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COMMUNICATION

The Evaluation of Fine-Particle Hydroxypropylcellulose as a Roller Compaction Binder in Pharmaceutical Applications

G. W. Skinner, W. W. Harcum, P. E. Barnum, and Jian-Hwa Guo*

Hercules Incorporated, 500 Hercules Road, Wilmington, DE 19808-1599

ABSTRACT

In solid dosage manufacturing, roller compaction technology plays an important role in providing cost control and a quality product. The objective of this study was to evaluate the effectiveness of fine-particle hydroxypropylcellulose (HPC) as a dry binder in roller compaction processing. The formula included acetaminophen (APAP), microcrystalline cellulose, fine-particle HPC, croscarmellose sodium, and magnesium stearate. The fine-particle HPC was incorporated into the formula at 4%, 6%, and 8% w/w levels. Three compaction pressures (30, 40, and 50 bars) were used for each formulation. The roller compaction equipment used in this study had a processing capacity of 40 to 80 kg/hr. A tablet compression profile was generated on a rotary tablet press, and compression forces used were 5, 10, 15, 20, and 25 kN. The significant criteria for tablet evaluation were capping, hardness, friability, ejection force, and drug dissolution. As the binder concentration of HPC increased, tablet capping decreased, and tablet friability improved. As the concentration of HPC increased, only slight differences were noted in tablet hardness. All the formulations pass the USP requirement of 80% APAP dissolved within 30 min. Using 8% HPC could eliminate the formula capping problem. The friability results were less than 1% at all compression forces. The minimum tablet ejection forces were found in the formulations prepared under 40 bars compaction pressure. The utility of fine-particle HPC as a roller compaction binder was established. The applicable binder

* To whom correspondence should be addressed. Current address: B. F. Goodrich Company, 9921 Brecksville Research Center, Brecksville Road, Cleveland OH 44141-3289. Telephone: 1-800-331-1144.

concentrations and roller compaction pressures were found. Using HPC at these binder levels and operating parameters could overcome capping and friability problems and achieve the optimal tablet dosage forms.

INTRODUCTION

The pharmaceutical industry uses many different processing techniques to prepare raw materials for compression into tablets. One method, roller compaction, has generated much interest over the years. Roller compaction is a process in which no moisture is added to the materials, and it uses less equipment than wet granulation processing. This process provides an alternative to wet granulation or direct compression because roller compaction can impart flow and density properties that are often lacking in direct-compression formulations (1–4).

Although there are advantages to roller compaction processing, it is not used frequently in the pharmaceutical industry. There is interest in the process, but few companies have been successful using this manufacturing technique. The commercial products that are processed using roller compaction do have an economic advantage due to fewer processing steps and less processing equipment needed. This interest exists because roller compaction requires less equipment and fewer processing steps, which in turn decreases the manufacturing cost.

Because of its unique thermoplastic properties, hydroxypropylcellulose (HPC) has been studied previously at different binder levels for roller compaction applications (1). There are studies available in which regular particle size HPC was evaluated in this process. In one previous study, the binder concentrations used were as high as 25%, and this may be due to use of larger particle size HPC.

Besides investigating the process and the design effects on the final products (5–7), there are many important tableting properties, such as hardness, friability, capping, and ejection forces, that should be monitored during roller compaction formulating and correlated with the processing factors. The objective of the research described here was to evaluate fine-particle HPC as a roller compaction binder for pharmaceutical applications. The active drug, acetaminophen (APAP), was roller com-

Table 1

Physical Testing Results of Roller-Compacted Granules

	Bulk Density (g/ml)	Tap Density (g/ml)	Average Particle Size (μm)
4% HPC			
Initial blend	0.3716	0.5258	178
30 bar	0.4681	0.6918	364
40 bar	0.4983	0.7118	383
50 bar	0.5263	0.7243	393
6% HPC			
Initial blend	0.3561	0.5336	205
30 bar	0.4975	0.7006	355
40 bar	0.4855	0.7036	361
50 bar	0.5076	0.7217	368
8% HPC			
Initial blend	0.3521	0.5152	182
30 bar	0.5032	0.6832	393
40 bar	0.5087	0.6936	431
50 bar	0.4856	0.6938	387

Table 2

Physical Testing Results for Tablets with 4% Hydroxypropylcellulose

	Compression Force (kN)	Ejection Force (kN)	Hardness (Kp)	Friability (% wt loss)
CF 1	5.2	0.046	2.4	100
CF 2	10	0.094	6.8	2.59
CF 3	15.1	0.146	9.7 (C)	5.83
CF 4	20.1	0.18	11.9 (C)	8.1
CF 5	25	0.191	12.7 (C)	7.52 (C)
**CF 3	15.04	0.21	8.8 (C)	15.1 (C)
CF 1	5.1	0.036	2	100
CF 2	9.8	0.08	4.8	2.79
CF 3	15.2	0.132	8.6	1.56
CF 4	20.1	0.16	10.6 (C)	3.89
CF 5	24.9	0.167	11.8 (C)	1.71
**CF 3	14.8	0.18	7.4 (C)	6.2
CF 1	4.9	0	1.6	100
CF 2	10	0.081	4.6	3.52
CF 3	15.2	0.117	7.7	3.08
CF 4	20	0.164	9.6	2.63 (C)
CF 5	25	0.19	11.9 (C)	3.72
**CF 3	14.7	0.19	7(C)	6.7

**CF 3 is compression force 15 kN at 75 rpm.
(C) = capping.

Table 3

Physical Testing Results for Tablets with 6% Hydroxypropylcellulose

	Compression Force (kN)	Ejection Force (kN)	Hardness (Kp)	Friability (% wt loss)
30 BAR				
CF 1	5.1	0	2.2	100
CF 2	10.2	0.085	5.1	1.91
CF 3	15.1	0.14	8.4	3.37 (C)
CF 4	20.1	0.168	10.5 (C)	1.3 (C)
CF 5	24.8	0.186	12.8 (C)	2.01 (C)
**CF 3	14.8	0.19	7.3	4.3
40 BAR				
CF 1	5.1	0	2	100
CF 2	10.2	0.075	5	1.98
CF 3	15.1	0.122	8.4	2.31
CF 4	19.9	0.16	10.4	1.18
CF 5	24.9	0.18	12.8	2.26 (C)
**CF 3	15.2	0.16	7.7	4.3 (C)
50 BAR				
CF 1	5	0	2.1	100
CF 2	10	0.062	5.4	2.3
CF 3	15.1	0.102	9.3	1.14
CF 4	19.9	0.153	11.7	1.15
CF 5	25	0.169	12.9	3.39 (C)
**CF 3	15.04	0.17	8.1	5.3 (C)

**CF 3 is compression force 15 kN at 75 rpm.
(C) = capping.

Table 4

Physical Testing Results for Tablets with 8% Hydroxypropylcellulose

	Compression Force (kN)	Ejection Force (kN)	Hardness (Kp)	Friability (% wt loss)
30 BAR				
CF 1	5.1	0	2.2	100
CF 2	10.1	0.06	5.5	1.5
CF 3	15.2	0.112	9.1	0.754
CF 4	19.9	0.149	11.6	0.753
CF 5	25.1	0.175	13.5	0.752
**CF 3	15.11	0.16	8.7	3.6
40 BAR				
CF 1	5	0	1.9	100
CF 2	10.1	0.06	5.4	1.5
CF 3	14.9	0.097	8.1	0.7
CF 4	19.8	0.127	10.8	0.8
CF 5	25	0.149	12.5	0.6
**CF 3	14.8	0.141	8.2	1.9
50 BAR				
CF 1	5	0	2	100
CF 2	10.1	0.056	5.3	1.7
CF 3	15.1	0.097	8.7	0.8
CF 4	20.2	0.135	10.4	0.9
CF 5	24.8	0.164	12.8	0.7
**CF 3	14.91	0.153	7.5	1.3

**CF 3 is compression force 15 kN at 75 rpm.

pacted, blended, and compressed into tablets. The roller-compacted granulation was evaluated for bulk and tap density and particle size distribution. Tablet evaluations included hardness, friability, capping, ejection forces, and dissolution tests.

MATERIALS AND METHODS

The materials used in the study were HPC (Klucel® EXF, Pharm, Hercules, Inc., Aqualon Division, Wilmington, DE), APAP powder USP (Rhone-Poulenc, Inc., Specialty Chemicals, Cranbury, NJ), magnesium stearate NF (Witco Corp., Organics Division, Chicago, IL), croscarmellose sodium (Ac-Di-Sol, NF, FMC Corp., Food and Pharmaceutical Division, Newark, DE), and microcrystalline cellulose (NF, FMC Corp., Food and Pharmaceutical Division).

The tablet formulation consisted of drug, binder, lubricant, disintegrant, and filler. In this case, the drug, APAP, was used at 50%, and fine-particle HPC was incorporated into the formula at 4%, 6%, and 8% w/w levels and was used as the binder. The lubricant, magnesium stearate,

Table 5

Dissolution Results for Tablets at T_{80}

	T_{80} (min)
4% HPC	
30 bar	6.7
40 bar	14.5
50 bar	17.9
6% HPC	
30 bar	13.1
40 bar	12.4
50 bar	17
8% HPC	
30 bar	15.7
40 bar	17.4
50 bar	25

Dissolution test: 900 ml, pH 5.8 buffer, 55 rpm.

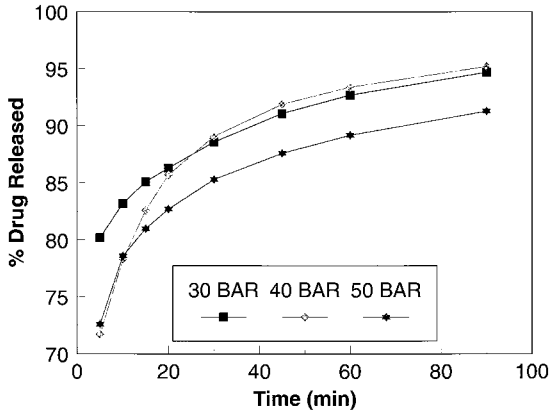


Figure 1. The dissolution results for tablets with 4% HPC.

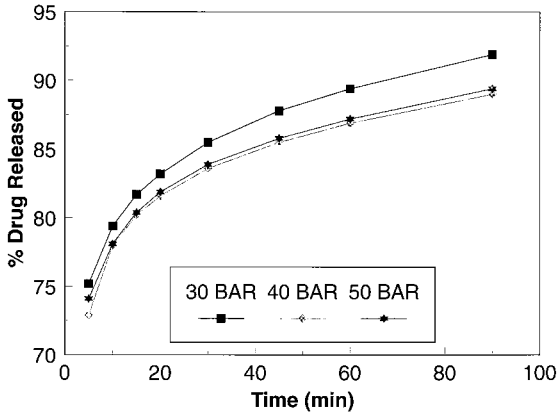


Figure 3. The dissolution results for tablets with 8% HPC.

was fixed at 0.5%, and the disintegrant, croscarmellose sodium, was fixed at 2% in the formulation. Microcrystalline cellulose was used as the diluent because it is the most commonly used excipient when processing materials by roller compaction. The standard operating parameters were established as follows: feed auger speed was 30 rpm, and screen sizes of 2.5 mm and 1.0 mm were used in combination in the granulator (mill). The Alexanderwerk's model WP50N/75 SS roller compactor (Horsham, PA) was used. This unit has a vacuum deaeration feature on the feed auger that helps improve the final product.

The materials that were roller compacted were APAP, microcrystalline cellulose, and HPC. The remaining two ingredients were added in a blending step before tablet compression occurred. Three compaction pressures (30, 40, and 50 bars) were used for each formulation. The roller compaction equipment used in this study had a processing capacity of 40 to 80 kg/hr. Samples were collected of the roller-compacted ribbon and the final milled product as the material came from the machine. The milled samples were tested for bulk and tap density, as well as sieve analysis. The roller compaction ribbon and final milled granules were examined under a scanning electron microscope (SEM). These roller-compacted materials were blended and then tableted using the instru-

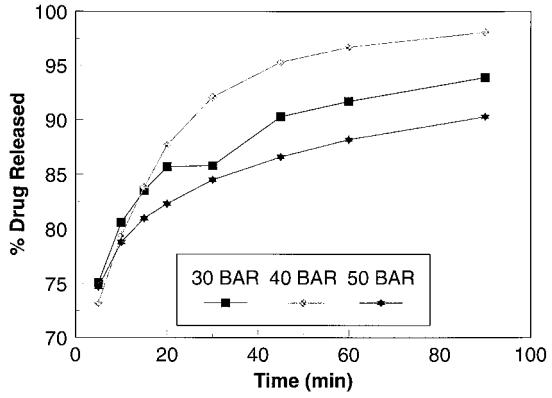


Figure 2. The dissolution results for tablets with 6% HPC.

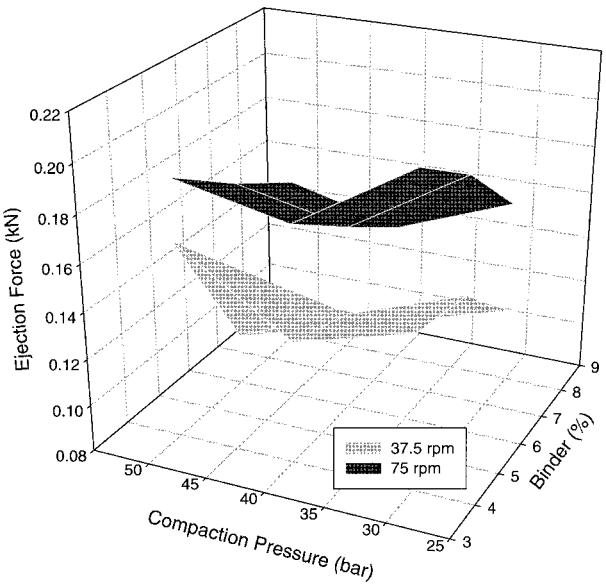
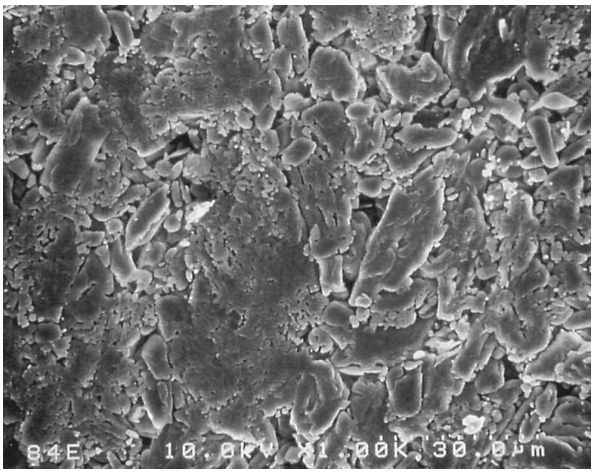
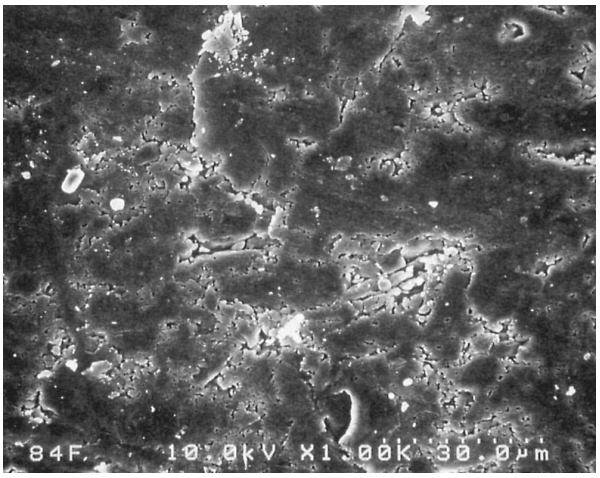


Figure 4. The ejection force of roller compaction formulations.



Magnification 1000X
10 µm

(a)



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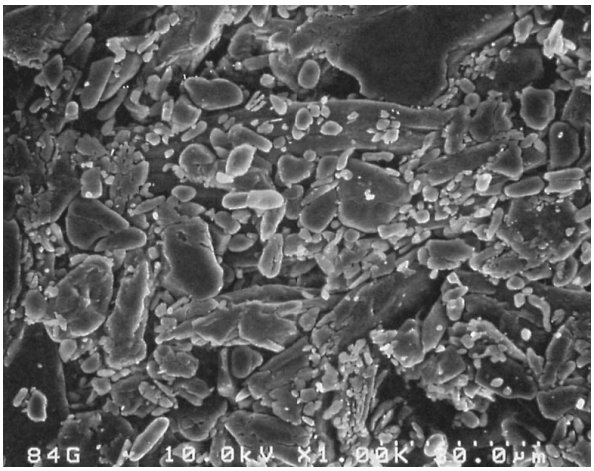
(b)



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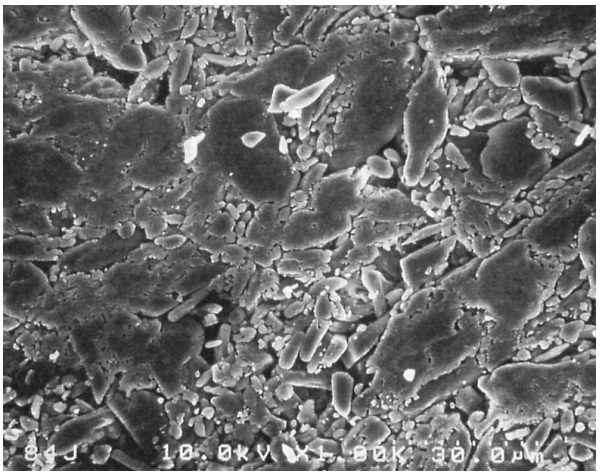


Magnification 1000X
10 µm

(d)

Figure 5. The scanning electron microscopy results for roller-compacted ribbons: (a) 4% HPC, 30 bar; (b) 4% HPC, 40 bar; (c) 4% HPC, 50 bar; (d) 6% HPC, 50 bar; (e) 8% HPC, 50 bar.

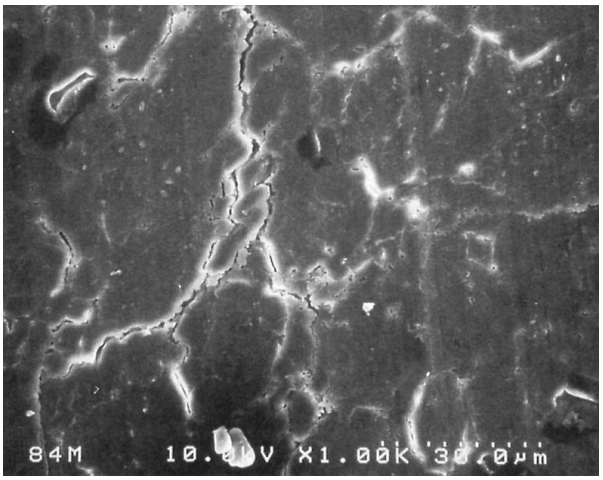
(*continued*)

mented rotary tablet press (Beta-press). A tablet compression profile was generated on a rotary tablet press, and compression forces used were 5, 10, 15, 20, and 25 kN. The ejection forces of these formulations were recorded as well.

Dissolution tests were conducted on the finished tablets using 5.8 pH phosphate buffer medium and 55 rpm paddle dissolution method. The time for releasing 80% of drug T_{80} from the formulation was reported.

RESULTS AND DISCUSSION

The physical test results for roller-compacted granules are shown in Table 1. It was found that the bulk



Magnification 1000X
10 μm

(e)

Figure 5. Continued

and tap density increased at all binder levels studied when compared with the initial blend material. The roller compaction process also increased the average particle size of the granulation. Before roller compaction, the majority of the starting blend material was retained on the 80-mesh screen. After roller compaction, the particle size distribution was more uniform, with the highest particle retention occurring on the 40 mesh. This particle size change helped to impart good granulation flow properties, which is important in tablet manufacturing.

The physical test results of tablets are represented in Tables 2 through 4, which include the compression force data, ejection force data, tablet hardness values, and tablet friability results. This study included tablets that were made using a compression force of 15 kN at 75 rpm, as well as 37.5 rpm. All other compression force data were generated using 37.5 rpm. This doubling of speed was done to check the potential of tablet capping at higher speeds, which would not be evident at our normal tablet press speed.

The formula that contained 4% HPC showed some capping problems (Table 2). The worst capping was seen when the materials were roller compacted at 30 bars. When roller compaction pressures were increased to 40 bars and 50 bars, the capping was decreased. The friability values decreased using these two pressures, which is an indication that formulation improvements had occurred.

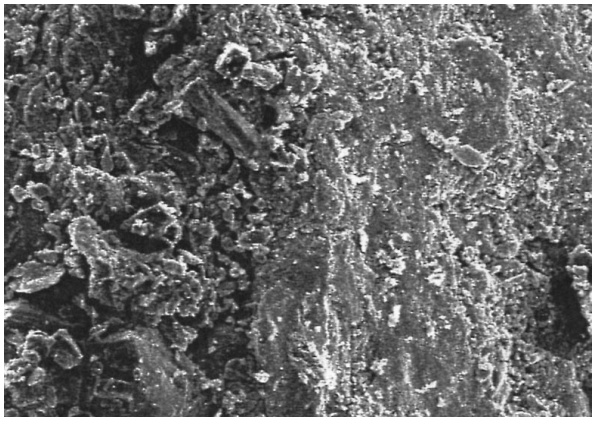
Table 3 shows the results for the formula containing 6% HPC. By increasing the roller compaction to 40 bars and 50 bars, it was possible to eliminate tablet capping that occurred during hardness testing for the tablets made of the 30-bar roller-compacted materials. Capping still remained a problem during the friability test performed on tablets compressed at 25 kN and those compressed at 75 rpm using 15-kN compression force. The improvements at 6% HPC binder level indicated that this concentration may be an effective binder level for this formulation.

Table 4 shows that, when 8% HPC was used in the formulation, the capping problem was completely eliminated. Friability values were below 1% at compression forces greater than 10 kN. As the HPC level increased, the differences between the 37.5-rpm tablet hardness data and the 75-rpm hardness data decreased. Using an 8% HPC level at either 37.5 rpm or 75 rpm had very little impact on tablet hardness results.

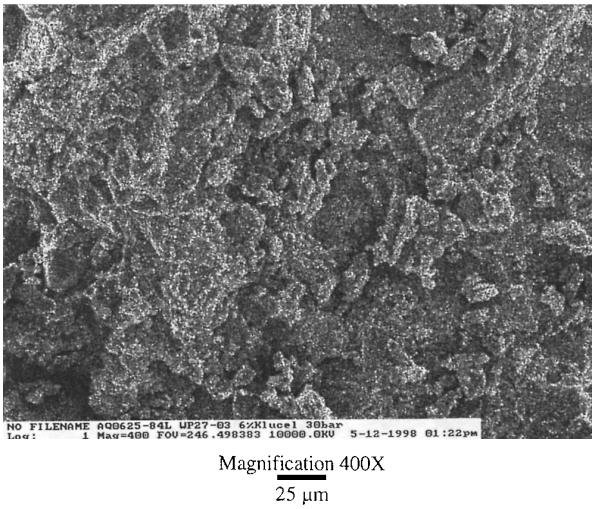
The dissolution results for the tablets are shown in Table 5 and Figs. 1 through 3. In all cases, the APAP was released in under 30 min, although the formulas that were roller compacted using 50-bar pressure had the slowest release profile in each study.

The ejection forces were also recorded during these experiments. This information is graphically shown in Fig. 4. The plot clearly indicates that the lowest ejection forces were found using 40-bar roller compaction pressures for all the compression speeds. Figures 5 and 6 show the SEM evaluation conducted on the roller compaction ribbons and the granules produced from the ribbon material. It was found that the most dense ribbon material was produced using a roller compaction compression force of 40 bars, and when the HPC level was increased, the ribbon or granule density also increased. These results, along with other physical and ejection data generated in this study, demonstrated that 40 bars may be the most appropriate roller compaction pressure to use for all the formulations.

Compaction is a form of pressure agglomeration in which active and nonactive ingredient particles or granules are forced together by mechanical force. Under high-pressure compaction, the particles are forced against each other even more and undergo elastic and plastic deformation, thereby increasing interparticle contact. HPC is a nonionic, water-soluble cellulose ether with remarkable thermoplastic characteristics, and it has a very high degree of plastic flow. Therefore, when HPC was used as a binder, it could provide toughness, absorb compression



(a)



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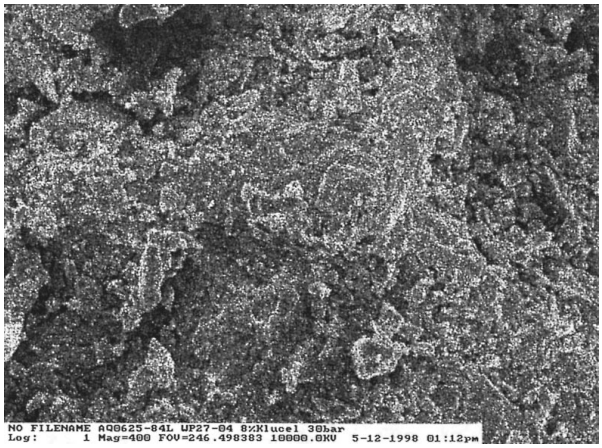

(c)

Figure 6. The scanning electron microscopy results for roller-compacted granules: (a) 4% HPC, 30 bar; (b) 6% HPC, 30 bar; (c) 8% HPC, 30 bar.

energy, and decrease the ejection force of the tableting process.

However, at extremely high compaction pressure, reduction in volume continues until the density of the materials approaches the true densities of the component ingredients, and the brittle particles may fracture under stress and lead to a more porous morphology for the overcompacted (50-bar) ribbons. When granules were milled from the overcompacted (50-bar) ribbons, their porous morphologic structure could be used to explain the higher ejection force for the tablets made from them.

CONCLUSIONS

The evaluation of HPC as a roller compaction binder has demonstrated its usefulness in imparting good compaction characteristics to the granulation. By incorporating an appropriate HPC level and operating parameters, it was possible to produce tablets with good physical characteristics. The exact concentration and roller compaction pressures to use for other formulas will depend on the physical properties of the active drug and the excipient used.

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