the surface roughness of pellets produced by extrusion–spheronization. In general, as exemplified by XPVP and lactose, starting materials with smaller particle size are able to pack more closely together to produce pellets with relatively smoother surfaces. The similar surface roughness of pellets containing different dry state particle size grades of MCC demonstrated that for starting materials that are prone to de-aggregation during the wet processing steps of extrusion–spheronization, surface roughness of the resultant pellets is governed by the particle size of the material upon deaggregation. In addition, with MCC, gel formation and subsequent shrinkage of the pellets on drying could have contributed to further smoothing of the pellet surfaces.

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REFERENCES

1. Rodriguez EC, Torrado JJ, Nikolakakis I, Torrado S, Lastres JL, Malamataris S. Micromeritic and packing properties of diclofenac pellets and effects of some formulation variables. Drug Dev Ind Pharm. 2001;27(8):847–55.
2. Chopra R, Podczeck F, Newton JM, Alderborn G. The influence of film coating on the surface roughness and specific surface area of pellets. Part Part Syst Charact. 2002;19(4):277–83.
3. Podczeck F, Brown S, Newton JM. Monitoring film coating with surface profilometry. Pharm Technol. 1999;23(5):48–56.
4. Andersson M, Holmquist B, Lindquist J, Nilsson O, Wahlund KG. Analysis of film coating thickness and surface area of pharmaceutical pellets using fluorescence microscopy and image analysis. J Pharm Biomed Anal. 2000;22(2):325–39.
5. Chopra R, Newton JM, Alderborn G, Podczeck F. Preparation of pellets of different shape and their characterization. Pharm Dev Technol. 2001;6(4):495–503.
6. Hellen L, Yliruusi J, Kristoffersson E. Process variables of instant granulator and spheroniser: II. Size and size distributions of pellets. Int J Pharm. 1993;96(1–3):205–16.
7. Hellen L, Yliruusi J. Process variables of instant granulator and spheroniser: III. Shape and shape distributions of pellets. Int J Pharm. 1993;96(1–3):217–23.
8. Hellen L, Yliruusi J, Merkku P, Kristoffersson E. Process variables of instant granulator and spheroniser: I. Physical properties of granules, extrudate and pellets. Int J Pharm. 1993;96(1–3):197–204.
9. Soh JLP, Yang L, Liew CV, Cui FD, Heng PWS. Importance of small pores in microcrystalline cellulose for controlling water distribution during extrusion–spheronization. AAPS PharmSciTech. 2008;9(3):972–81.
10. Sinha VR, Agrawal MK, Kumria R. Influence of formulation and excipient variables on the pellet properties prepared by extrusion spheronization. Curr Drug Deliv. 2005;2(1):1–8.
11. Heng PWS, Koo OMY. A study of the effects of the physical characteristics of microcrystalline cellulose on performance in extrusion spheronization. Pharm Res. 2001;18(4):480–7.
12. Liew CV, Gu L, Soh JLP, Heng PWS. Functionality of cross-linked polyvinylpyrrolidone as a spheronization aid: a promising alternative to microcrystalline cellulose. Pharm Res. 2005;22(8):1387–98.
13. Verheyen P, Steffens KJ, Kleinebudde P. Use of crospovidone as pelletization aid as alternative to microcrystalline cellulose: effects on pellet properties. Drug Dev Ind Pharm. 2009;35(11):1325–32.
14. Sarkar S, Heng PWS, Liew CV. Insights into the functionality of pelletization aid in pelletization by extrusion–spheronization. Pharm Dev Technol. 2013;18(1):61–72.
15. Bornhöft M, Thommes M, Kleinebudde P. Preliminary assessment of carrageenan as excipient for extrusion/spheronisation. Eur J Pharm Biopharm. 2005;59(1):127–31.
16. Thommes M, Kleinebudde P. The behavior of different carrageenans in pelletization by extrusion/spheronization. Pharm Dev Technol. 2008;13(1):27–35.
17. Agrawal AM, Howard MA, Neau SH. Extruded and spheronized beads containing no microcrystalline cellulose: influence of formulation and process variables. Pharm Dev Technol. 2004;9(2):197–217.
18. Charoenthai N, Kleinebudde P, Puttipipatkhachorn S. Use of chitosan-alginate as alternative pelletization aid to macrocrystalline cellulose in extrusion/spheronization. J Pharm Sci. 2007;96(9):2469–84.
19. Chatlapalli R, Rohera BD. Rheological characterization of diltiazem HCl/cellulose wet masses using a mixer torque rheometer. Int J Pharm. 1998;175(1):47–59.
20. Chatlapalli R, Rohera BD. Physical characterization of HPMC and HEC and investigation of their use as pelletization aids. Int J Pharm. 1998;161(2):179–93.
21. Alvarez L, Concheiro A, Gómez-Amoza JL, Souto C, Martínez-Pacheco R. Powdered cellulose as excipient for extrusion–spheronization pellets of a cohesive hydrophobic drug. Eur J Pharm Biopharm. 2003;55(3):291–5.
22. Fechner PM, Wartewig S, Füting M, Heilmann A, Neubert RHH, Kleinebudde P. Properties of microcrystalline cellulose and powder cellulose after extrusion/spheronization as studied by Fourier transform Raman spectroscopy and environmental scanning electron microscopy. AAPS J. 2003;5(4):XXI–II.

23. Dukić-Ott A, Thommes M, Remon JP, Kleinebudde P, Vervaet C. Production of pellets via extrusion–spheronisation without the incorporation of microcrystalline cellulose: a critical review. Eur J Pharm Biopharm. 2009;71(1):38–46.
24. Fielden KE, Newton JM, Rowe RC. The effect of lactose particle size on the extrusion properties of microcrystalline cellulose–lactose mixtures. J Pharm Pharmacol. 1989;41(4): 217–21.
25. Fielden KE, Newton JM, Rowe RC. The influence of lactose particle size on spheronization of extrudate processed by a ram extruder. Int J Pharm. 1992;81(2–3):205–24.
26. Wan LSC, Heng PWS, Liew CV. Spheronization conditions on spheroid shape and size. Int J Pharm. 1993;96(1–3):59–65.
27. Fielden KE, Newton JM, Rowe RC. The influence of moisture content on spheronization of extrudate processed by a ram extruder. Int J Pharm. 1993;97(1–3):79–92.
28. Goyanes A, Souto C, Martínez-Pacheco R. Control of drug release by incorporation of sorbitol or mannitol in microcrystalline-cellulose-based pellets prepared by extrusion–spheronization. Pharm Dev Technol. 2010;15(6):626–35.
29. Ghanam D, Kleinebudde P. Suitability of a flat die press for the manufacture of pharmaceutical pellets by extrusion/spheronization. Drug Dev Ind Pharm. 2011;37(4):456–64.
30. Newton M, Petersson J, Podczeck F, Clarke A, Booth S. The influence of formulation variables on the properties of pellets containing a self-emulsifying mixture. J Pharm Sci. 2001;90(8):987–95.
31. Sarkar S, Wong TW, Liew CV. Importance of wet packability of component particles in pellet formation. AAPS PharmSciTech. 2013;14:1267–77.
32. Kleinebudde P. The crystallite-gel-model for microcrystalline cellulose in wet-granulation, extrusion, and spheronization. Pharm Res. 1997;14(6):804–9.
33. Suzuki T, Kikuchi H, Yamamura S, Terada K, Yamamoto K. The change in characteristics of microcrystalline cellulose during wet granulation using a high-shear mixer. J Pharm Pharmacol. 2001;53(5):609–16.