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RESEARCH PAPER

Influence of Process Variables on Physical Properties of the Pellets Using Extruder and Spheronizer

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ABSTRACT

Placebo pellets containing lactose and microcrystalline cellulose (Avicel PH101®) ratio 60:40 were prepared by the extrusion-spheronization process. The influence of processing variables, including the spheronizer speed, the spheronization time, the binder type, and the concentration and amount of water content on physical properties of the pellets, were studied. The sphericity of pellets was increased with increasing spheronizer speed during wet mass process. When spheronization time was increased, sphericity, smooth surface, and particle size of pellets were increased. Increasing binder concentration will increase particle size. Pellets using HPC-M® as a binder at high spheronizer speeds showed spherical shape, narrow size distribution, and good flow properties when compared with Methocel E-15LV®, HPC-L®, and Methocel A4M®. In addition, increasing HPC-M concentration had no effect on shape and particle size of pellets. The amount of water content was found to affect shape, flow rate, and density. In summary, suitable conditions consisted of 2% w/w of HPC-M, 40% w/w of water, and 15 min of spheronization time at 951 rpm of spheronizer speed.

INTRODUCTION

The core of multiple-unit dosage forms or pellets could possibly be manufactured by various techniques, such as extrusion–spheronization, solution–suspension layering, powder layering, spray drying, and spray congealing. One of the most widely used pelletization processes in the pharmaceutical industry is extrusion and

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spheronization, which is suitable for formulation with high doses of drug not requiring core or seed. The processing time is short. However, the formulations and the conditions used to prepare pellets are somewhat important for extrusion and spheronization.

Jalal et al. (1) showed that the spheronizing process resulted in an improved granulation, shape, and narrow size distribution compared with a conventionally processed wet granulation. Many researchers investigated the effect of process variables on granule properties prepared with the extrusion and spheronization technique (2–7). O'Connor and Schwartz (8) studied the effects of drug, diluent, and drug-to-diluent ratio on properties of pellets. In addition, the effects of granulating liquid on the properties of the pellets were also determined (9–13).

We studied some factors that had an effect on pellets prepared by the extrusion and spheronization process using lactose and microcrystalline cellulose (Avicel PH 101®) as diluent. The effects of various binders such as Methocel E-15LV®, HPC-L®, HPC-M®, and Methocel A4M® on properties of pellets were also evaluated.

MATERIALS AND METHODS

Materials

The following materials were used: lactose hydrous (USP/NF/BP/EP, The Lactose Company of New Zealand, Hawera, New Zealand), microcrystalline cellulose (Avicel PH 101, Asahi Chemical Industry Co., Ltd., Japan), hydroxypropylmethylcellulose (Methocel E-15LV, The Dow Chemical Company, Orpington, USA), hydroxypropyl cellulose L (HPC-L) and hydroxypropyl cellulose M (HPC-M, Nippon Soda Co., Ltd., Japan), and methylcellulose (Methocel A4M, The Dow Chemical Company). All others reagents were of commercial grade and used without further purification.

Equipment

The equipment used was as follows: analytical balance (Sartorious, Germany), planetary mixer (Gypto-Peerless Ltd., England), extruder and spheronizer (Pharmaceutical and Medical Supply Co., Ltd., Thailand), hot-air oven (Memmertt, Germany), scanning electron microscope (JEOL, JSM-T220, Japan), sieve shaker (Hessenwerk Darmstadt, Germany), standard sieve (laboratory test sieve ASTME 11, Endecotts, Ltd., London, UK), and cube mixer (Kasuga E.W. Ltd., Japan).

Preparation of Placebo Pellets

The amount of ingredients used in each formulation and conditions for preparation are shown in Tables 1 and 2. Lactose and Avicel PH 101 were mixed for 5 min in a planetary mixer. Binder solution was then poured and mixed until wet mass was obtained. The wet mass was

Table 1

Amount of Ingredients and Conditions Used to Prepare Pellets

	Percent of Each Ingredient (% w/w)			
Formulation	Lactose	Avicel PH 101	Binder (%)	
1	59.20	39.47	Methocel E-15 LV	1.33
2	59.00	39.33	Methocel E-15 LV	1.67
3	58.80	39.20	Methocel E-15 LV	2.00
4	59.20	39.47	HPC-L	1.33
5	59.00	39.33	HPC-L	1.67
6	58.80	39.20	HPC-L	2.00
7	59.80	39.87	Methocel A4M	0.33
8	59.60	39.73	Methocel A4M	0.67
9	59.20	39.47	HPC-M	1.33
10	59.00	39.33	HPC-M	1.67
11	58.80	39.20	HPC-M	2.00
12	58.60	39.07	HPC-M	2.33

Each formulation contained 40% of water content base on dry basis with 414 rpm and 951 rpm of spheronizer speeds and each spheronizer speed prepared with 5, 10, and 15 min of spheronization times.

Table 2

Amount of Water Content Base on Dry Basis and Conditions Used to Prepare Pellets

Formulation	% of Water Base on Dry Basis
13	35
14	42
15	44
16	50

Each formulation contained lactose 58.80% w/w, Avicel PH 101 39.20% w/w, and HPC-M 2.00% w/w at spheronizer speed 951 rpm and spheronization time 15 min.

transferred to an extruder and screened through a 1-mm sieve at 26 rpm. Extrudates were obtained and transferred to a spheronizer. The various conditions of the spheronizer (speed 414,951 rpm, time at 5, 10, and 15 min) were set and operated. Finally, placebo pellets at each condition of the studies were obtained and dried in a hot air oven at 60°C for 12 hr.

Placebo Pellet Evaluation

Determination of Pellet Appearance

Photomicrographs of pellet sample were taken with a scanning electron microscope. The samples were coated with gold before the microscopic determination using ion sputtering.

Particle Size Distribution

Particle size distribution was determined by sieve analysis. One hundred grams of pellets were put on the top of the sieve with a series of openings ranging from 1.41, 1.00, 0.84, 0.41, to 0.20 mm. The results were reported as percentage of weight retained on each sieve size. The average pellet size was given corresponding to 50% size on the cumulative percentage undersize axis by using the method of El-Gindy et al. (14).

Bulk Density and Tapped Density

The bulk density and tapped density were determined from the weight of a 40-g sample carefully charged into a 100-ml graduated cylinder, and volume was recorded. The pellets were taped from the height of 5 cm until a constant volume was obtained and tap density calculated. Both densities were averaged from three determinations.

Flow Rate and Angle of Repose

Forty grams of pellets was filled in a glass funnel with a 6-mm internal stem diameter fixed on a clamp. The time was recorded when the pellets start to flow until finish. Flow rate was calculated in g/min, and angle of repose was also determined.

Percent Friability

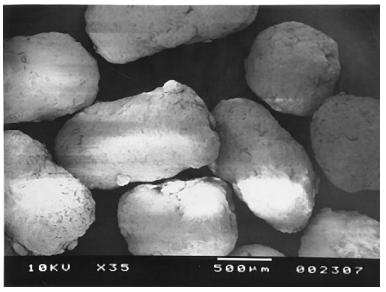
Pellets retained on 14/20 mesh cut and five stainless spheres (each sphere weight 1.06 g and diameter 6.35 mm) were filled into the polyvinylchloride container. The container was firmly closed with the cap and rotated in the cube mixer for 5 min. Pellets finer than 20 mesh were sieved off. The percent friability, averaged from two determinations, was calculated as percentage of weight loss.

RESULTS AND DISCUSSION

Effect of Spheronizer Speed, Spheronization Time, Binder Type, and Binder Concentration on Appearance and Physical Properties of Lactose-Avicel PH 101 Placebo

The microscopic appearance of lactose-Avicel PH 101 placebo pellets in this study are presented in Figures 1–8. The results indicated that spheronizer speed, spheronization time, binder type, and binder concentration had an effect on the appearance of the placebo pellets. Forming the suitably shaped pellets during the spheronization step will require the extrudates with sufficiently plastic property that are spheronized by the forces that occurred from movement of the friction plate of the spheronizer. With friction, the extrudates are initially broken down into a short length and later form spherical pellets. Therefore, in all spheronization times, binder types, and binder concentrations studied, pellets obtained from higher spheronizer speeds were more spherical than those from low spheronizer speeds. This may be due to the forces from higher speeds. Increasing spheronization time increases the time to apply the forces.

When spheronization time was increased, a shorter rod shape was obtained with low spheronizer speeds and a sphericity with a smooth surface was obtained with high spheronizer speeds. When the binder concentration was increased, the longer rod shape was obtained with low



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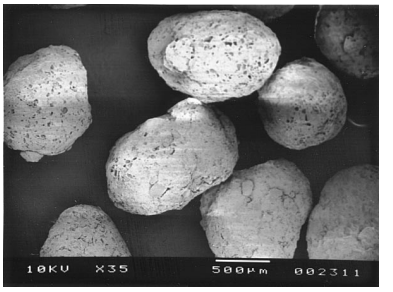

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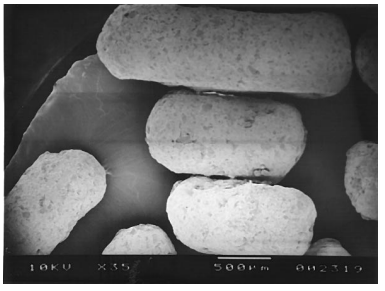

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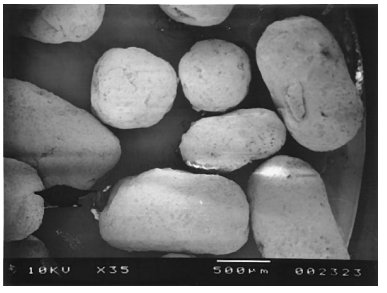

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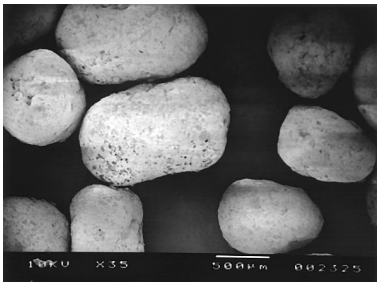

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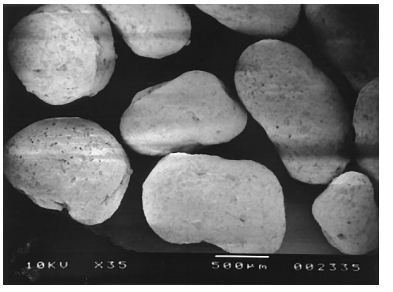

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Figure 1. Photomicrographs of lactose-Avicel PH 101 pellets using various concentrations of Methocel E-15LV as a function of spheronization times at a spheronizer speed of 414 rpm (×35) (A5, A10, A15 are 1.33% w/w of binder concentration at 5, 10, 15 min of spheronization time; B5, B10, B15 are 1.67% w/w of binder concentration at 5, 10, 15 min of spheronization time; and C5, C10, C15 are 2.00% of binder concentration at 5, 10, 15 min of spheronization time).

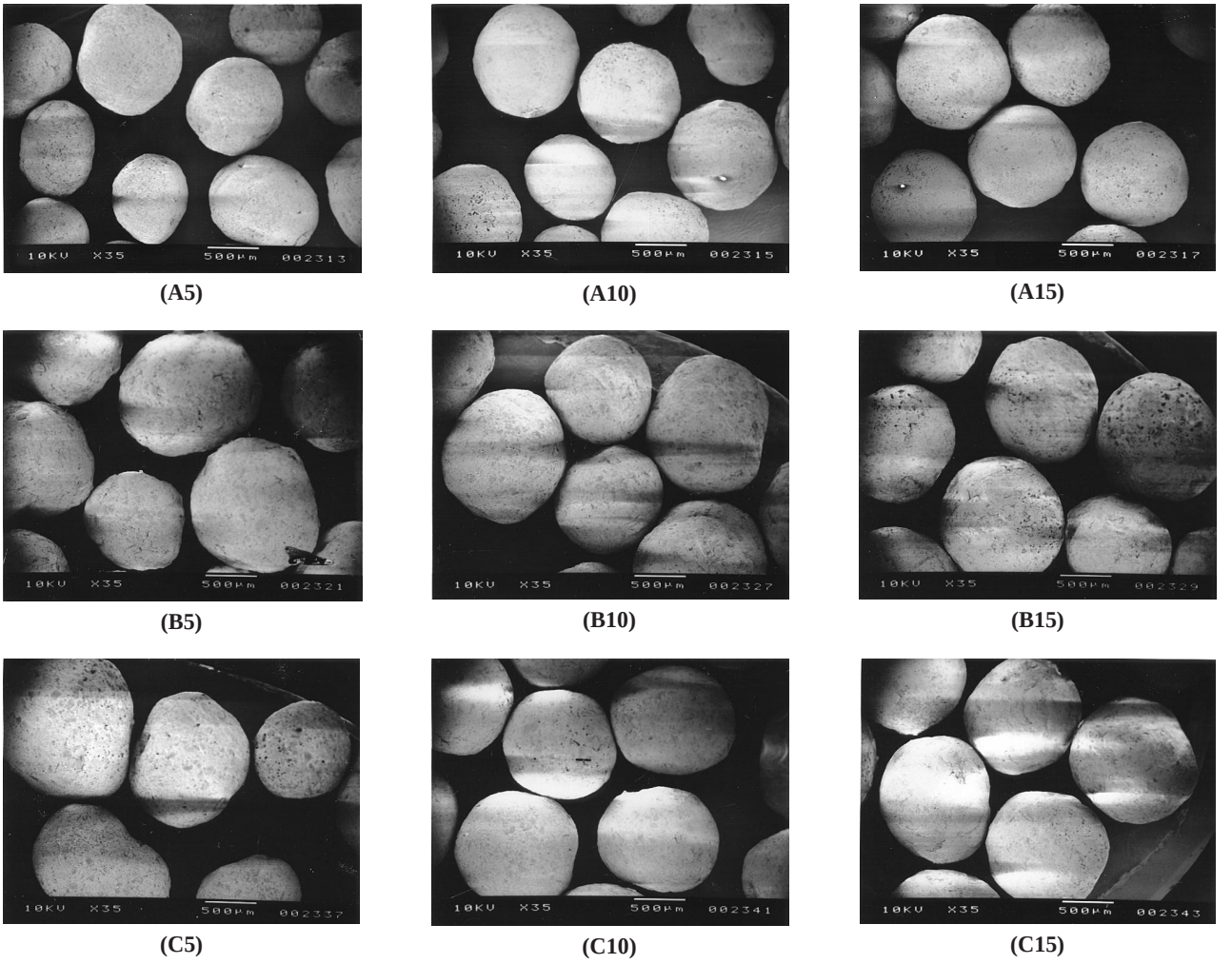


Figure 2. Photomicrographs of lactose-Avicel PH 101 pellets using various concentrations of Methocel E-15LV as a function of spheronization times at a spheronizer speed of 951 rpm (×35) (A5, A10, A15 are 1.33% w/w of binder concentration at 5, 10, 15 min of spheronization time; B5, B10, B15 are 1.67% w/w of binder concentration at 5, 10, 15 min of spheronization time; and C5, C10, C15 are 2.00% w/w of binder concentration at 5, 10, 15 min of spheronization time).

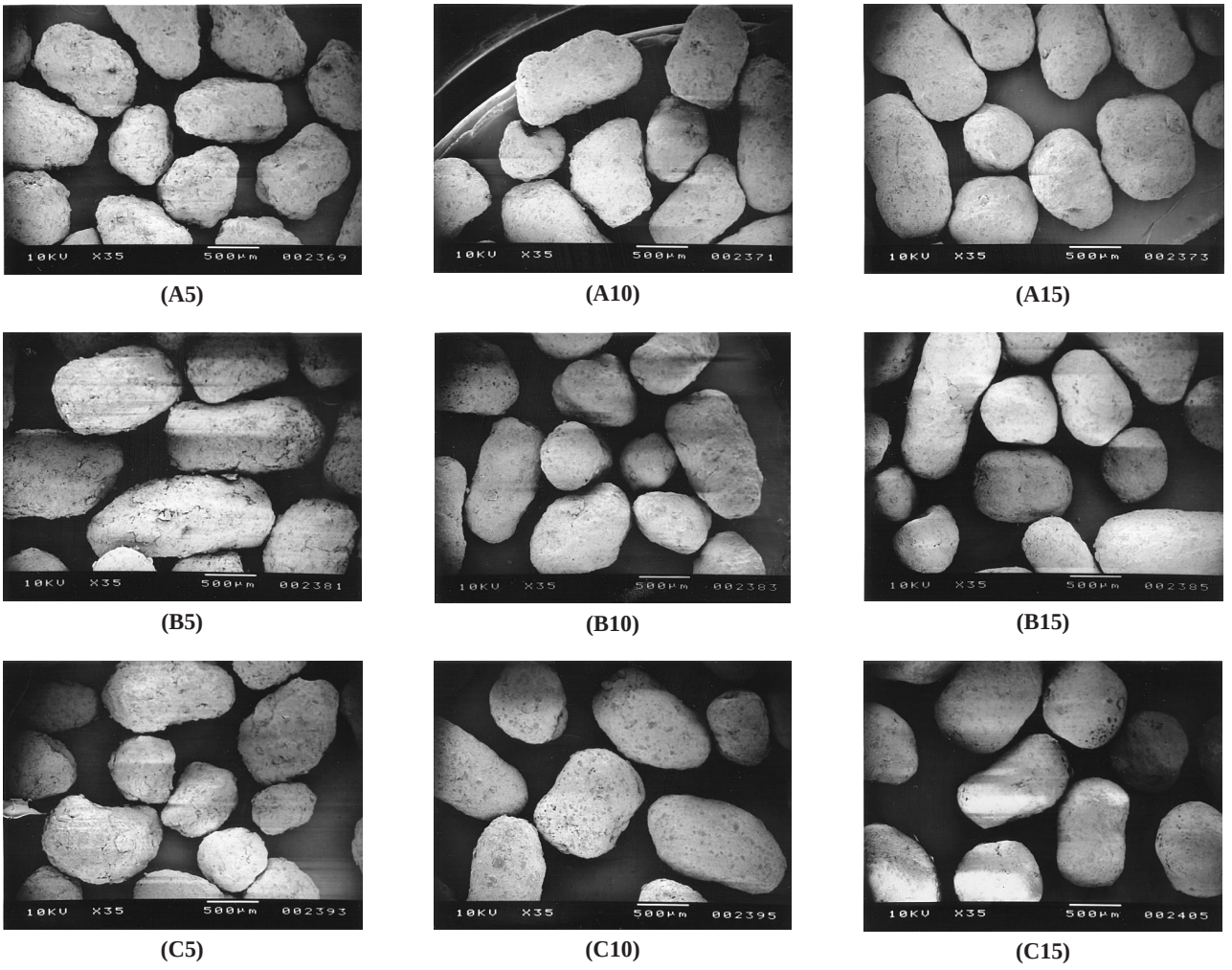


Figure 3. Photomicrographs of lactose-Avicel PH 101 pellets using various concentrations of HPC-L as a function of spheronization times at a spheronizer speed of 414 rpm (×35) (A5, A10, A15 are 1.33% w/w of binder concentration at 5, 10, 15 min of spheronization time; B5, B10, B15 are 1.67% w/w of binder concentration at 5, 10, 15 min of spheronization time; and C5, C10, C15 are 2.00% w/w of binder concentration at 5, 10, 15 min of spheronization time).

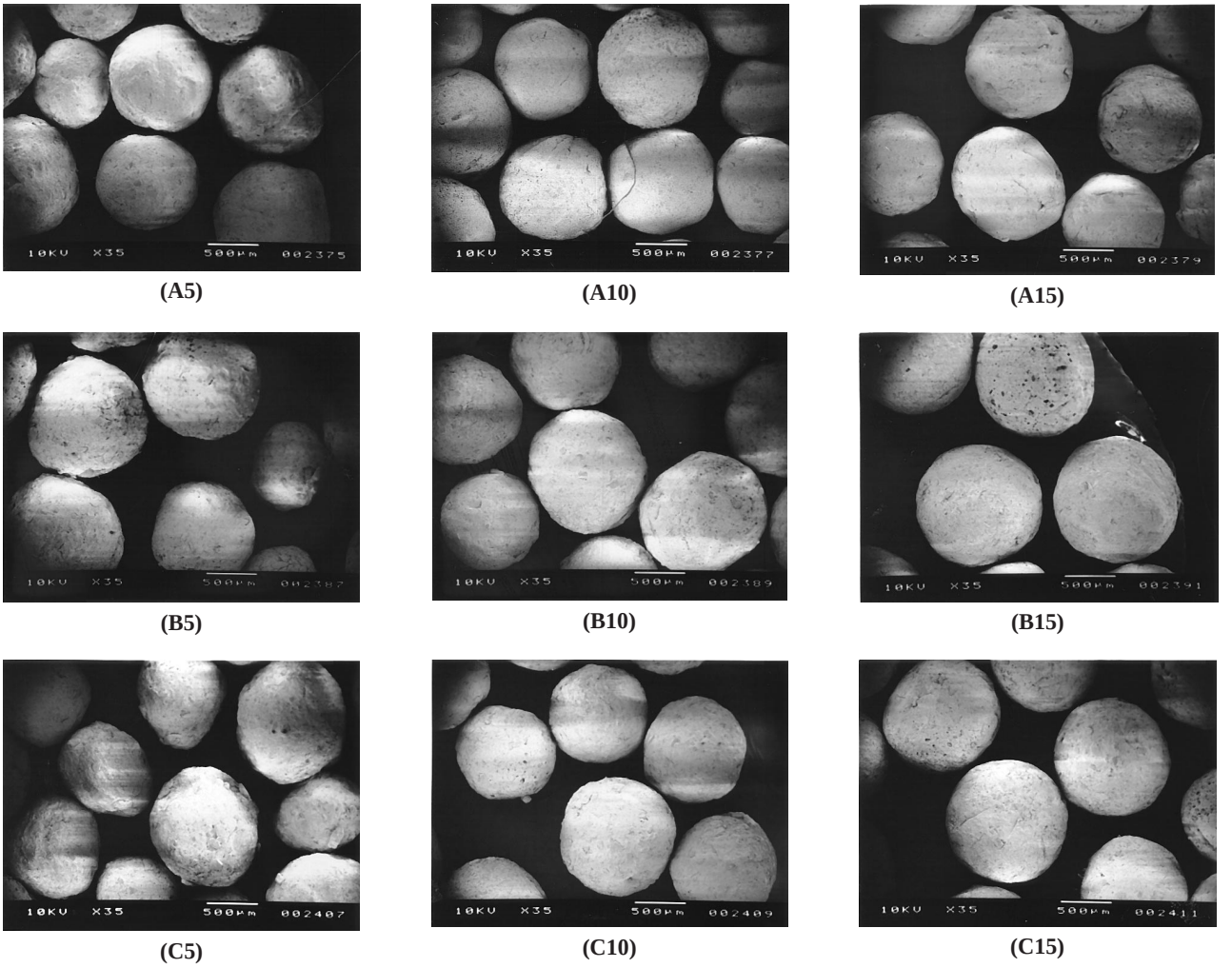


Figure 4. Photomicrographs of lactose-Avicel PH 101 pellets using various concentrations of HPC-L as a function of spheronization times at a spheronizer speed of 951 rpm (×35) (A5, A10, A15 are 1.33% w/w of binder concentration at 5, 10, 15 min of spheronization time; B5, B10, B15 are 1.67% w/w of binder concentration at 5, 10, 15 min of spheronization time; and C5, C10, C15 are 2.00% w/w of binder concentration at 5, 10, 15 min of spheronization time).

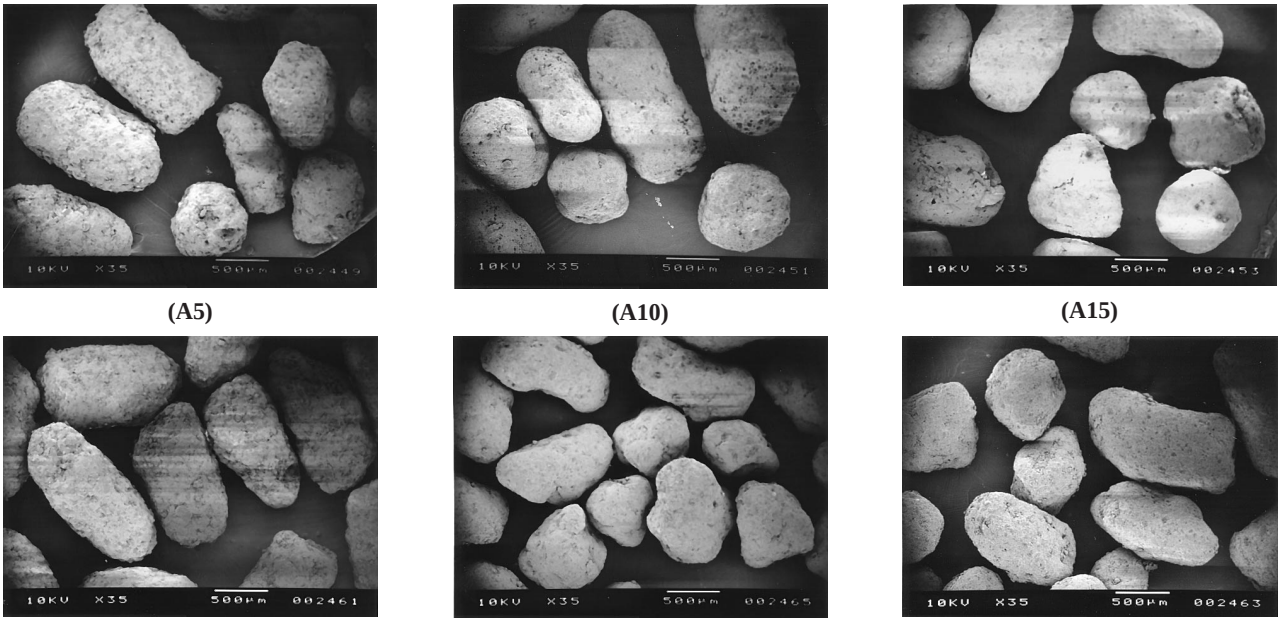


Figure 5. Photomicrographs of lactose-Avicel PH 101 pellets using various concentrations of Methocel A4M as a function of spheronization times at a spheronizer speed of 414 rpm (×35) (A5, A10, A15 are 0.33% w/w of binder concentrations at 5, 10, 15 min of spheronization time; B5, B10, B15 are 0.67% w/w of binder concentration at 5, 10, 15 min of spheronization time).

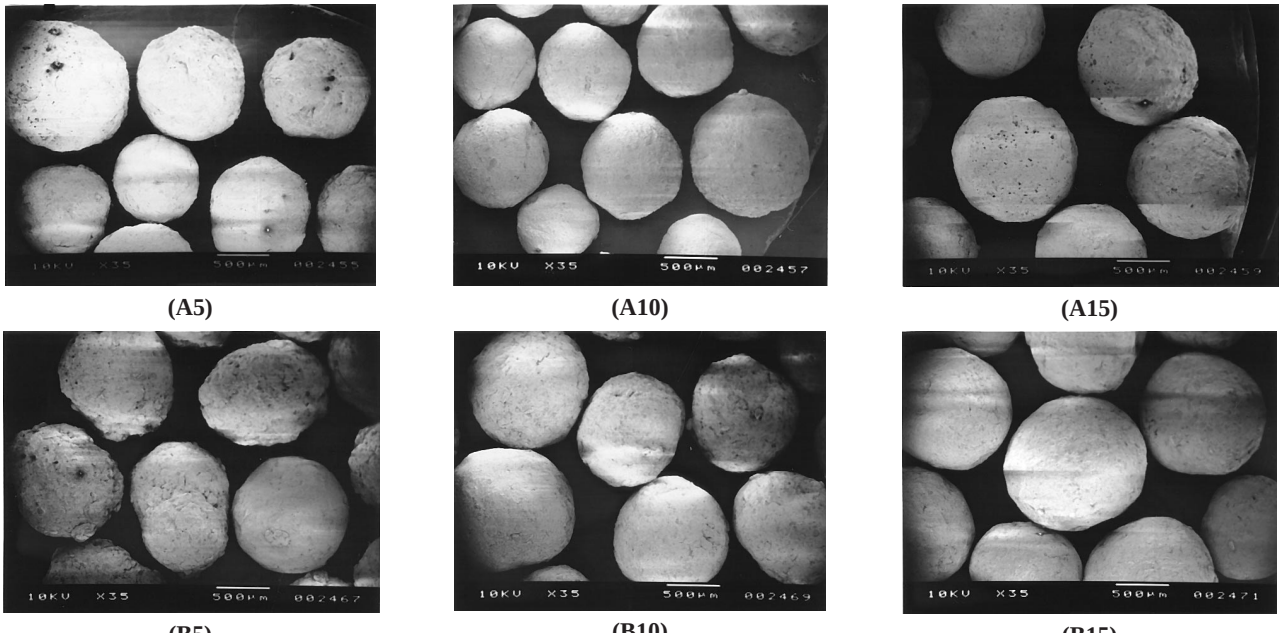


Figure 6. Photomicrographs of lactose-Avicel PH 101 pellets using various concentrations of Methocel A4M as a function of spheronization times at a spheronizer speed of 951 rpm (×35) (A5, A10, A15 are 0.33% w/w of binder concentration at 5, 10, 15 min of spheronization time; B5, B10, B15 are 0.67% w/w of binder concentration at 5, 10, 15 min of spheronization time).

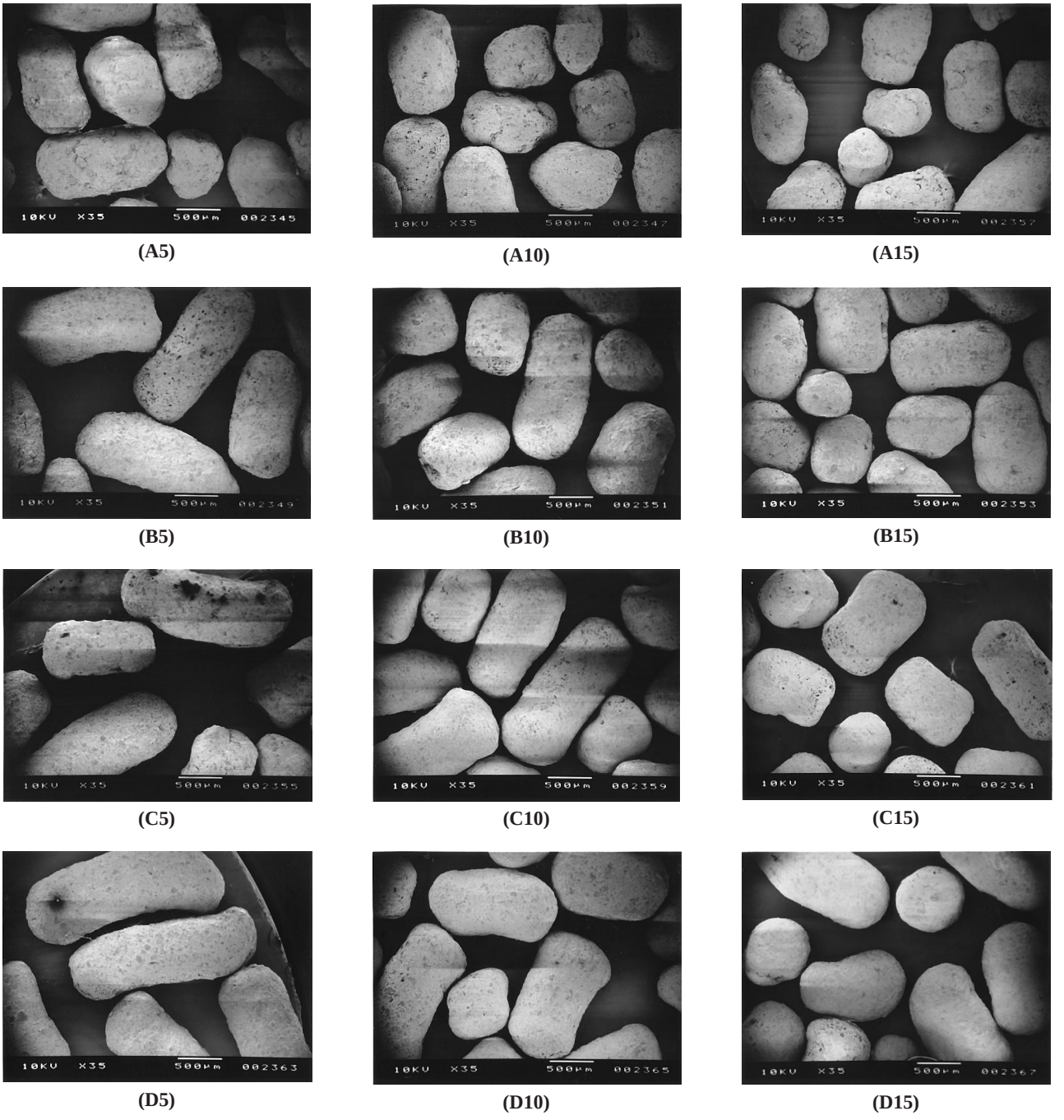
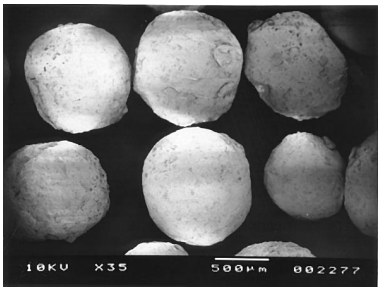


Figure 7. Photomicrographs of lactose-Avicel PH 101 pellets using various concentrations of HPC-M as a function of spheronization times at a spheronizer speed of 414 rpm (×35) (A5, A10, A15 are 1.33% w/w of binder concentration at 5, 10, 15 min of spheronization time; B5, B10, B15 are 1.67% w/w of binder concentration at 5, 10, 15 min of spheronization time; C5, C10, C15 are 2.00% w/w of binder concentration at 5, 10, 15 min of spheronization time; and D5, D10, D15 are 2.33% w/w of binder concentration at 5, 10, 15 min of spheronization time).



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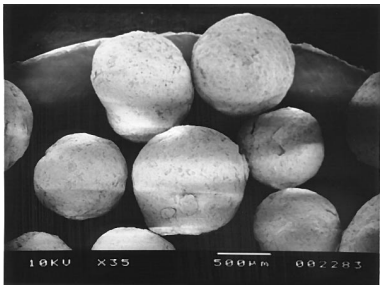

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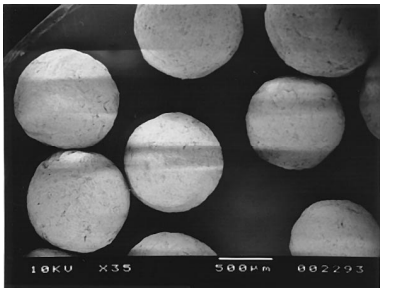

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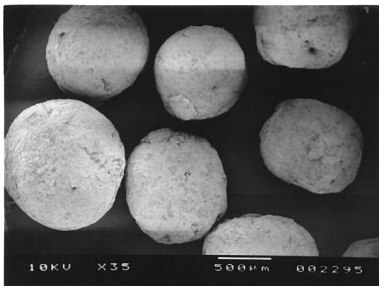

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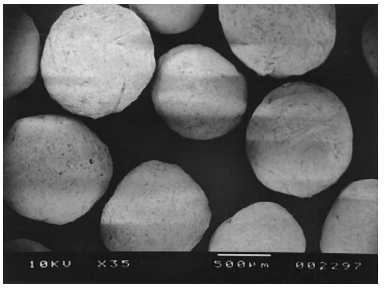

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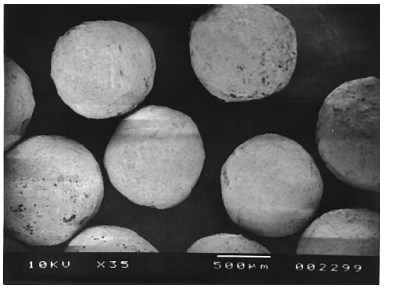

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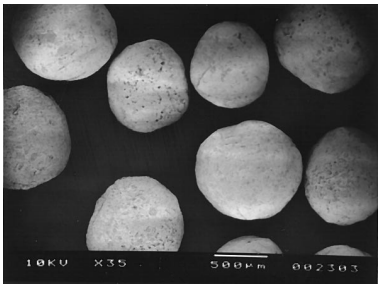

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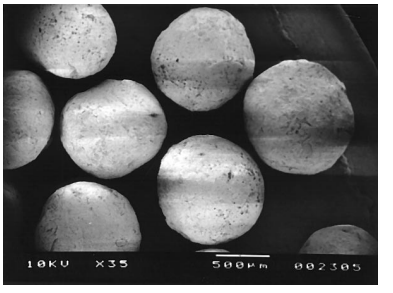

(D15)

Figure 8. Photomicrographs of lactose-Avicel PH 101 pellets using various concentrations of HPC-M as a function of spheronization times at a spheronizer speed of 951 rpm (×35) (A5, A10, A15 are 1.33% w/w of binder concentration at 5, 10, 15 min of spheronization time; B5, B10, B15 are 1.67% w/w of binder concentration at 5, 10, 15 min of spheronization time; C5, C10, C15 are 2.00% w/w of binder concentration at 5, 10, 15 min of spheronization time; and D5, D10, and D15 are 2.33% w/w of binder concentration at 5, 10, 15 min of spheronization time).

Table 3

Sieve Analysis of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times and Concentrations of Hydroxypropylmethylcellulose (Methocel E-15LV)

Concentration (% w/w)	Spheronization Time (min)	% Weight Retained[a]					
		Sieve No.					
		14	18	20	40	60	Pan
1.33	5	6.44	25.71	32.90	33.30	1.62	0.02
	10	11.72	27.19	29.61	30.16	1.31	0.01
	15	10.04	28.16	32.66	28.83	0.32	0.00
1.67	5	43.20	30.21	13.02	10.03	2.84	0.70
	10	47.59	27.47	12.98	9.30	2.35	0.31
	15	54.26	26.73	11.70	6.06	1.14	0.10
2.00	5	29.99	29.96	17.23	18.90	3.74	0.18
	10	37.55	26.63	15.26	17.96	2.57	0.05
	15	32.53	24.52	16.50	23.71	2.65	0.08

[a]Averaged from two determinations.

spheronizer speeds and decreasing sphericity with larger size pellets was obtained from high spheronizer speeds. Increased binder concentration increased binding properties, except for placebo pellets using HPC-M as a binder. Spheronization time and binder concentration at high spheronizer speeds using HPC-M as a binder created pellets that were more spherical than when using other binders.

The physical properties of lactose-Avicel PH 101 placebo pellets in this study are shown in Tables 3–13. The results indicated that spheronization time, binder type, and binder concentration had no effect on bulk density, tapped density, percent friability, and angle of repose. The angle of repose was low, which indicated good flow property. Flow rate of pellets varied by spheronization time, binder type, and concentration. However, the range of flow rate for all pellets indicated good flow. For particle size distribution, mean particle size and percent sieve fraction on 14/20 mesh cut depended on spheronization time, binder types, and binder concentrations. Mean particle size of pellets was increased with increasing spheronization time. When spheronization time was

Table 4

Sieve Analysis of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times and Concentrations of Hydroxypropyl Cellulose (HPC-L)

Concentration (% w/w)	Spheronization Time (min)	% Weight Retained[a]					
		Sieve No.					
		14	18	20	40	60	Pan
1.33	5	13.01	30.25	22.68	24.29	7.98	1.80
	10	19.54	30.74	20.57	19.42	8.81	0.91
	15	24.77	34.11	22.34	15.86	2.76	0.40
1.67	5	22.00	33.31	17.13	15.22	8.92	3.42
	10	40.85	30.72	12.93	8.74	5.90	0.86
	15	54.62	29.18	10.01	4.53	1.51	0.15
2.00	5	14.94	35.79	20.65	16.76	8.82	3.06
	10	27.97	32.29	18.60	14.19	6.38	0.58
	15	40.23	34.04	17.29	7.86	0.56	0.02

[a]Averaged from two determinations.

Table 5

Sieve Analysis of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times and Concentrations of Hydroxypropylmethylcellulose (Methocel A4M)

Concentration (% w/w)	Spheronization Time (min)	% Weight Retained[a]					
		Sieve No.					
		14	18	20	40	60	Pan
0.33	5	13.22	31.77	24.41	26.30	4.38	0.21
	10	16.97	32.02	22.81	24.66	3.51	0.03
	15	16.48	33.39	22.42	24.82	2.69	0.17
0.67	5	21.89	37.59	15.91	16.89	5.41	4.69
	10	36.56	24.27	14.28	9.03	4.23	1.62
	15	41.57	33.12	14.02	7.17	3.03	1.05

[a]Averaged from two determinations.

increased, pellets combined with the fine particles that occurred in the process. However, increasing spheronization time at each binder concentration had no effect on the percent sieve fraction on 14/20 mesh cut. These results may be explained by the fact that changing of mean particle size occurred with increasing spheronization time; however, particle size was still in the range of 14/20 mesh cut.

By increasing the binder concentration, the pellets increased in mean particle size but decreased in percent sieve fraction on 14/20 mesh cut. This can be explained by the fact that increasing mean particle size may decrease the desirable particle size range. These results did not include the pellets using HPC-M as a binder. Pellets using HPC-M as a binder had a more narrow size distribution than pellets using the other binders, especially at 2.33% w/w of HPC-M. In addition, it was observed that increasing the concentration of HPC-M at each spheronization time did not change the mean particle size at the spheronization times and binder concentrations studied. The percent sieve fraction on 14/20 mesh cut of pellets using HPC-M as a binder was higher than

Table 6

Sieve Analysis of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times and Concentrations of Hydroxypropyl Cellulose (HPC-M)

Concentration (% w/w)	Spheronization Time (min)	% Weight Retained[a]					
		Sieve No.					
		14	18	20	40	60	Pan
1.33	5	5.60	35.27	29.01	21.97	6.21	1.91
	10	11.65	38.02	24.83	16.75	7.38	1.37
	15	16.92	37.14	22.22	14.34	7.68	1.67
1.67	5	8.73	40.48	27.13	15.03	7.25	1.38
	10	9.92	39.39	24.57	17.36	7.08	1.40
	15	10.72	41.11	24.39	14.12	8.03	1.63
2.00	5	2.09	30.40	40.78	21.75	4.22	0.57
	10	5.72	32.75	38.16	18.58	4.42	0.38
	15	7.84	38.09	36.09	15.94	1.88	0.03
2.33	5	2.12	27.59	50.03	19.13	1.01	0.03
	10	3.17	33.83	48.25	14.57	1.15	0.02
	15	3.99	34.80	45.13	15.49	0.62	0.01

[a]Averaged from two determinations.

Table 7

Granule Size of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times, Types, and Concentrations of Binders

Binder	Concentration (% w/w)	Granule Size (mm)[a] Spheronization Time (min) 5	10	15
Methocel E-15LV	1.33	0.89	0.93	0.95
	1.67	1.46	1.57	1.65
	2.00	1.14	1.20	1.12
HPC-L	1.33	0.88	0.97	1.12
	1.67	1.01	1.40	1.78
	2.00	0.93	1.13	1.32
Methocel A4M	0.33	0.93	0.97	0.99
	0.67	1.06	1.39	1.54
HPC-M	1.33	0.82	0.93	0.10
	1.67	0.90	0.91	0.93
	2.00	0.80	0.87	0.96
	2.33	0.86	0.902	0.93

[a]Averaged from two determinations.

Table 8

Percent Sieve Fraction on 14/20 Mesh Cut of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times, Types, and Concentrations of Binders

Binder	Concentration (% w/w)	Sieve Fraction on 14/20 Mesh Cut (%)[a] Spheronization Time (min) 5	10	15
Methocel E-15LV	1.33	58.61	56.80	60.82
	1.67	43.23	40.45	38.43
	2.00	47.19	41.89	41.02
HPC-Ld	1.33	52.93	51.31	56.45
	1.67	50.44	43.65	39.19
	2.00	56.44	50.89	51.33
Methocel A4M	0.33	56.18	54.83	55.81
	0.67	53.50	48.55	47.14
HPC-M	1.33	64.28	62.85	59.36
	1.67	67.61	63.96	65.50
	2.00	71.18	70.91	74.18
	2.33	77.62	82.08	79.93

[a]Averaged from two determinations.

Table 9

Bulk Density of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times, Types, and Concentrations of Binders

Binder	Concentration (% w/w)	Bulk Density (g/ml, ± SD)[a] Spheronization Time (min) 5	10	15
Methocel E-15LV	1.33	0.82 (0.01)	0.82 (0.02)	0.82 (0.01)
	1.67	0.83 (0.01)	0.85 (0.00)	0.83 (0.01)
	2.00	0.87 (0.01)	0.87 (0.01)	0.86 (0.00)
HPC-L	1.33	0.83 (0.01)	0.85 (0.00)	0.83 (0.02)
	1.67	0.85 (0.02)	0.84 (0.01)	0.83 (0.01)
	2.00	0.82 (0.00)	0.82 (0.01)	0.83 (0.00)
Methocel A4M	0.33	0.84 (0.01)	0.84 (0.01)	0.83 (0.01)
	0.67	0.84 (0.02)	0.84 (0.01)	0.84 (0.01)
HPC-M	1.33	0.81 (0.01)	0.83 (0.01)	0.84 (0.02)
	1.67	0.83 (0.01)	0.85 (0.01)	0.86 (0.02)
	2.00	0.81 (0.00)	0.83 (0.01)	0.83 (0.01)
	2.33	0.82 (0.01)	0.84 (0.00)	0.86 (0.01)

[a]Averaged from three determinations.

Table 10

Tapped Density of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times, Types, and Concentrations of Binders

Binder	Concentration (% w/w)	Tapped Density (g/ml, ± SD)[a]		
		Spheronization Time (min)		
		5	10	15
Methocel E-15LV	1.33	0.86 (0.01)	0.85 (0.01)	0.86 (0.01)
	1.67	0.87 (0.01)	0.88 (0.01)	0.86 (0.01)
	2.00	0.90 (0.02)	0.92 (0.01)	0.89 (0.00)
HPC-L	1.33	0.88 (0.01)	0.90 (0.01)	0.88 (0.03)
	1.67	0.88 (0.01)	0.86 (0.01)	0.84 (0.01)
	2.00	0.84 (0.01)	0.83 (0.01)	0.81 (0.01)
Methocel A4M	0.33	0.89 (0.00)	0.88 (0.01)	0.88 (0.01)
	0.67	0.88 (0.01)	0.89 (0.01)	0.88 (0.02)
HPC-M	1.33	0.83 (0.01)	0.86 (0.01)	0.87 (0.02)
	1.67	0.85 (0.01)	0.87 (0.00)	0.89 (0.02)
	2.00	0.83 (0.00)	0.86 (0.01)	0.87 (0.01)
	2.33	0.87 (0.01)	0.87 (0.00)	0.87 (0.01)

[a]Averaged from three determinations.

Table 11

Flow Rate of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times, Types, and Concentrations of Binders

Binder	Concentration (% w/w)	Flow Rate (g/min, ± SD)[a]		
		Spheronization Time (min)		
		5	10	15
Methocel E-15LV	1.33	266.41 (13.26)	283.99 (11.35)	224.72 (10.40)
	1.67	232.91 (11.05)	266.11 (3.59)	241.16 (3.61)
	2.00	255.39 (10.18)	269.69 (7.23)	242.90 (13.04)
HPC-L	1.33	251.43 (3.38)	296.14 (6.10)	264.81 (6.31)
	1.67	265.08 (8.57)	273.54 (6.15)	252.13 (13.45)
	2.00	252.36 (15.37)	243.68 (2.86)	238.15 (8.82)
Methocel A4M	0.33	259.62 (7.74)	266.47 (1.46)	269.17 (9.23)
	0.67	261.64 (10.91)	236.06 (4.88)	241.92 (7.48)
HPC-M	1.33	241.14 (10.99)	252.98 (13.93)	278.16 (10.83)
	1.67	251.89 (14.57)	265.50 (10.89)	282.55 (9.13)
	2.00	249.12 (14.90)	282.07 (12.80)	282.42 (5.48)
	2.33	247.55 (3.83)	252.03 (11.90)	258.18 (8.87)

[a]Averaged from three determinations.

Table 12

Angle of Repose of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times, Types and Concentrations of Binders

Binder	Concentration (% w/w)	Angle of Repose (degree, ± SD)[a] Spheronization Time (min) 5	10	15
Methocel E-15LV	1.33	30.83 (0.55)	28.49 (0.27)	25.65 (1.43)
	1.67	30.30 (0.97)	27.93 (1.36)	28.24 (1.11)
	2.00	28.17 (0.31)	28.09 (1.44)	28.05 (0.56)
HPC-L	1.33	23.98 (1.74)	24.21 (1.50)	20.64 (1.38)
	1.67	23.81 (1.40)	22.27 (0.78)	23.79 (1.34)
	2.00	29.35 (1.47)	25.42 (1.22)	25.35 (0.82)
Methocel A4M	0.33	26.46 (0.95)	23.85 (0.51)	23.58 (0.84)
	0.67	28.24 (0.71)	22.32 (1.38)	26.07 (0.53)
HPC-M	1.33	26.03 (1.67)	28.46 (0.93)	27.24 (0.15)
	1.67	29.57 (1.23)	28.12 (1.54)	29.08 (1.20)
	2.00	28.05 (1.63)	23.04 (0.97)	27.32 (0.88)
	2.33	27.02 (1.66)	24.76 (0.83)	24.28 (1.71)

[a]Averaged from three determinations.

Table 13

Percent Friability of Lactose-Avicel PH 101 Pellets Prepared with Various Spheronization Times, Types, and Concentrations of Binders

Binder	Concentration (% w/w)	Percent Friability (%)[a] Spheronization Time (min) 5	10	15
Methocel E-15LV	1.33	0.32	0.31	0.33
	1.67	0.19	0.31	0.41
	2.00	0.33	0.38	0.43
HPC-L	1.33	0.22	0.18	0.19
	1.67	0.30	0.08	0.15
	2.00	0.25	0.06	0.16
Methocel A4M	0.33	0.10	0.10	0.13
	0.67	0.10	0.12	0.13
HPC-M	1.33	0.65	0.56	0.53
	1.67	0.33	0.47	0.46
	2.00	0.22	0.45	0.46
	2.33	0.07	0.10	0.18

[a]Averaged from two determinations.

the others. This may be due to the more narrow size distribution obtained.

Effect of the Amount of Water on Appearance and Physical Properties of Lactose-Avicel PH 101 Pellets

The microscopic appearance of lactose-Avicel PH 101 pellets at various amounts of water are presented in Fig. 9. The results show that the optimal amount of water that gave spherical-shaped pellets was in the range of 40–44% w/w based on dry basis. When the lower amount of water (≈35% w/w) was used, the spherical-shaped pellets were not obtained. It may be explained that the lower amount of water did not give enough plastic properties to the wet mass during the wetting process and in some cases the extrudates were broken. When the higher amount of water was used, larger pellets were observed. This was because the extrudates became overwet and plastic mass did not break into short rods but further aggregated to produce larger pellets (4,6,12).

The physical properties of lactose-Avicel PH 101 pellets in this study are shown in Table 14. The results showed the amount of water in the range of 40–44%

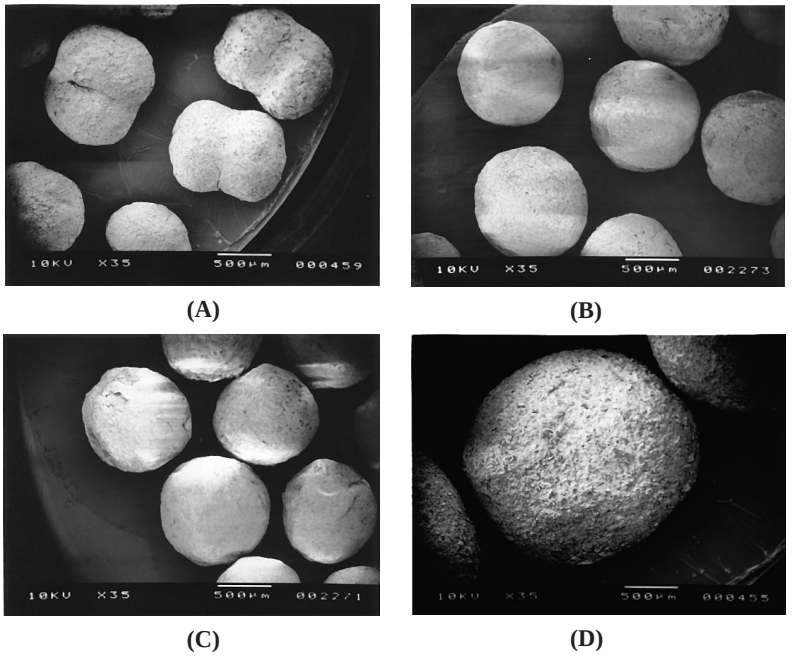

Figure 9. Photomicrographs of lactose-Avicel PH 101 pellets using various amounts of water at 2.00% w/w of HPC-M, 15 min of spheronization time, and a spheronizer speed of 951 rpm (×35) (A, B, C, and D are 35%, 42%, 44%, and 50% of water base on a dry basis, respectively).

Table 14

Physical Properties of Lactose-Avicel PH 101 Pellets Prepared with Various Amounts of Water by Using 2.00% w/w of HPC-M and 15 min of Spheronization Time

	Amount of Water (% base on dry basis)		
Physical Properties	40	42	44
Sieve analysis[a]			
% weight retained on sieve no.			
14	7.84	8.27	4.47
18	38.09	42.59	40.16
20	36.09	34.61	37.83
40	15.94	13.92	17.41
60	1.88	0.61	0.12
Pan	0.03	0.00	0.00
Granule size (mm)[a] by sieve analysis	0.97	1.01	0.97
% sieve fraction on 14/20 mesh cut pellets[a]	74.18	77.20	77.99
Bulk density (g/ml, ± SD)[b]	0.83 (0.01)	0.81 (0.01)	0.84 (0.01)
Tapped density (g/ml, ± SD)[b]	0.87 (0.01)	0.86 (0.00)	0.84 (0.01)
Flow rate (g/min, ± SD)[b]	282.42 (5.48)	255.86 (8.31)	246.94 (2.84)
Angle of repose (degree, ± SD)[b]	27.32 (0.88)	27.22 (1.03)	27.27 (1.15)
Percent friabillty[a]	0.4630	0.3675	0.1935

[a]Averaged from two determinations.
[b]Averaged from three determinations.

w/w of water base on a dry basis produced pellets of narrow size distributions. The mean particle size and percent friability of lactose-Avicel PH 101 pellets prepared with 40, 42, and 44% w/w of water base on a dry basis were not significantly different at the 95% confident level. Flow rate, percent sieve fraction on 14/20 mesh cut, bulk density, and tapped density of the pellets decreased with increasing amount of water.

From these results, the formulation that consisted of lactose-Avicel PH 101 (60:40), 2.00% w/w of HPC-M as a binder, 40% w/w of water base on a dry basis, and 15 min of spheronization time at 951 rpm of spheronizer speed gave good placebo pellets. The pellets prepared from the previously mentioned conditions had narrow particle size distribution, high desirable particle size and flow rate, low angle of repose and percent friability, and no difference between bulk density and tapped density.

CONCLUSION

In this study, there were many factors that affected the appearance and physical properties of lactose-Avicel PH 101 pellets. These factors were spheronizer speed, spheronization time, binder type, binder concentration, and amount of water.

Increasing in sphericity, smooth surface, and mean particle size of the pellets were obtained when spheronization time and spheronizer speed were increased. Size and shape of the pellets were changed with various types and concentrations of binders except for pellets using HPC-M as a binder. Pellets using HPC-M as a binder were spherical (at high spheronizer speeds) and had a narrow size distribution and a high desirable particle size and flow rate compared with pellets using other binders. In addition, increasing HPC-M concentration had no effect on shape and mean particle size of pellets. When spheronization time, amount of water, binder type, and binder concentration were studied, the pellets with a low angle of repose, a low percent friability, and no difference between bulk density and tapped density were obtained. The selected formulation for preparing lactose-Avicel PH 101 (60:40) placebo pellets consisted of 2.00% w/w of HPC-M, 40% w/w of water base on a dry basis during wet mass process, and 15 min of spheronization time at 951 rpm.

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