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Research Paper

Functionality of Cross-Linked Polyvinylpyrrolidone as a Spheronization Aid: A Promising Alternative to Microcrystalline Cellulose

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Purpose. This work seeks to explore and demonstrate the functionality of cross-linked polyvinylpyrrolidone (crospovidone) as a spheronization aid and a promising alternative to microcrystalline cellulose (MCC).

Methods. Pellets were prepared with various grades of crospovidone using both small- and large-scale extrusion–spheronization. A Box-Behnken experimental design was employed to elucidate the effects of operating variables on the quality of the pellets. Size and shape analyses of these pellets were conducted and compared to those prepared using MCC.

Results. Crospovidone was believed to behave like a liquid repository in its interaction with water during extrusion–spheronization, although its binding ability was weaker than that of MCC. Spherical pellets of narrow size distribution could be made from the finer crospovidone grades with different lactose grades. However, crospovidone-based formulations required higher water levels than weight-equivalent MCC-based formulations. Crospovidone pellets were of equivalent quality to those prepared with MCC, especially in the shape, size, and yield.

Conclusions. Crospovidone can be successfully employed as a spheronization aid to produce good pellets without the need of a binder, unlike most of the previously proposed materials. This study exemplified the enormous potential of crospovidone to serve as a competent alternative to MCC in the production of pellets by extrusion–spheronization.

KEY WORDS: cross-linked polyvinylpyrrolidone; extrusion–spheronization; microcrystalline cellulose; pellets; spheronization aid.

INTRODUCTION

Pellets may be prepared using extrusion–spheronization, solution/suspension layering, rotary processing, high shear/melt granulation, and powder layering. Other less widely employed methods of pelletization include spray congealing/drying, balling and compression. Among these pelletization techniques, extrusion–spheronization is comparatively more widely used, as it is able to achieve a robust and reproducible pellet production process.

To prepare good pellets from extrusion–spheronization, the wetted mass must fulfill certain conditions (1). During extrusion, the wetted powder material must be able to form a cohesive yet plastic mass that remains homogeneous throughout the extrusion process. For spheronization, a precise balance between plasticity and brittleness of the extrudates is needed to complete the process effectively. Very often, the wetted powder materials do not possess the requisite attributes to yield desirable pellets. Hence, there is a need for a spheronization aid to alter the rheological properties of the wetted masses to achieve the desired condition for pellets to be successfully prepared.

Microcrystalline cellulose (MCC) has been widely regarded as an indispensable excipient for extrusion–spheronization. Pellets produced with MCC often have a narrow size distribution, high sphericity, and desirable mechanical properties. The unsurpassed efficiency of MCC in extrusion–spheronization has been attributed to its high internal porosity and large surface area, enabling the moistened mass to retain a large amount of usable moisture for lubrication during extrusion (2). This moisture then plasticizes the surface of the extrudates for remodeling their shape into pellets during spheronization (3). In addition, the ability of MCC to bind together the components of the wetted powder mass is critical to its performance during extrusion–spheronization.

A wide range of materials has been investigated as extrusion–spheronization aids (Table I). They can be broadly classified as additives to facilitate extrusion–spheronization or alternative spheronization aids. In the case of the additives, they do not function as spheronization aids *per se* but rather as adjuvant to the main spheronization aid to enhance its effectiveness. The various proposed spheronization aids and the properties of their pellets are compared in Table II.

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ABBREVIATIONS: MCC, microcrystalline cellulose; MMD, mass median diameter; MTR, mixer torque rheometry.

Table I. Excipients Proposed for Use in Extrusion–Spheronization

Type	Excipient	Role/function	Reference
Additives to facilitate/enhance the effectiveness of a spheronization aid	Hydrophobic or waxy materials, e.g., liquid paraffin, glyceryl palmitostearate	Lubricants	(5)
	Silicates, e.g., kaolin and veegum	Cohesive binders. Improve plasticity of the wetted mix, facilitate rounding during spheronization.	(5)
	Weak bases and acids, e.g., hydroxides and carbonates, citric and fumaric acids	Drug release and dissolution enhancers	(5)
	Surface active agents, e.g., sodium lauryl sulfate	Plasticization enhancers	(3,6)
	Hydrophilic polymers, e.g., sodium carboxymethylcellulose (Na CMC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP)	Adhesive binders	(2,7)
	β-Cyclodextrin	Filler	(8)
	Chitosan	Binder. Retardation of drug release	(9–11)
Spheronization aid. As replacements for MCC	L-Hydroxypropylcellulose (L-HPC)		(12)
	Powdered cellulose		(13,14)
	HPMC, hydroxyethylcellulose (HEC)		(2)
	Pectinic acid		(15,16)
	k-carrageenan		(17)

Most of these materials possess some form of physical similarities to MCC, such as very poor water/alcohol solubility and their ability to absorb water. However, many of these excipients lack the binding ability of MCC and necessitate the inclusion of binders to the formulation before pellets of good quality (favorable physical properties) could be successfully formed. Furthermore, when these excipients were used, the quality of their pellets was often reported to be inferior to that of those prepared with MCC, in spite of the efforts expended in optimization and process control.

Collating the findings from various researchers (Table II), it appeared that a superior spheronization aid must possess the following attributes in order to produce pellets of comparable or even higher quality than those prepared using MCC. These desirable attributes are: (a) water insolubility, (b) large water absorption and retention capacity (liquid repository) to achieve an optimal rheological condition for extrusion and spheronization, (c) binding properties, (d) sufficiently large surface area for interaction with water and the constituent ingredients present in the formulation, and (e) ability to enhance drug release.

Cross-linked polyvinylpyrrolidone, also known as crospovidone, is a synthetic water-insoluble cross-linked homopolymer of *N*-vinyl-2-pyrrolidone. Crospovidone is available commercially in several grades, differing mainly in particle size. Morphologically, the coarser grade (Polyplasdone XL) consists of large, discrete particles while the finer grades (Polyplasdone XL-10, Polyplasdone INF-10) are composed of smaller agglomerates. Crospovidone is commonly used as a superdisintegrant in solid dosage forms at concentrations of 2–5%, although the smallest particle size grade can also be used to adsorb gases and toxins in the gastrointestinal tract (4).

Although crospovidone and MCC share some similarity in their functionality as spheronization aids, their chemical properties differ considerably. Because MCC is of natural origin, there are considerable batch-to-batch variations due to changes in source, processing, climatic, and environmental factors. The ability to alter the inherent physical properties of MCC is limited, as they are to a great extent source determined. In contrast, crospovidone is totally synthetic, wherein lies its advantage. Much could still be done to modify the physical characteristics of crospovidone to further enhance its physical properties for the purpose for which it is intended. Crospovidone is also chemically more stable with well-defined physicocheminal attributes. The major disadvantage of crospovidone today is its relatively higher cost. It is imperative, however, that as the use level increases, unit cost of the excipient can be reduced.

Preliminary studies showed that crospovidone possessed many of the above-mentioned features of a good spheronization aid and was thus of tremendous interest for further investigations. In this study, the functionality and possible mechanism of action for crospovidone as a spheronization aid was investigated using both small- and large-scale extrusion–spheronization studies. Effects of operating variables on the quality of pellets formed in the large-scale extrusion–spheronization studies were evaluated using a Box-Behnken experimental design. Results were compared to a standard grade of MCC to evaluate the potential and feasibility of crospovidone as a possible substitute for MCC.

MATERIALS AND METHODS

Materials

Three grades of crosprovidone—Polyplasdone XL, Polyplasdone XL-10, and Polyplasdone INF-10 (ISP, Wayne, NJ, USA)-were characterized and evaluated for their use as a

Table II. Comparison of Previously Proposed Spheronization Aids with MCC

	Comparison with MCC			
Spheronization aid	Physical properties	Processing variables	Quality of pellets	Other comments
L-HPC (12)	Insoluble in water and alcohols.	Less sensitive to water content.	Sphericity, aspect ratio and roundness were inferior to those of MCC.	Small particle size L-HPC grades were more useful as spheronization aids.
	Swells in water.	Larger amounts of water required.	Faster dissolution but no disintegration. More porous than MCC pellets.	
Powdered cellulose (13,14)	Similar chemical structure	Additional binder is required.	MCC pellets showed superior physical and mechanical properties (friability, density and hardness) Cellulose pellets were smaller with a broader size distribution as well as higher surface roughness Faster drug release from cellulose pellets but no disintegration.	
HPMC, HEC (2,7)	Water soluble, insoluble in alcohols.	Nonaqueous granulating liquid must be used.	MCC pellets were less friable and smoother.	Could be employed in controlled release formulations by varying HPMC/HEC grade.
	Wider size distribution	Additional binder is required.	Faster drug release due to disintegration/erosion of HPMC and HEC pellets.	
	Poorer compressibility	Higher water requirements		
	Smaller surface area than MCC			
	Higher lot-to-lot variation			
Pectinic acid (15,16)	Water insoluble	Less water needed	Sphericity and other shape factors are highly dependent on the type of drug when pectinic acid (PA) is used.	Universality of application is lower than MCC; sensitive to the type and amount of drug loaded.
	Ability of PA to retain water was inferior to that of MCC.	More sensitive to changes in water content.	PA pellets were rougher with surface cracks but not as strong as MCC pellets.	
	Swell in the presence of water	Must be carried out at elevated temperatures.	Fragmentation and disintegration of PA pellets; rapid drug release.	
k-Carrageenan (17)	Insoluble in cold water	Higher water requirements	Comparable pellet quality could be achieved with carrageenan.	Potentially problematic for water sensitive drugs due to large water binding capacity. May require longer drying.
	Swell in the presence of water	Less sensitive to changes in water content.		
	Much larger water binding capacity than MCC			
	Exhibited suitable plastic and brittle properties for spheronization			

Table III. Physical Properties of Crospovidone Grades[a]

Crospovidone Grade	Mean size (μm)	Span	D_m (μm)	Compressibility Bulk density (g ml^{-1})	Tapped density (g ml^{-1})	Carr index (%)	Hausner ratio
XL	127.65 (8.05)	1.54 (0.10)	36.2 (4.24)	0.26 (0.00)	0.34 (0.00)	32.5 (0.00)	1.325 (0.00)
XL-10	31.26 (1.01)	1.68 (0.02)	7.74 (0.26)	0.28 (0.01)	0.43 (0.01)	50.8 (0.83)	1.51 (0.02)
INF-10	19.71 (0.18)	1.48 (0.09)	3.89 (0.44)	0.30 (0.02)	0.48 (0.02)	63.3 (1.96)	1.63 (0.05)

[a] Standard deviations are provided in parentheses.

spheronization aid against a standard MCC grade, Avicel PH 101 (Asahi, Osaka, Japan). Three grades of lactose α-monohydrate (Pharmatose 100 M, Pharmatose 200 M and Pharmatose 450 M) from DMV International (Veghel, The Netherlands) were employed as the bulk materials and distilled water as the moistening liquid in the preparation of pellets.

Physical Characterization of Crospovidone Grades

Particle Size and Size Distribution

Particle size of crospovidone grades were determined by laser diffraction (Dry Powder Module, LS2300, Coulter Corporation, USA). Mean particle size, X_{50}, was automatically determined while particle size distribution (span) was calculated according to Eq. (1). Four repeats were determined and the results are presented in Table III.

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

where X_{10}, X_{50}, and X_{90} are the diameters of powder particles at the 10th, 50th, and 90th percentiles of the cumulative percent undersize plot, respectively.

Compressibility

Compressibility studies were performed on a tapping apparatus (Stampfvolumeter, JEL, Germany). The powder was sieved lightly into the graduated cylinder with an inner diameter of 28 mm and cut exactly to 100 ml. Excess powder was scraped off carefully with a spatula and the weight of the filled powder was recorded. The powder was tapped until no further change in volume was observed. Bulk and tapped densities were calculated from their initial and final volumes. Carr index and Hausner ratio were subsequently derived according to the methods described previously (18,19). Five repeats were obtained and results were averaged (Table III).

Micromeritic Properties

Micromeritic properties were determined using mercury intrusion porosimetry (Model 9320, Micromeritics, USA) at a pressure range of 3–30,000 psia. Pore size distribution can be observed from the plot of differential specific intrusion volume *versus* pore diameter (Fig. 1). From the cumulative specific intrusion volume of the crospovidone powders, the median pore diameter (D_m),which is defined as the pore diameter corresponding to 50% of the maximum intruded volume of mercury, was determined and is reported in Table III.

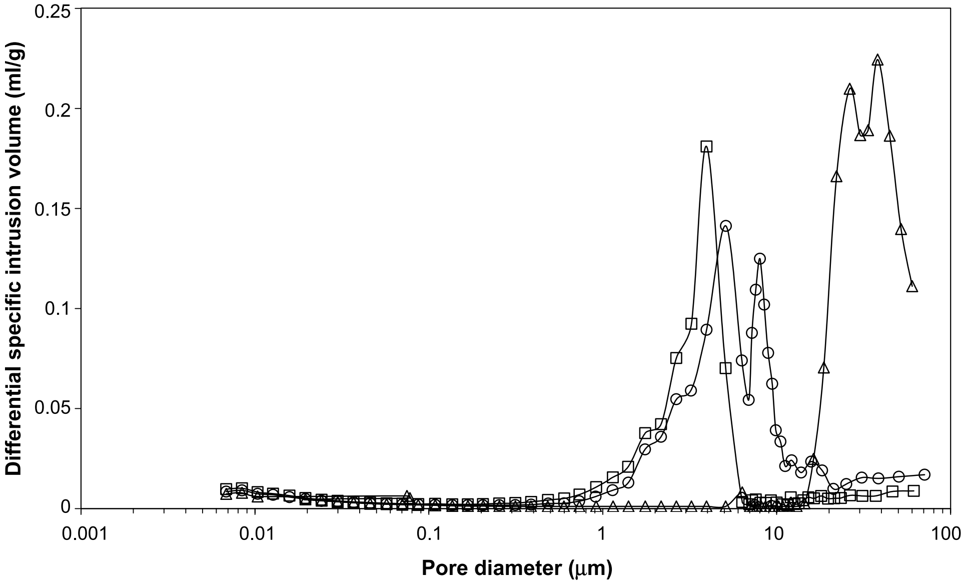

Fig. 1. Mercury intrusion porosimetry data. Pore size distribution of (△) Polyplasdone XL, (○) Polyplasdone XL-10, and (□) Polyplasdone INF-10.

Torque Rheological Properties

Binary mixtures (25 g) consisting of the spheronization aid (crospovidone or MCC) and bulk material (Pharmatose 200 M) in a ratio of 1:3 were prepared geometrically. Rheological profiles of the binary mixtures were determined at different water levels with mixer torque rheometry (MTR) according to the methods previously described (20). The amount of water added was expressed as a percentage of the total powder weight. Added water levels ranged from 45% to 65% w/w, 40% to 55% w/w, and 20% to 40% w/w for XL-10–lactose, INF-10–lactose, and MCC–lactose mixtures, respectively. Each run was completed within 16 min and triplicates were obtained.

Preparation and Sizing of Pellets Prepared by Small-Scale Extrusion–Spheronization

Water was sprayed into 30 g of binary powder mixture (prepared in the same way as described in the preceding section) and wet massed for 10 min. The moistened mass was manually extruded through a 1.0-mm aperture size mesh before spheronization with a cross-hatched patterned frictional plate of 120 mm diameter. Extrudates were spheronized at 1250 rpm (tip speed-471 m/min) for 5 min. Pellets were oven-dried at 60°C for 8 h.

Dried pellets were sieved through a nest of sieves (Endecotts, UK) of aperture sizes to give a √2 progression from 250 μm to 2800 μm on a mechanical sieve shaker (Retsch *vs* 1000, Germany) at 1 mm amplitude for 10 min. Mean size and size distribution of the pellets were characterized by the mass median diameter (MMD) and span, respectively. The oversized fraction was defined as the size fraction above 2800 μm and expressed as a quotient, in percentage of its weight to the total weight of pellets.

Preparation of Pellets by Large-Scale Extrusion–Spheronisation

Experimental Design

A Box-Behnken experimental design (21,22) was employed to elucidate the effects of the operating variables on the quality of the pellets. At any one time, two variables were varied at two levels (–1, 1) while the other two remained constant at level zero. The operating levels for each variable (Table IV) were selected based on the results of the preliminary studies.

The four variables were: XL-10 concentration [*C,c*], water concentration coefficient [*W,w*], spheronization speed [*S,s*], and spheronization time [*T,t*]. In this way, the experimental conditions for a particular run were readily represented with its respective code. Hence, the code for run 1 was *cw* since both XL-10 and water concentrations were low while the other two variables remained at level zero. Run 4 was coded as *CW* as both parameters were set at the high level. The coding

Table IV. Experimental Matrix of the Box-Behnken Design

			Coded values				Actual values			
Block	Run	Run code	[*C*]	[*W*]	[*S*]	[*T*]	[*C*] (%)	[*W*]	[*S*] (rpm)	[*T*] (min)
i	1	*cw*	−1	−1	0	0	20	1.4	480	8.5
	2	*Cw*	1	−1	0	0	30	1.4	480	8.5
	3	*cW*	−1	1	0	0	20	1.6	480	8.5
	4	*CW*	1	1	0	0	30	1.6	480	8.5
ii	5	*st*	0	0	−1	−1	25	1.5	410	2
	6	*St*	0	0	1	−1	25	1.5	550	2
	7	*sT*	0	0	−1	1	25	1.5	410	15
	8	*ST*	0	0	1	1	25	1.5	550	15
iii	9	*cs*	−1	0	−1	0	20	1.5	410	8.5
	10	*Cs*	1	0	−1	0	30	1.5	410	8.5
	11	*cS*	−1	0	1	0	20	1.5	550	8.5
	12	*CS*	1	0	1	0	30	1.5	550	8.5
iv	13	*wt*	0	−1	0	−1	25	1.4	480	2
	14	*wt*	0	1	0	−1	25	1.6	480	2
	15	*wT*	0	−1	0	1	25	1.4	480	15
	16	*WT*	0	1	0	1	25	1.6	480	15
v	17	*ct*	−1	0	0	−1	20	1.5	480	2
	18	*ct*	1	0	0	−1	30	1.5	480	2
	19	*cT*	−1	0	0	1	20	1.5	480	15
	20	*CT*	1	0	0	1	30	1.5	480	15
vi	21	*ws*	0	−1	−1	0	25	1.4	410	8.5
	22	*Ws*	0	1	−1	0	25	1.6	410	8.5
	23	*wS*	0	−1	1	0	25	1.4	550	8.5
	24	*WS*	0	1	1	0	25	1.6	550	8.5
vii	25		0	0	0	0	25	1.5	480	8.5
	26		0	0	0	0	25	1.5	480	8.5
	27		0	0	0	0	25	1.5	480	8.5
	28	*CWST*	1	1	1	1	30	1.6	550	15

[*C*], XL-10 concentration; [*W*], water concentration coefficient; [*S*], spheronization speed; [*T*], spheronization time.

system facilitated comparison between the different runs and enabled the effects of changing levels to be elucidated.

The theoretical amount of water required for spheronization (added water level) was calculated based on a linear equation shown below (23).

$$\begin{aligned} &\mathit{Added\ water\ level}\ (\%) \\ &\quad = a(\mathit{Percentage\ of\ spheronization\ aid}) \\ &\qquad + b(\mathit{Percentage\ of\ lactose}) \end{aligned} \tag{2}$$

The coefficient, b, was the amount of water required by lactose and fixed at 0.2 while a, the water concentration coefficient of the spheronization aid was varied according to the levels stipulated in the matrix of the Box-Behnken design.

Preparation of Pellets by Large-Scale Extrusion–Spheronization

Powder blends of XL-10 and Pharmatose 200 M in the ratio of 1:3 (1 kg) were mixed in a double cone tumbling mixer (AR 401, Erweka, Germany) at 6 rpm for 30 min. The powder mixture was transferred to a planetary mixer (Kenwood Major, UK) and moistened over 20 min with the requisite amount of water stipulated in the experimental design. The resultant wetted mass was extruded through a radial screw extruder (E140, Niro, UK) fitted with a screen of 1 mm thickness and 1 mm circular dies. One kilogram of the extrudates was spheronized in a spheronizer (S320, Niro, UK) with a 300-mm diameter frictional plate at the designated speeds and times. Pellets were oven-dried at 60°C for 8 h.

For comparison, pellets were similarly prepared with MCC and lactose in the same proportion at a spheronization speed of 600 rpm (tip speed-565 m/min) for 10 min. The water levels were varied from 38% to 45% of the total powder weight. The equivalent water coefficient values were calculated from Eq. (2).

Size and Shape Analysis of Pellets Prepared by Large-Scale Extrusion–Spheronization

Size Analysis

Mean size, size distribution, and the oversized fraction of pellets were determined according to the methods described earlier. The % yield of pellets was defined as the fraction of pellets between 710 and 1400 μm. Modal class fraction referred to the size fraction with the highest pellet yield.

Shape Analysis

For each batch, 50 pellets were randomly selected for shape analysis. Shape analysis was performed using an image analyzer (PC Image 2.2, Foster Findlay Associates, UK) which consisted of a computer system connected to a video camera (SSC-M370CE, Sony, Japan) mounted on a stereomicroscope (SZH, Olympus, Japan). Average projected area (A) and perimeter (P) of the pellets were determined from their digitized images. Aspect ratio, circularity, and e_R values were calculated for each batch of pellets. Circularity values emphasize the spherical shape of pellets while the elongation of pellets was described by the aspect ratio (24). For perfectly spherical pellets, these two shape descriptors would bear values of unity. Another shape factor, e_R, takes into consideration both deviation of shape from sphericity and surface irregularities. It was believed to be able to differentiate between more or less elliptical particles (25,26). r_e refers to the mean radius determined from all the radii measured from each of the boundary points to the center of the object. The values of b, l, A, and P are the breadth, length, area, and perimeter of the two-dimensional particle outline, respectively. The value f is a correction factor (27).

$$\mathit{Aspect\ ratio} = l/b \tag{3}$$

$$\mathit{Circularity} = (4\pi A)/P^2 \tag{4}$$

$$e_R = \frac{2\pi r_e}{Pf} - \sqrt{1 - \left(\frac{b}{l}\right)^2} \tag{5}$$

$$f = 1.008 - 0.231\left(1 - \frac{b}{l}\right) \tag{6}$$

RESULTS

Small-Scale Extrusion–Spheronization

Visual Observations

At equivalent water levels for obtaining pellets with a mean size of 1 mm, the wetted crospovidone–lactose mixture appeared to possess much higher surface wetness than that of MCC–lactose mixture. The former was also mixed and extruded with greater ease. Its extrudates were continuous, long, and smooth, without the characteristic shark-skinned

Table V. Process Reproducibility (Physical Properties of Pellets)

Run	Mean size (mm)	Span	Yield (%)	Oversized fraction (%)	Circularity	Aspect ratio	e_R
25	1.10	0.21	98.53	0.02	0.93	1.21	0.46
26	1.09	0.21	97.75	0.15	0.92	1.25	0.40
27	1.10	0.23	97.86	0.14	0.92	1.25	0.40
Average	1.10	0.21	98.05	0.10	0.92	1.24	0.42
SD	0.00	0.01	0.42	0.01	0.00	0.03	0.03
% RSD	0.38	5.19	0.43	66.71	0.46	2.23	7.64

% RSD, % relative standard deviation; SD, standard deviation.

Table VI. Physical Properties of Pellets Prepared with XL-10 and Pharmatose 200M (1:3)

Block	Run	Run code	Mean size (mm)	Span	Yield (%)	Oversized fraction (%)	Circularity	Aspect ratio	e_R
i	1	*cw*	1.13	0.26	98.26	0.10	0.92	1.21	0.45
	2	*cw*	1.08	0.17	97.11	0.11	0.90	1.27	0.40
	3	*cW*	1.26	0.24	93.49	0.62	0.93	1.16	0.50
	4	*CW*	1.10	0.23	97.41	0.47	0.92	1.25	0.42
ii	5	*st*	1.06	0.22	97.48	0.14	0.85	1.43	0.29
	6	*st*	1.24	0.41	89.80	1.08	0.85	1.23	0.40
	7	*sT*	1.07	0.19	99.24	0.00	0.92	1.32	0.38
	8	*ST*	—	—	—	—	—	—	—
iii	9	*cs*	1.07	0.18	98.42	0.19	0.90	1.34	0.36
	10	*cs*	1.06	0.22	98.31	0.01	0.89	1.40	0.33
	11	*cS*	—	—	—	—	—	—	—
	12	*CS*	—	—	—	—	—	—	—
iv	13	*wt*	1.06	0.24	94.97	0.14	0.87	1.32	0.35
	14	*wt*	1.08	0.22	96.14	0.58	0.89	1.25	0.41
	15	*wT*	1.13	0.28	97.93	0.12	0.93	1.22	0.44
	16	*WT*	1.24	0.26	95.88	0.39	0.94	1.19	0.47
v	17	*ct*	1.07	0.24	95.34	0.26	0.92	1.25	0.40
	18	*ct*	1.07	0.21	96.35	0.29	0.86	1.32	0.34
	19	*cT*	—	—	—	—	—	—	—
	20	*CT*	1.27	0.17	91.68	1.38	0.93	1.20	0.45
vi	21	*ws*	1.06	0.21	98.17	0.10	0.88	1.37	0.34
	22	*ws*	1.08	0.19	97.18	0.28	0.90	1.41	0.32
	23	*wS*	—	—	—	—	—	—	—
	24	*WS*	—	—	—	—	—	—	—
vii	28	*CWST*	1.31	0.27	73.84	0.62	0.95	1.11	0.57

—, Pellets could not be formed.

appearance of extrudates prepared with MCC. This observation was also noted in large-scale extrusion–spheronization.

Performance of Crospovidone Grades

Particle size and span of pellets prepared from XL-10 and INF-10 are presented in Figs. 3 and 4, respectively. However, pellets could not be prepared from the largest particle size grade of crospovidone, XL, irrespective of the lactose grade used.

Large-Scale Extrusion–Spheronization

Process Reproducibility

Variables in runs 25, 26, and 27 were set at level zero, which corresponded to the central value for each of these variables (Table IV). As three runs were identical in operating parameters, the properties of their pellets would represent the reproducibility of this process. Variations between these three runs were found to be very small for most of the factors evaluated as indicated by the very small % RSD values (Table V). These results established the excellent reproducibility, thus eliminating the need for replicates for the other runs stipulated in the matrix. At the same time, these conditions were proven to be satisfactory for pellet production, albeit all variables at level zero.

Effect of Operating Variables on Pellet Quality

Physical properties of pellets from each experiment of the Box-Behnken design were tabulated in Table VI. From this table, the effects of the various operating variables were further examined and discussed in the subsequent section.

Physical Properties of Pellets Prepared with MCC

The physical properties of MCC pellets are presented in Table VII.

Table VII. Physical Properties of Pellets Prepared With MCC and Pharmatose 200M (1:3)

Added water level (%)	Water concentration coefficient	Mean size (μm)	Span	Yield (%)	Oversized fraction (%)	Circularity	Aspect ratio	e_R
39	0.96	710	0.57	38.87	0.00	0.94	1.11	0.58
41	1.04	910	0.27	84.45	0.00	0.95	1.09	0.60
43	1.12	1100	0.27	99.78	0.00	0.94	1.12	0.58
45	1.2	1570	0.31	88.06	0.00	0.93	1.11	0.57

DISCUSSION

Postulated Mechanism of Pellet Formation

For an excipient to function effectively as a spheronization aid, the added water level must be adequate for surface hydration and saturation of its internal pore spaces. The saturated pores are analogous to a reservoir that can control the uptake and release of water under certain pressure conditions such as during extrusion and spheronization. While many excipients are able to hydrate in the presence of water, they lack an internal water store of adequate rigidity that could be utilized to modulate the amount of water released under pressure for lubrication during extrusion and for surface plasticization during spheronization. By far, MCC is the ideal excipient that can achieve this precise control and balance of water movement in and out of the pores during extrusion–spheronization. Two models have been proposed to explain the role of MCC in extrusion–spheronization where it has been likened to a sponge (28) and a crystallite gel (29).

In this study, crospovidone was found to possess similar abilities to control the distribution and release of water during extrusion–spheronization. It was believed that crospovidone possesses an internal reservoir of water that could be mobilized under appropriate pressure ranges. The water holding and controlling capability of crospovidone was possibly related to its cross-linked arrangement which could form a mesh-like structure around the internal water reservoir. The mesh-like structure possesses both rigidity and flexibility to allow the absorption–release–reabsorption of water during wet massing (moistening), extrusion (lubrication and moistening) and spheronization (surface plasticity). In this respect, it is similar to the sponge model proposed by Fielden et al. (28) for MCC.

MTR can be used to assess the mixing resistance of moistened powder masses in granulation studies (20,30). Functionality and performance of a spheronization aid hinge strongly on its interaction with water, which will, in turn, be reflected in the consistency of the wetted mass containing the spheronization aid. The relationship between the torque rheological characteristics of wetted masses (containing MCC) and their eventual ability to be spheronized has been reported (20). Torque rheological behaviors for the moistened crospovidone–lactose mixtures gave valuable insights on the interaction of crospovidone with water during wet massing. The moistened XL–lactose mixture failed to achieve a sufficiently cohesive state for any appreciable torque responses to be generated. Therefore, only the torque profiles of the other two crospovidone–lactose and the MCC–lactose mixture (Fig. 2) were presented. Larger amounts of water had to be added before the crospovidone powder mixture can produce cohesiveness to provide resistance during mixing in the MTR which was then reflected as torque responses. This observation suggested that the capacity of crospovidone for moisture was high, but appreciable binding occurred only at higher water contents than was seen for MCC. Moreover, the higher magnitude of torque responses generated for the MCC–lactose mixture also reiterated the stronger binding properties of MCC.

The compromised binding ability of crospovidone could be attributed to its physical structure and morphology. Under the scanning electron microscope, crospovidone particles appeared to be granular with rough surfaces (4). On the other hand, MCC particles were elongated, needle-shaped, and fractured, which confers extra binding strength via mechanical interlocking. On the contrary, mechanical interlocking was not expected to be pronounced in crospovidone as the particles are comparatively more regularly shaped.

Disparities between the binding properties of MCC and crospovidone were also manifested as differences in operating variables and water requirements during pellet production. The working range of added water levels for pellet production was higher for the crospovidone grades (small-scale extrusion–spheronization), reflecting larger amounts of moisture required to quench the internal pores. This gave rise to the much wetter appearance of its moistened masses and subsequently forming extrudates that were longer and smoother. Using MCC as a spheronization aid, pellets can be produced at a spheronization speed of 1500 rpm (tip speed-565 m/min) for 5 min (31). On the other hand, the optimal spheronization speed for crospovidone had to be reduced to 1250 rpm (tip speed-471 m/min). Although pellets (containing crospovidone) could be produced at the start of the spheronization at higher speeds (1500 rpm), these were not strong enough to remain as integral entities under prolonged strong shear forces.

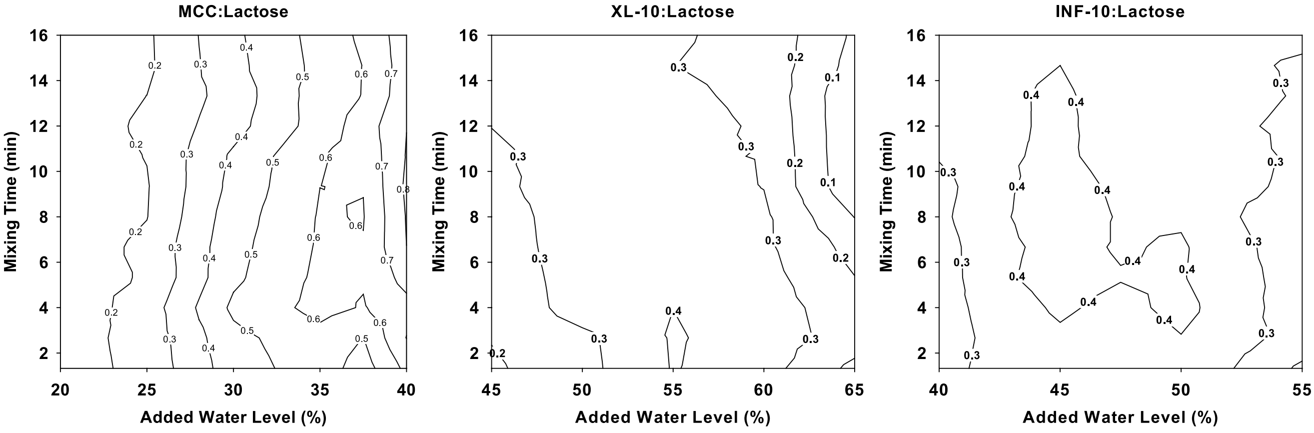

Fig. 2. Effect of added water levels and mixing times on the torque profiles of MCC–lactose, Polyplasdone XL-10–lactose, and Polyplasdone INF-10–lactose powder mixtures. Torque values in [Nm] Newton meter.

Performance of Various Crospovidone Grades in Small-Scale Extrusion–Spheronization

Of the three crospovidone grades evaluated, only the large particle size grade, XL, failed to exhibit spheronization aid properties regardless of the lactose grade and spheronization conditions employed. To provide a plausible explanation of this phenomenon, its physical properties and behavior in the torque rheology were examined.

First, its large particle size reduced the surface area for effective contact and interaction with the other constituent ingredients (added water and lactose) in the powder mass. Its sheer size also made it more difficult for the entrapped water (within the core of the particles) to participate in the toggling between moisture release/absorption during spheronization. This poor interaction was also demonstrated by the unappreciable torque responses generated for the XL–lactose mixture, irrespective of the amount of water added. There was no observable increase in cohesion or integration with the addition of water to the powder mass. Hence, the mixer blades of the MTR were able to rotate within the bulk material with minimal resistance.

The strong binding of moistened masses containing MCC is provided by the hydrogen bonding forces contributed by MCC surfaces. Likewise for crospovidone, its ability to participate in hydrogen bonding enabled it to be a substitute for MCC. For such interactions, surface area is crucial but the large particle size of XL effectively reduced the surface area for hydrogen bonding-thus the minimal binding strength of the XL–lactose mixtures.

Contrary to XL, pellets were prepared with the other two crospovidone grades. Between XL-10 and INF-10, the coarser XL-10 required a higher amount of water to produce pellets of comparable sizes (Fig. 3). This was because smaller sized particles had larger specific surface area (4) for hydrogen bonding and interaction with bulk material to contribute to the spheronization aid function. Thus, pellets could be formed at a lower water level when the finer crospovidone grades were used as spheronization aids.

At very low water levels, the crospovidone particles were not sufficiently hydrated to perform its binding function and facilitate spheronization efficiently. Consequently, a considerable portion of the powder mixture appeared brittle and dry, and could not be rounded effectively into pellets. As the added water level increased, size distribution of the pellets began to narrow, owing to better wetting and more effective spheronization. For both XL-10 and INF-10, the span values of their pellets reached a minimum at 60% and 55% water, respectively (Fig. 4). These water levels could be regarded as the optimal levels for attaining pellets with the narrowest size distribution, corresponding to a mean pellet size of approximately 1.2 mm. Further increase in added water levels resulted in an overwetted state where uncontrolled coalescence of pellets occurred. Some of the overwetted extrudates adhered onto the spheronizer wall or the rotational plate instead of flowing with the bulk in a rope-like motion as they were being spheronized.

Evidently, pellet batches containing XL-10 and INF-10 as the spheronization aid could be prepared with high yields within the desirable size fraction with water level range of

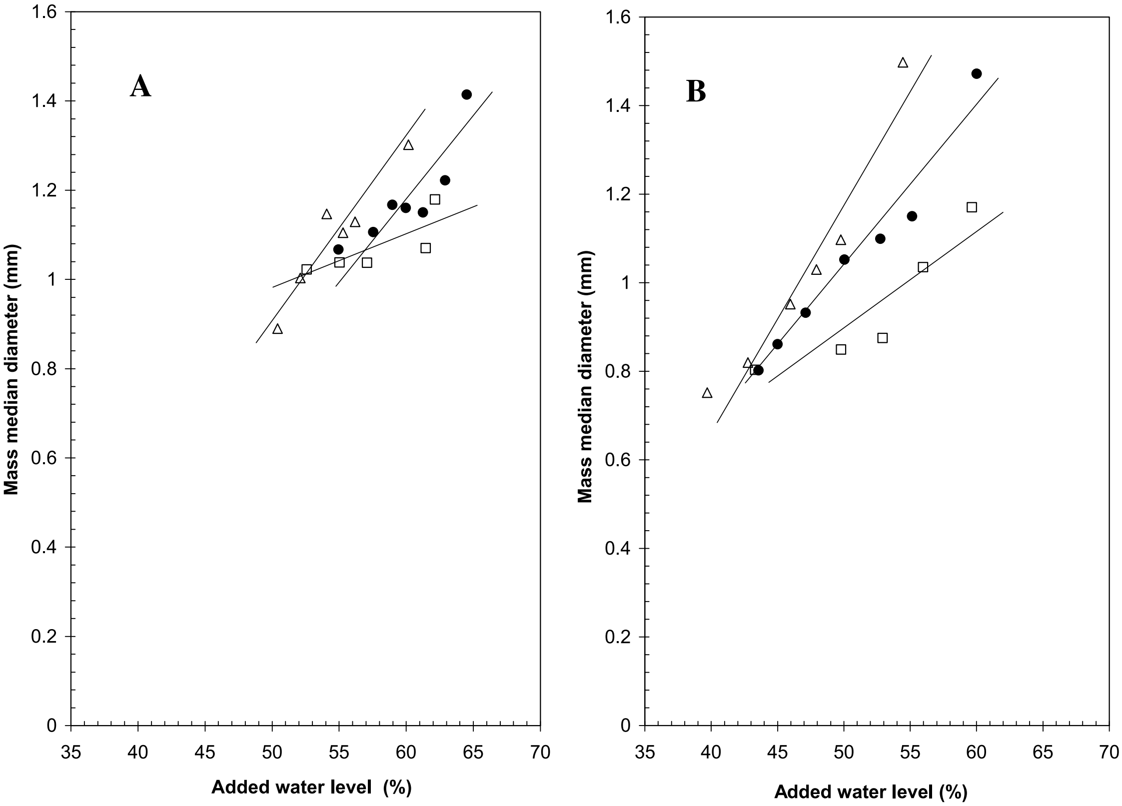

Fig. 3. Small-scale extrusion–spheronization studies on the effect of the added water level on mean pellet size prepared using (A) Polyplasdone XL-10 or (B) Polyplasdone INF-10 with (△) Pharmatose 100M, (●) Pharmatose 200M, and (□) Pharmatose 450M.

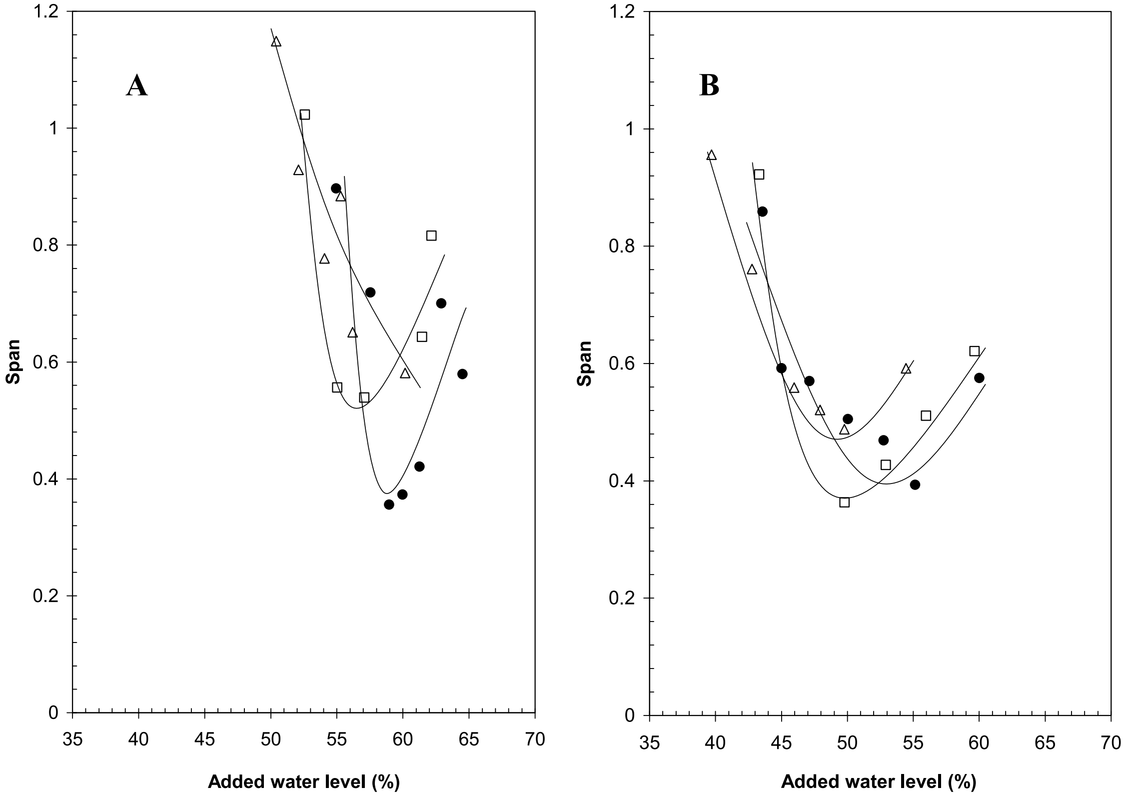

Fig. 4. Small-scale extrusion–spheronization studies on the effect of the added water level on pellet span prepared using (A) Polyplasdone XL-10 or (B) Polyplasdone INF-10 with (△) Pharmatose 100M, (●) Pharmatose 200M, and (□) Pharmatose 450M.

40–60%. Furthermore, pellet growth rate was reproducible and predictable with increases in water levels.

Effects of Operating Variables in Large-Scale Extrusion–Spheronization

Pellets in blocks ***ii***, ***iv***, ***vi***, and ***vii*** were prepared when the spheronization aid concentration was set at 25%. This makes them useful for comparison with the MCC pellets which were also prepared with 25% MCC or MCC–lactose ratio of 1:3. Within these four blocks, only runs 8, 23, and 24 failed to produce pellets successfully. Inspection of their operating parameters showed that high spheronization speeds were employed in these three runs, despite variations in the spheronization time (run 8) and added water level (runs 23 and 24). Excessive lump formation and wall adhesion tend to occur when a high spheronization speed was employed (runs 8, 11, 12, 23, and 24) unless the spheronization time was short (runs 5 and 6) or when the XL-10 concentration and water levels were high (run 28). Elevated levels of spheronization speed and/or time could result in excessively high shear forces that the extrudates were unable to withstand. The inability to withstand strong shear forces was indicative of weak cohesive and binding properties of the extrudates. Clearly, a balanced system of supplied mechanical energy, residence time, and added water level is critical for the extrudates to attain the precise equilibrium between cohesiveness and surface plasticity so that they can remain as integrated entities and be spheronized.

On the whole, the runs in block ***i*** (i.e., runs 1–4) yielded pellets with more favorable properties (Table VI). In particular, the shape factors of pellets in these runs were superior (circularity: 0.90–0.93; aspect ratio: 1.16–1.27; e_R: 0.40–0.50). As spheronization speed and time were kept constant, runs in this block represented the interaction between XL-10 concentration and water level. This suggested that these two variables and their interaction were most influential in the formation of high- quality pellets.

The ability and performance of XL-10 as a spheronization aid is inevitably associated with the concentration of water present. With adequate water levels, XL-10 was able to modify the rheological properties of the wetted mass so as to produce a plastic yet cohesive mass suitable for successful pellet formation. During wet massing, water served to moisten and bind the wetted masses containing XL-10. Thereafter, it aided in the lubrication and plasticization of the wetted mass during extrusion and spheronization with XL-10 acting as a repository for excess moisture. Because XL-10 absorbs water more readily than lactose, a larger amount of water was needed when the concentration of the former was increased. When XL-10 concentration was kept constant, higher water levels tended to produce larger pellets with an accompanying increase in the % oversized fraction. This was due to coalescence of overwetted agglomerates, leading to a snow-balling effect. Nevertheless, spherical pellets with a comparatively narrow size distribution and good yield could be obtained by modulating the levels of XL-10 concentration and water only.

Pellets with the most favorable shape factors were formed in run 28, in which all the variables were set at the high level

(Table VI), suggesting that this was the most promising combination for producing highly spherical pellets in the current study. More notably, such good pellets were produced even though existing conditions were not fully optimized.

Comparison of Crospovidone Pellets with MCC Pellets

For MCC, pellets with the most favorable shape factors (Table VII) were prepared with 41% and 43% water (corresponding to water coefficient values of 1.04 and 1.12) whereas pellets from run 28 (Table VI) were chosen to represent the performance of XL-10.

Crospovidone (XL-10) pellets compared very favorably to those of MCC, especially in their shape factors. Although larger pellets were produced with crospovidone, they were of a narrow size distribution with very little oversized fraction and an acceptable yield. Owing to their differences in the moisture holding ability, crospovidone required higher amounts of added water. As there is less likelihood of interlocking and relatively lower overall cohesiveness (as shown by the MTR experiments), less aggressive formation conditions (longer spheronization at reduced speeds) are required to avoid high shear induced attrition. Elevated water levels ensured sufficient liquid saturation in crospovidone to allow its binding properties to be demonstrated while the longer spheronization times compensated for the reduced speed. This is because it is imperative that the overall supplied energy is adequate for spherical pellets to be produced (32).

CONCLUSION

Three grades of crospovidone were evaluated for their abilities to function as spheronization aids in extrusion–spheronization of which the two finer crospovidone grades, XL-10 and INF-10 showed great potential in functioning as effective spheronization aids. The mechanism of pellet formation using crospovidone as a spheronization aid has been postulated as such: added water is readily taken up by crospovidone, forming a hydration layer around the particles. With increasing water levels, its internal pores are gradually filled and saturated. The cross-linked structure of crospovidone behaves as a mesh to prevent the loss of water trapped within the internal pores; thus providing a repository for water, like a reservoir. In these aspects, its mechanism of action resembled the sponge model proposed for MCC. Although both crospovidone and MCC are capable of hydrogen bonding, the binding ability of crospovidone was comparatively lower, perhaps owing to the lack of mechanical interlocking. This gave rise to compensatory increases in water requirements before crospovidone could demonstrate appreciable binding properties. The weaker binding capability of crospovidone was demonstrated in its torque rheological properties, greater ease of mixing and extrusion, as well as the inability of its pellets to withstand high spheronization speeds. For MCC, its fibrous and needle-shaped structure was believed to contribute to its increased binding strength by mechanical interlocking, thus holding on the added water and bulk material more easily.

Crospovidone concentration and water level were deemed to be most critical in obtaining pellets of desirable quality. The best pellets were produced when all the variables were set at the higher operating level and were of comparable quality to those prepared with MCC. Most significantly, these pellets could be produced under a relatively broad range of conditions that have yet to be fully optimized. These findings proved that a robust pelletization process is possible with the finer crospovidone grades which served to facilitate and aid pellet formation in extrusion–spheronization. In contrast to most of the previously proposed materials, crospovidone does not require the addition of binders before it can perform its spheronizing functions. Like MCC, it is able to yield high-quality pellets as a single functional excipient in the formulation. With more extensive studies and further material optimization, there is tremendous potential for crospovidone to serve as a competent alternative to MCC in extrusion–spheronization.

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