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Roller compaction and tableting of microcrystalline cellulose/drug mixtures

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Abstract

Different types of microcrystalline cellulose (MCC) and blends of MCC, a mainly plastic deforming material and ibuprofen, used as a mainly fragmenting material were roller compacted. All MCC types, except Avicel® CE-15, produced excellent quality granules but the corresponding tablet mechanical strength was low. Addition of ibuprofen reduced the number of usable roller compactor parameter combinations. The presence of 25% ibuprofen had a negative influence on granule quality while the tablet mechanical strength improved. A further increase of the ibuprofen concentration yielded an acceptable granule quality and a high tablet mechanical strength due to the fragmentation and sintering properties of ibuprofen. It remained difficult to predict the influence of roller compactor pressure on the final tablet mechanical strength. Differences in MCC particle density influenced the dissolution rate more than the particle size. The presence of an additional dry binder did not improve granule strength and decreased the dissolution rate. The t_{90} release values of the 75% ibuprofen tablets was low for hydrophilic gum–MCC associations, Avicel® PH-301 and PH-302. © 1998 Elsevier Science B.V.

Keywords: Roller compaction; Microcrystalline cellulose; Ibuprofen; Tablet; Granule

1. Introduction

Microcrystalline celluloses (MCC) are extensively used in direct compression and wet granulation as a dry binder, a filler and a disintegrant. Their application and behaviour in dry granulation processes using roller compaction is not well documented. Roller compaction is a continuous dry compaction process consisting of the densification of powder between two counter rotating rolls. The strips formed are subsequently milled to the desired granules. Only Falzone et al. (1992) modeled the behaviour of Avicel® PH-101 during roller compaction by evaluating the compressibility and mean geometric particle size of the granules. They found that the influence of the roll speed and the interaction between the roll speed

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and horizontal screw speed was important, but they did not include compaction pressure as a variable process parameter in the experiments. Sheskey and Dasbach (1995) used Avicel® PH-102 for the roller compaction production of granules for the formulation of immediate release tablets. They found that not the binder level but the roller compaction pressure affected the drug release from the tablets containing Avicel® PH-102. This work compares the roller compaction behaviour of different types of MCC. It also describes the influence of increasing drug concentrations on the roller compaction behaviour of different types of MCC using ibuprofen as a mainly fragmenting model drug. Finally the influence of the roller compaction pressure on granule and tablet quality was evaluated.

2. Materials and methods

2.1. Roller compactor

The Fitzpatrick L83 Chilsonator (Fitzpatrick, Elmhurst, USA) consisted of two counter rotating rolls, having smooth surfaces. One of the rolls could move horizontally and was connected to two hydraulic jacks. An air-hydraulic booster system converted an air pressure (P_{air}) into a 25 × bigger oil pressure (P_{oil}). A vertical screw, having a de-aerating and a predensification function transported the powder to the nip of the rolls. This vertical screw was fed by a horizontal screw fixed in the powder reservoir. The adjustable parameters of the compactor were: the air pressure (P_{air}), the roll speed (R_S) and the velocity of the horizontal (H_S) and the vertical (V_S) screw. Roll speed ranged from 3 to 13 rpm, H_S from 3 to 60 rpm and V_S from 100 to 1000 rpm. The P_{air} could be adjusted from 100 to 300 kPa, resulting in a maximum hydraulic pressure and a compaction pressure of 2.5 and 6.9 MPa, respectively. The compactor was instrumented with a piëzoelectric pressure sensor (Greisinger, Regenstauf, Germany) to measure the instantaneous force between the compacting rolls and with a displacement transducer (LVDT, Solartron Metrology, Mulheim, Germany) to determine the instantaneous gap between the rolls (Inghelbrecht et al., 1997). When the torque on the vertical screw exceeded its maximal allowable value due to an excess of powder, the motor of the horizontal screw stopped automatically until overfeeding disappeared, and then the motor restarted automatically. This interruption of the horizontal screw motor could influence the feeding and consequently the forces acting between the rolls, the horizontal displacement of the movable roll and the compact quality. Its working was avoided during these experiments.

2.2. Roller compaction and granulation process

Blends (w/w) of Avicel® CE-15, Avicel® RC-581, Avicel® PH-101 (mean particle size 50 μm, bulk density 0.28 g/ml), Avicel® PH-105 (mean particle size 20 μm, bulk density 0.25 g/ml) and Avicel® PH-302 (mean particle size 90 μm, bulk density 0.39 g/ml) (FMC, Philadelphia, USA) and 0, 25, 50 and 75% ibuprofen (<25 μm, Knoll, Nottingham, UK) respectively, were prepared by mixing the powders during 30 min in a Hobart mixer A200 (Hobart, London, UK). The materials and blends were examined by back scatter emission using a XL30 electronic microscope (Philips, Amsterdam, Netherlands). The powders were compacted at several combinations of the four compactor parameter settings: air pressure (P_{air}), resulting in a 25 times higher oil pressure (P_{oil}) between the rolls, roll speed (R_S), speed of the vertical screw (V_S) and of the horizontal screw (H_S). The influence of the V_S was only studied on Avicel® RC-581. As no influence of the V_S on granule quality was seen and as the largest range over which the H_S values could be varied was reached at the highest V_S value, the V_S was set at its maximum value of 1000 rpm for all experiments. The oil pressure was set once at a low value of 2.3 MPa and once at a high pressure of 6.9 MPa. Using both pressures, the minimal and maximal H_S value was determined for three different R_S values (3, 8, 12 rpm). After roller compaction, 400 g compact was milled during 6 min using a Frewitt granulator type MGI 624 (Frewitt, Fribourg, Switzerland) equipped with a 1 mm sieve with squared wiring and set at a rotor

speed of 130 rpm. The distance between rotor and sieve was kept minimal.

2.3. Granule evaluation

The size distribution of the granules was evaluated by sieve analysis. This analysis was performed on 150 g granules, sieved on a sieve-shaker (Retsch, Haan, Germany) for 10 min at an amplitude of 2 mm. The sieves used were 90, 180, 250, 500, 710 and 1000 μm. The percentage granules remaining on each sieve was calculated. The process yield was compared for the different powder mixtures using the 250–1000 μm fraction.

The friability of the granules was determined by subjecting 10 g of the 250–500 μm fraction together with 200 glass-beads (average diameter of 4 mm) to falling shocks for 10 min in a friabilator (Erweka, Frankfurt am Main, Germany) set at a speed of 25 rpm. After 10 min, the glass-beads were removed. The remaining material was sieved through a 250 μm screen, which was put on a sieve-shaker for 2 min at an amplitude of 2 mm. The material remaining on the 250 μm screen was weighed and the percent friability was calculated (Remon and Schwartz, 1987).

The tap- and bulk density of the granules was determined by pouring 30 g of each granule blend (fraction >250 μm) into a cylinder. The bulk density (g/cm^3) was determined when the granules were poured into the cylinder. Then the cylinder was tapped for 250, 500, 750, 1000 and 1250 times. When no difference in volume was observed the corresponding tap density (g/cm^3) was calculated.

2.4. Tablet production

Each blend of Avicel® PH-101, Avicel® PH-105, Avicel® PH-302, Avicel® RC-581 and Avicel® CE-15 containing 0, 25, 50 and 75% ibuprofen, respectively was compacted at the same roller compactor parameter combination sets: a R_S of 8 rpm, a V_S of 1000 rpm and a H_S of 9 rpm. The P_{air} was adjusted in order to obtain an oil pressure of 2.3 and 6.9 MPa, respectively. This allowed examination of whether roller compaction pressure had an influence on tablet strength for the different ibuprofen concentrations. Additional tablets containing 75% ibuprofen and 25% Avicel® PH-101 and PH-301 were made to further illustrate the influence of density and particle size on dissolution profiles. The granule fraction between 500 and 710 μm was selected for tablet production. 0.5% magnesium stearate (<90 μm; specific surface of 7.25 m^2/g; Ludeco, Brussels, Belgium) was added to the blend and was mixed during 1 min in a Turbula mixer Type T2A (W.A. Bachafen, Basel, Switzerland). Tablets with a total weight of 700 mg and a diameter of 13 mm were compressed on an eccentric press (Korsch Type EKO, Frankfurt, Germany). To evaluate the differences in tablet mechanical strength between the different types of MCC, a tableting force of 5880 N was chosen. The tablet mechanical strength was determined by a Pharma Test strength tester PTB311 (Pharma, Hainburg, Germany) and the friability by a friabilator (Erweka, Frankfurt am Main, Germany). Dissolution tests (VanKel, Edison, USA) were performed on the tablets made of granules containing 75% ibuprofen compacted at an oil pressure of 6.9 MPa, following the USP XXIII specifications. The dissolution medium was 900 ml phosphate buffer pH 7.2. Temperature was set at 37°C and the paddle speed at 150 rpm. Ibuprofen determination occurred at 221 nm with a UV spectrophotometer (Beckmann DU 65, Fullerton, USA).

The difference in mean tablet mechanical strength between formulations of granules roller compacted at 2.3 and 6.9 MPa was evaluated using a two tailed unpaired t-test. For some formulations a non-parametric test was used (Mann–Whitney test). Differences in mean tablet mechanical strength between the different formulations (0, 25, 50 and 75% ibuprofen) were compared with a one way ANOVA test.

3. Results

A selection of the friability and sieve fraction data obtained for granules made of different MCC types and ibuprofen/MCC mixtures at different compactor parameter setting combinations is shown in Table 1. These granules were also

Table 1
Roller compactor oil pressure, P_{oil} (MPa) and the corresponding friability (%), granule yield within the fraction 250–1000 μm (%) and bulk and tap density (g/cm^3) for the different formulations used for tablet production

Formulation	P_{oil} (MPa)	Friability (%)	Fraction 250–1000 μm (%)	Bulk density g/cm^3)	Tap density (g/cm^3)
Avicel® PH-101	2.3	40.2	51.2		
	6.9	20.8	57.8	0.56	0.64
Avicel® PH-101 + 25% ibuprofen	2.3	48.8	55.5		
	6.9	36.7	55.5	0.59	0.67
Avicel® PH-101 + 50% ibuprofen	2.3	52.5	58.3		
	6.9	35.1	73.1	0.53	0.62
Avicel® PH-101 + 75% ibuprofen	2.3	34.7	72.0		
	6.9	30.8	82.0	0.52	0.59
Avicel® PH-105	2.3	60.8	57.8		
	6.9	34.2	60.8	0.52	0.60
Avicel® PH-105 + 25% ibuprofen	2.3	68.9	36.4		
	6.9	46.5	57.8	0.59	0.66
Avicel® PH-105 + 50% ibuprofen	2.3	64.2	46.7		
	6.9	42.2	67.2	0.55	0.61
Avicel® PH-105 + 75% ibuprofen	2.3	23.8	83.9		
	6.9	27.3	84.9	0.54	0.60
Avicel® PH-302	2.3	57.8	34.6		
	6.9	31.9	43.2	0.57	0.61
Avicel® PH-302 + 25% ibuprofen	2.3	68.0	59.2		
	6.9	37.8	51.8	0.63	0.69
Avicel® PH-302 + 50% ibuprofen	2.3	63.4	49.8		
	6.9	46.6	74.0	0.57	0.63
Avicel® PH-302 + 75% ibuprofen	2.3	49.0	77.4		
	6.9	38.3	83.5	0.55	0.60
Avicel® RC-581	2.3	36.8	67.3		
	6.9	22.6	76.6	0.66	0.77
Avicel® RC-581 + 25% ibuprofen	2.3	80.7	53.2		
	6.9	87.9	65.7	0.71	0.74
Avicel® RC-581 + 50% ibuprofen	2.3	60.5	61.6		
	6.9	68.1	76.4	0.60	0.67
Avicel® RC-581 + 75% ibuprofen	2.3	46.9	72.0		
	6.9	50.4	77.3	0.56	0.63

Table 1 (continued)

Formulation	P_{oil} (MPa)	Friability (%)	Fraction 250–1000 μm (%)	Bulk density (g/cm^3)	Tap density (g/cm^3)
Avicel® CE-15	2.3	92.4	33.2		
	6.9	63.8	62.4	0.68	0.75
Avicel® CE-15+25% ibuprofen	2.3	88.0	61.7		
	6.9	55.5	63.8	0.62	0.71
Avicel® CE-15+50% ibuprofen	2.3	46.9	65.7		
	6.9	50.0	71.2	0.56	0.64
Avicel® CE-15+75% ibuprofen	2.3	35.3	77.8		
	6.9	38.3	88.4	0.54	0.61

The other parameter settings were $R_S = 8$ rpm, $V_S = 1000$ rpm and $H_S = 9$ rpm.

used for tableting. The compaction of the pure MCC types was possible with a large number of roller compactor parameter setting combinations. For each R_S, the H_S was varied over a wide range of settings. A higher R_S value resulted always in a broader H_S range. A higher pressure resulted in a lower friability and a higher process yield. The objective for a good granule quality was set at a friability below 50% and a process yield above 70%. Roller compaction of Avicel® PH-302, Avicel® PH-105 and Avicel® PH-101 provided a very good friability at 6.9 MPa for all the parameter setting combinations used. The best friability and highest process yield were obtained using a high H_S value. Avicel® PH-302, PH-105 and PH-101 granules showed at the high H_S value a friability ranging between 27 and 32%, between 16 and 21% and between 19 and 22%, respectively. The process yield for the combinations using the highest H_S ranged between 67 and 68%, between 67 and 72% and between 59 and 73% for Avicel® PH-302, PH-105 and PH-101, respectively. At a P_{oil} value of 6.9 MPa, an acceptable granule quality was obtained for Avicel® RC-581 and this for all combinations of the compactor parameter settings. Nevertheless, the lowest friability and process yield for Avicel® RC-581 were obtained using a low H_S value for the three R_S values used (friability 22–29%, yield 74–77%). Compaction of pure Avicel® CE-15 never resulted in an acceptable granule quality.

When adding 25, 50 and 75% ibuprofen, respectively to all MCC types, the usable roller compactor parameter setting combinations decreased dramatically. There was almost no displacement of the movable roll. Addition of 25% ibuprofen to all MCC types except to Avicel® CE-15, resulted in a poor granule quality compared to the pure product but a progressive increase of the ibuprofen concentration from 25 to 75% improved the quality again. In the next part of the report the results of compaction experiments at ibuprofen concentrations of 25, 50 and 75%, respectively are compared. At an oil pressure of 6.9 MPa and at a high H_S the friability of the Avicel® PH-105 granules remained substantially unchanged and varied between 27 and 42% but the yield increased from 48–63% to 67–75% and 76–86%, respectively. With Avicel® PH-101 the friability decreased from 37–55% to 31–39% and 26–32% and the yield increased from 50–62% to 70–75% and 75–82%, respectively. With Avicel® PH-302 the friability remained also substantially unchanged and varied between 35 and 47% but the yield increased from 51–59% to 64–77% and 80–84%, respectively. When 25% ibuprofen was added to Avicel® RC-581, the granule friability increased from 22–29% to 77–88% at an oil pressure of 6.9 MPa. Increasing the ibuprofen concentration to 50–75% resulted in a decreased friability and a higher yield.

Table 2
Tablet hardness (N) and friability (%) of tablets compressed at a pressure of 5880 N from the granule fraction 500–710 μm of each formulation, roller compacted at an oil pressure P_{oil} of 2.3 and 6.9 MPa

Formulation	$P_{oil} = 2.3$ MPa		$P_{oil} = 6.9$ MPa	
	Hardness (N)	Friability (%)	Hardness (N)	Friability (%)
Avicel® PH-101	37.84[a]	3.0	13.31[a]	100.0
Avicel® PH-101 + 25% ibuprofen	73.54[b]	5.2	25.57[b]	7.2
Avicel® PH-101 + 50% ibuprofen	61.49[b]	2.6	57.92[b]	3.6
Avicel® PH-101 + 75% ibuprofen	92.34[b]	2.8	87.96[b]	3.3
Avicel® PH-105	69.43[a]	1.4	34.14[a]	4.1
Avicel® PH-105 + 25% ibuprofen	31.13	3.9	31.23	5.7
Avicel® PH-105 + 50% ibuprofen	59.37	3.2	55.57	3.9
Avicel® PH-105 + 75% ibuprofen	81.5	3.3	85.28	3.9
Avicel® PH-302	14.77[a]	100.0	10.16[a]	100.0
Avicel® PH-302 + 25% ibuprofen	32.57[a]	7.4	29.39[a]	4.5
Avicel® PH-302 + 50% ibuprofen	61.26[a]	3.8	56.73[a]	5.4
Avicel® PH-302 + 75% ibuprofen	73.54[a]	3.8	65.95[a]	4.9
Avicel® RC-581	14.87[a]	100.0	4.22[a]	100.0
Avicel® RC-581 + 25% ibuprofen	15.96[a]	16	20.34[a]	10.5
Avicel® RC-581 + 50% ibuprofen	64.90	4.4	67.32	4.1
Avicel® RC-581 + 75% ibuprofen	84.30	3.9	82.50	1.2
Avicel® CE-15	4.90	100.0	not possible	not possible
Avicel® CE-15 + 25% ibuprofen	15.6[a]	35.2	10.19[a]	100.0
Avicel® CE-15 + 50% ibuprofen	56.4	3.5	57.20	3.7
Avicel® CE-15 + 75% ibuprofen	92.5[a]	3.4	75.10[a]	3.7

[a] Significantly different mean (two-tailed unpaired t-test).
[b] Significantly different median (Mann–Whitney test).

Only at an ibuprofen concentration above 75% an acceptable granule quality was obtained (friability 43–50%, yield 72–81%). When ibuprofen was added to Avicel® CE-15 only one or two H_S values were usable for one R_S value. The friability and yield for each blend was almost the same for all the parameter settings used at one pressure and was always better than for pure Avicel® CE-15. When using increasing ibuprofen concentrations and an oil pressure of 6.9 MPa the granule friability decreased from 55%–68% to 48–53% and 36–42% and the yield increased from 60–64% to 71–79% and 86–88%. At an ibuprofen concentration above 50% granules of acceptable quality were obtained.

When compacting pure ibuprofen, few parameter setting combinations were possible but the granule friability was very low and the yield high. However a large amount of non-compacted powder was produced during roller compaction. Due to the electrostatic behaviour of milled ibuprofen, a high variability of the friability and sieve fraction results was observed. Mixing ibuprofen with one of the MCC types avoided the electrostatic problems.

Processed pure Avicel® RC-581 and CE-15 showed higher tap densities (0.8 g/ml) than Avicel® PH-101, 105 and 302 (0.6 g/ml). The addition of 25% ibuprofen increased the tap density of the Avicel® PH-101, PH-105 and PH-302 mixtures, while larger ibuprofen concentrations again reduced the tap density. For all formulations containing Avicel® PH-101, PH-105 and PH-302 the tap density was similar. The addition of 25% ibuprofen did not increase the value of the tap density for Avicel® RC-581 and CE-15 but the tap density decreased progressively for increasing ibuprofen concentrations.

Table 2 shows the mechnanical strength (N) and the friability (%) of tablets formulated with different types of MCC and increasing ibuprofen concentrations. Granules used for the production

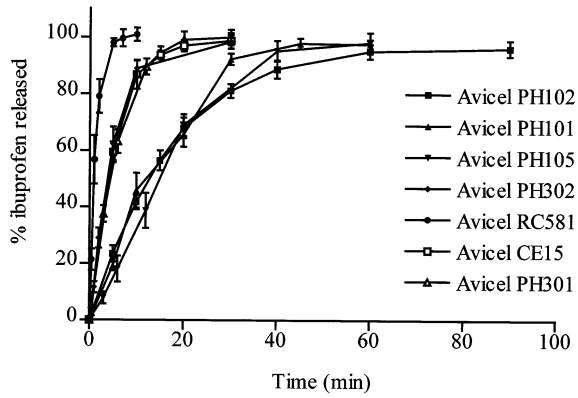

Fig. 1. Dissolution profiles of tablets containing different types of microcrystalline cellulose and 75% ibuprofen. The granules were roller compacted at an oil pressure of 6.9 MPa, a R_S of 8 rpm, a V_S of 1000 rpm and a H_S of 9 rpm. ● Avicel® RC581, □ Avicel® CE-15, ■ Avicel® PH-102, ▼ Avicel® PH-105, ▲ Avicel® PH-101, △ Avicel® PH-301, ◆ Avicel® PH-302.

of the tablets were roller compacted at an oil pressure of 2.3 and 6.9 MPa. There was a significant difference in mean tablet mechanical strength between the different formulations at each roller compaction pressure (one way ANOVA test; $p < 0.05$) except between Avicel® RC-581 and Avicel® RC-581 + 25% ibuprofen at 2.3 MPa and between Avicel® PH-105 and Avicel® PH-105 + 25% ibuprofen at 6.9 MPa (one way ANOVA, $p > 0.05$). For each blend it was examined if there was a significant difference (two-tailed unpaired t-test) in mean mechanical strength when using granules compacted at oil pressure values of 2.3 and 6.9 MPa (Table 2). There was a significant difference in mean mechanical strength ($p < 0.05$) between tablets made with Avicel® RC-581 and Avicel® RC-581 + 25% ibuprofen, and between tablets containing Avicel® CE-15 + 25 or 75% ibuprofen, and between the Avicel® PH-105 and Avicel® PH-101 formulation containing no ibuprofen. The Mann–Withney test also showed a significant difference in mean median value for the 25, 50 and 75% ibuprofen concentrations ($P < 0.05$) using Avicel® PH-101. For Avicel® PH-302 all the mixtures showed a significant difference in mean tablet mechanical strength (two-tailed unpaired t-test, $P < 0.05$).

Fig. 1 shows the release profiles of ibuprofen tablets containing different types of MCC and 75%

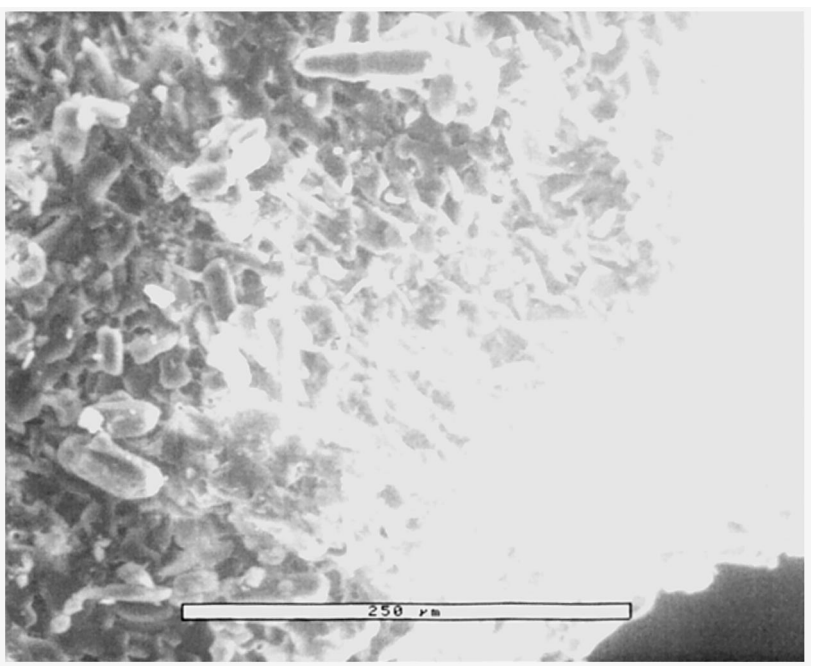

Fig. 2. Electronic microscope picture of an ibuprofen roller compact produced at an oil pressure of 6.9 MPa and heated at 70°C for 24 h.

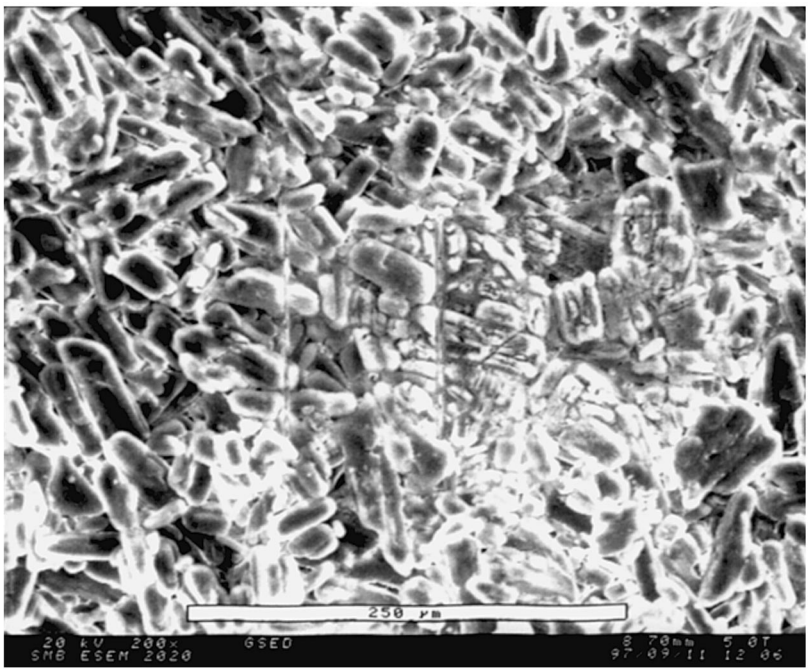

Fig. 3. Electronic microscope picture of an ibuprofen roller compact produced at an oil pressure of 6.9 MPa.

ibuprofen. The tablets were made of granules roller compacted at an oil pressure of 6.9 MPa, a R_S of 8 rpm, a H_S of 9 rpm and a V_S of 1000 rpm. 50% of the ibuprofen was released after 54 s, 3.5, 4, 4.2, 10, 12.6 and 15 min for Avicel® RC-581, Avicel® PH-302, Avicel® CE-15, Avicel® PH-301, Avicel® PH-101, Avicel® PH-102 and Avicel® PH-105, respectively. The t_{90} release values can be divided into 3 groups. For Avicel® RC-581 a t_{90} value of 3.6 min, for Avicel® PH-302, Avicel® PH-301 and Avicel® CE-15 a value of 13, 12.3 and 12 min and for Avicel® PH-101, Avicel® PH-105 and Avicel® PH-102 a value of 32, 35 and 41.8 min, respectively were recorded. Avicel® RC-581 tablets disintegrated quickly into fast dispersing granules. Avicel® CE-15, Avicel® PH-301 and Avicel® PH-302 tablets disintegrated more slowly into granules which on their own needed a certain disintegration time. Avicel® PH-101, PH-102 and PH-105 tablets required a long disintegration time into slowly dissolving granules, but the dissolution from the PH-101 granules was faster than from the PH-105 and PH-102 ones.

4. Discussion

The behaviour of pure MCC, MCC with hydrophilic gums and MCC/ibuprofen blends during roller compaction and the subsequent tableting process was studied. Falzone et al. (1992) demonstrated that the vertical screw speed had no significant influence on the granules when compacting plastic deforming materials like Avicel® PH-101. Similar results were obtained in this study. The compaction of pure MCC allowed many roller compactor parameter setting combinations to be used. For all types of MCC except for Avicel® RC-581 the best quality granules were obtained using a high H_S value. Roller compaction of Avicel® PH-105, Avicel® PH-101 and Avicel® PH-302 resulted in a very good granule quality at an hydraulic pressure of 69 MPa and a high H_S value. The smaller particle size of Avicel® PH-105 resulted in somewhat stronger granules compared to Avicel® PH-101 but granule strength was much lower for Avicel® PH-302. Very small differences in particle structure were seen under the electronic microscope between Avicel® PH-

105 and Avicel® PH-101, having both a fiber like structure, while larger differences were observed with Avicel® PH-302, having a more aggregated structure. However, Roberts and Rowe (1986) found that yield pressure and strain rate were independent of particle size when comparing Avicel® PH-101, 102 and 105. They found that the irregularity of the particles increased with particle size. This irregularity of the particles could be important for the granule strength and might contribute to the differences in granule strength between Avicel® PH-101, 105 and 302. The behaviour of Avicel® PH-302 was very similar to Avicel® RC-581 while the addition of guar gum (Avicel® CE-15) lowered granule quality. The presence of sodium carboxymethylcellulose in Avicel® RC-581 and guar gum in Avicel® CE-15 as additional dry binder did not improve the strength of the granules. Also other dry binders such as gelatine, polyvinylpyrrolidone, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, starch and xanthan gum were tested, even in high concentrations (10–15%) in order to improve the granule strength, but none of this binders was able to decrease the friability of the granules and seems to question the utility of using dry binders in roller compaction.

The addition of ibuprofen to the formulation always resulted in a reduction of the parameter setting combination possibilities. The relationship between tap density and friability was not always clear, probably due to the precompaction effects of the materials in the nip area just above the rolls which counteracted the influence of differences in tap density. The addition of a small amount of ibuprofen reduced the binding properties of MCC in granules. Only at an ibuprofen concentration above 75% the binding was improved. It is hypothesized that a small amount of ibuprofen disturbs the binding of the MCC fibers, which was compensated by the fragmentation and sintering ability of the drug at higher concentrations. The investigation on the influence of roller compaction pressure on tablet mechanical strength did not allow a general conclusion to be drawn. The highest tablet mechanical strength was obtained at the highest ibuprofen concentration. Nesic et al. (1990) reported on the behaviour of ibuprofen showing fragmentation and cold sintering at high compaction pressure. This two phenomena could probably explain the positive influence of increasing ibuprofen concentrations on roller compacted granules. In order to confirm sintering during the roller compaction process pure ibuprofen compacts were compared with identical compacts heated at 70°C during 24 h as a reference material for sintering (Li, 1990). The electronic microscope picture 1 (Fig. 2) shows the compact, heated at 70°C during 24 h while picture 2 (Fig. 3) shows the normal compact. On both pictures sintering is observed. Many investigators studied the plastic deformation of MCC (Avicel® PH-101, 102 and 105) using the yield pressure (Roberts and Rowe, 1986, 1987; McKenna and McCafferty, 1982). The well time had a significant influence on the type and extent of binding for MCC. When tablets were produced from roller compacted granules the phenomenon work-hardening has also to be taken into account. The extent of plastic deformation is reduced after a first compression due to work-hardening of the material (Malkowska and Khan, 1983; Li and Peck, 1990; Falzone et al., 1992; Kochhar et al., 1995). Especially plastic deforming products seemed sensitive to work-hardening. This explains why the granules in this study produced weaker tablets than the powder.

A fast drug release was observed for the MCC tablets containing 75% ibuprofen (roller compaction oil pressure of 6.9 MPa). The presence of hydrophilic gums decreased the dissolution time. This was more pronounced in the presence of sodium carboxymethylcellulose. The comparison of the t_{90} value of the Avicel® PH-101, 102, 105 and of the Avicel® PH-301, 302 products seemed to indicate that the dissolution rate was more influenced by the bulk density than by their average particle size.

5. Conclusions

It can be concluded that roller compaction is a suitable method for the compaction of MCC, except for Avicel® CE-15. The best granule quality was obtained using a high pressure and a high

H_S value. Addition of the fragmenting material ibuprofen changed the roller compaction behaviour of the plastic deforming MCC, depending on the ibuprofen concentration. It is hypothesized that a small amount of ibuprofen disturbs the binding of the MCC fibers, which was compensated by the fragmentation and sintering ability of the drug at higher concentrations. The presence of an additional dry binder in some MCC types did not improve granule quality but improved the dissolution rate. Tablet strength improved with increasing concentrations of ibuprofen. During tablet production a decrease in the ability to deform plastically was seen for the MCC due to work hardening. The comparison of the t_{90} values of the Avicel® PH-101, 102, 105 and of the PH-301, 302 products seemed to indicate that the dissolution rate was more influenced by the bulk density than by their average particle size.

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