

Research paper

Influence of wet granulation and lubrication on the powder and tableting properties of codried product of microcrystalline cellulose with β -cyclodextrin

Jen-Sen Wu, Hsiu-O Ho, Ming-Thau Sheu*

Graduate Institute of Pharmaceutical Sciences, Taipei Medical College, Taipei, Taiwan, ROC

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Abstract

The individual influence of wet granulation and lubrication on the powder and tableting properties of codried product of microcrystalline cellulose (MCC) with β -cyclodextrin (β -CD) was examined in this study. Avicel PH 101 and 301 were included for comparison. The codried product, Avicel PH 101 and 301 were granulated with water, and the granules were milled to retain three different size fractions: 37–60 μm , 60–150 μm , and 150–420 μm . The original Avicels and codried product were lubricated with magnesium stearate in three different percentages (0.2, 0.5, and 1.0%). The results showed that the powder flowability and disintegration of codried product and Avicels were significantly improved after wet granulation. However, the compactibility of codried product and Avicels decreased with increasing particle size. Nevertheless, the compactibility of the codried excipient after granulation was still better than the non-granulated Avicel PH 101 and 301. On the other hand, codried product and Avicels were sensitive to lubrication and resulted in decreasing compactibility and increasing disintegration. Because of the rounder shape of particles, the codried excipient was more sensitive to magnesium stearate and produced weaker tablets than did Avicels. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Microcrystalline cellulose (MCC) is a very popular pharmaceutical excipient in direct compression. The compactibility of MCC is mostly offered by plastic deformation and mechanical interlocking between particles [1]. However, the irregular shape, which contributes to interlocking bonding, results in poor flowability of MCC. In order to increase powder flowability and reduce weight variation of tablets, granulation is often recommended when MCC is used in tablet formulations. However, a dramatic decrease in the compactibility of MCC has been reported when MCC is subjected to wet granulation [2]. Meanwhile, the compressibility of MCC was also influenced negatively by the slugging method reported by Beten et al. [3]. Although the powder flowability of MCC can also be improved by the addition of a lubricant like magnesium stearate, the lubricant may form a hydrophobic film around the granules leading to a decrease in the crushing strength of MCC tablets

[4,5]. Therefore, it is desirable to improve this limit of MCC by the involvement of another excipient while retaining all the advantages of MCC.

According to Bavitz and Schwartz [6], the functionality of MCC has been modified by blending with starch, lactose, dicalcium phosphate or codrying with starch, calcium sulfate etc. However, all these modifications offer direct compression tableting performance that falls short of that for MCC alone. A previous study reported that a codried product of MCC slurry with β -CD had better compactibility, powder flowability, and disintegration properties than did MCC alone [7]. Therefore, it would be interesting to find out whether this codried product is superior when used in various pharmaceutical processes including wet granulation and lubrication.

In this study, the individual effect of wet granulation and lubrication with magnesium stearate on codried sample were evaluated and compared with other commercial products of MCC, Avicel PH 101 and Avicel PH 301.

* Corresponding author. Graduate Institute of Pharmaceutical Sciences, Taipei Medical College, 250 Wu-Hsing Street, Taipei, Taiwan, ROC. Tel./fax: +886-2-2377-1942.

E-mail address: mingsheu@tmc.edu.tw (M.-T. Sheu).

2. Materials and methods

2.1. Materials

Wood pulp, Temalfa 94[®], was obtained from Tembec Inc. (Canada). Avicel PH 301[®] (degree of polymerization (DP) \approx 165) and Avicel PH 101[®] (DP \approx 230) were obtained from FMC Corporation (Philadelphia, PA). Ringdex-B[®] β -cyclodextrin, NF) was supplied by Sanraku Corporation (Japan). Magnesium stearate was obtained from Mallinckrodt Corporation (Raleigh, NC).

2.2. Sample preparation

2.2.1. Preparation of MCC slurry

First, 400 g wood pulp was hydrolyzed in 3 l of 2.5 N HCl solution at 100°C for 60 min. The hydrolyzed product was then washed with distilled water until the pH value of the washing solution was near neutral, and no white precipitation appeared with the addition of 0.1 N AgNO₃ solution. The hydrolyzed product was next centrifuged to eliminate water. The final product which retained about 50.0 \pm 0.1% w/w of moisture was designated as the MCC slurry. The DP of this MCC slurry was about 230 and was measured according to NF 18.

2.2.2. Preparation of codried product of MCC with β -CD

The MCC slurry was blended with 20% w/w β -CD and mixed well by hand in a plastic bag. The mixtures were then transferred to a planetary mixer (KitchenAid Inc., Model K5SS, USA) and granulated with a fixed amount of water (54.5% w/w) at a speed set at no. 2 until homogeneous. The wet mass was next screened through a standard 30 mesh sieve, and the granules were dried at 60 \pm 1°C for 12 h. Dried granules were then milled and screened to retain the fraction between 60 and 150 μ m in size. Since water content has been reported to influence both the powder flowability and the compactibility of MCC, the water content of all

MCC samples and granules was controlled at around 3–5%, which is the optimal range for MCC [8].

2.2.3. Granulation and lubrication of Avicels and codried product

The codried product, Avicel PH 101, and Avicel PH 301 were individually granulated with a fixed amount of water (56.5% w/w) at the same conditions as described in the preparation of codried product. Dried granules were then milled and screened to retain three fractions of different particle size range: (a) 37–60 μ m; (b) 60–150 μ m; (c) 150–420 μ m. The original codried product, Avicel PH 101, and Avicel PH 301 were individually lubricated with three different percentages of magnesium stearate and mixed by hand in a plastic bag for 10 min. The percentages of magnesium stearate for lubricating were 0.2, 0.5, and 1.0%.

2.2.4. Powder physical properties

An ABD fine particle characteristics measuring instrument (Japan) was used for the determination of the bulk density, tapped density, and repose angle of the powders. Carr's index was calculated as the ratio of the difference between tapped density and bulk density to tapped density. The water content of the powder samples was determined using an Ohaus Moisture Determination Balance (Model MB200, Ohaus Co., USA). Coated with gold, the powder morphology was examined by scanning electron microscopy (SEM) at magnifications of 500 \times with a Hitachi S-2400 apparatus (Japan) using an accelerating voltage of 15 kV.

2.2.5. Tablet compression and physical properties

Tablets (9 mm concave) were compressed using various forces by a Carver laboratory press (Model C, Fred S. Carver Inc., USA). The movement of the press was set at a rising speed of 0.5 cm/s, and a dwelling time of zero was used during compression. A total weight of 250 mg was prepared for each tablet. Friability was evaluated by drop-

Table 1

Powder flowability and water content of various MCC products and their three different size fractions: (a) 37–60 μ m; (b) 60–150 μ m; (c) 150–420 μ m; obtained by wet granulation^a

	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Water content (% w/w)
Codried product	39.0 \pm 1.0	0.565 \pm 0.008	0.644 \pm 0.002	12.4 \pm 1.4	5.1 \pm 0.1
Codried product (a)	39.7 \pm 0.6	0.503 \pm 0.006	0.640 \pm 0.001	21.4 \pm 0.9*	5.3 \pm 0.1
Codried product (b)	35.0 \pm 0.5*	0.608 \pm 0.002	0.681 \pm 0.004	10.7 \pm 0.4*	4.9 \pm 0.1
Codried product (c)	36.7 \pm 0.6*	0.707 \pm 0.003	0.732 \pm 0.003	3.4 \pm 0.2*	4.4 \pm 0.1
Avicel 101	44.2 \pm 0.8	0.296 \pm 0.002	0.427 \pm 0.001	30.7 \pm 2.1	3.7 \pm 0.1
Avicel 101 (a)	44.7 \pm 0.7	0.363 \pm 0.015	0.504 \pm 0.010	28.0 \pm 1.8	3.8 \pm 0.0
Avicel 101 (b)	39.5 \pm 0.5*	0.434 \pm 0.006	0.526 \pm 0.003	17.5 \pm 0.8*	3.6 \pm 0.1
Avicel 101 (c)	38.0 \pm 0.0*	0.529 \pm 0.007	0.549 \pm 0.006	3.6 \pm 0.3*	3.5 \pm 0.1
Avicel 301	44.3 \pm 0.6	0.398 \pm 0.002	0.541 \pm 0.003	26.5 \pm 0.7	3.6 \pm 0.0
Avicel 301 (a)	40.2 \pm 0.3*	0.521 \pm 0.004	0.641 \pm 0.007	18.7 \pm 1.2*	4.2 \pm 0.0
Avicel 301 (b)	38.2 \pm 0.6*	0.631 \pm 0.007	0.705 \pm 0.004	10.5 \pm 0.5*	3.8 \pm 0.1
Avicel 301 (c)	38.2 \pm 0.8*	0.743 \pm 0.002	0.793 \pm 0.002	6.4 \pm 0.1*	3.0 \pm 0.1

^a All values are means \pm SD of three determinations; **P* < 0.05 vs. non-granulated MCC products.

Table 2

Crushing strength (Newton) of tablets produced from various MCC products and their three different size fractions: (a) 37–60 μm ; (b) 60–150 μm ; (c) 150–420 μm ; obtained by wet granulation^a

	Compression force (metric ton)			
	0.25	0.50	0.75	1.00
Codried product	282.1 \pm 23.6	\geq 300	\geq 300	\geq 300
Codried product (a)	273.5 \pm 32.8	293.9 \pm 25.2 ^b	\geq 300 ^b	\geq 300 ^b
Codried product (b)	228.0 \pm 20.3 ^c	276.3 \pm 31.9 ^{b,c}	\geq 300 ^b	\geq 300 ^b
Codried product (c)	186.9 \pm 18.3 ^c	211.2 \pm 28.8 ^{b,c}	263.4 \pm 12.3 ^{b,c}	286.6 \pm 14.3 ^b
Avicel 101	189.8 \pm 23.1	209.3 \pm 23.1 ^b	258.3 \pm 16.6 ^b	257.6 \pm 26.8 ^b
Avicel 101 (a)	202.0 \pm 22.5	229.1 \pm 20.0 ^{b,c}	269.2 \pm 15.4 ^b	292.3 \pm 26.2 ^{b,c}
Avicel 101 (b)	162.6 \pm 22.5 ^c	183.7 \pm 18.0 ^{b,c}	233.6 \pm 25.4 ^{b,c}	255.2 \pm 20.7 ^b
Avicel 101 (c)	166.0 \pm 15.2 ^c	164.0 \pm 22.3 ^c	206.1 \pm 17.0 ^{b,c}	209.2 \pm 25.5 ^{b,c}
Avicel 301	157.2 \pm 20.6	169.0 \pm 17.0	203.4 \pm 17.9	203.6 \pm 13.5
Avicel 301 (a)	151.7 \pm 19.4	191.7 \pm 25.8	205.0 \pm 43.8	234.3 \pm 25.0
Avicel 301 (b)	110.1 \pm 20.1	132.9 \pm 18.8	162.9 \pm 20.4	173.0 \pm 17.4
Avicel 301 (c)	73.9 \pm 16.6	97.1 \pm 11.8	107.5 \pm 12.8	124.4 \pm 16.9

^a All values are means \pm SD of ten determinations.

^b $P < 0.05$ vs. 0.25 metric ton of compression force for the individual sample.

^c $P < 0.05$ vs. non-granulated MCC products at the same compression force.

ping ten tablets 100 times in a Roche friabilator (Model AE-20, Aikho Engineering, Taiwan). Disintegration was examined according to the United States Pharmacopoeia (USP XXIII) with six tablets for a period of 30 min. Crushing strength was determined with a Pharma Test (PTB-311, Germany) and the average of ten tablets was reported.

2.3. Statistical methods

Statistical evaluation of powder flowability was performed using one-way ANOVA test, and $P < 0.05$ was considered to be statistically significant. Otherwise, the statistical evaluation of the crushing strength of tablets was performed using two-way ANOVA test. Differences

between treatments were tested using Newman–Keuls multiple comparison, and $P < 0.05$ was considered to be statistically significant. The WINKS 4.21 professional edition (TexaSoft Inc.) was used to carry out all statistical tests in this study.

3. Results and discussion

The influence of wet granulation on the powder properties of MCC samples was examined, and the results are listed in Table 1. The powder flowability was evaluated by the angle of repose and Carr index, where smaller values of both parameters indicate better flowability. The angle of repose

Table 3

Disintegration of tablets produced from various MCC products and their three different size fractions: (a) 37–60 μm ; (b) 60–150 μm ; (c) 150–420 μm ; obtained by wet granulation^a

	Compression force (metric ton)			
	0.25	0.50	0.75	1.00
Codried product	I (2.3 \pm 0.6) ^b	I (4.6 \pm 1.5)	I (8.8 \pm 1.3)	I (10.9 \pm 1.9)
Codried product(a)	II	II	II	II
Codried product (b)	I (2.0 \pm 1.1)	I (3.6 \pm 1.7)	I (6.4 \pm 2.2)	I (9.7 \pm 2.9)
Codried product (c)	I (1.1 \pm 0.2)	I (1.9 \pm 0.4)	I (3.6 \pm 1.6)	I (7.3 \pm 2.0)
Avicel 101	VI	VI	VI	VI
Avicel 101 (a)	III	IV	V	II
Avicel 101 (b)	II	II	II	II
Avicel 101 (c)	II	I (5.2 \pm 2.7)	II	II
Avicel 301	I (3.3 \pm 2.5)	I (8.1 \pm 1.8)	I (11.2 \pm 7.6)	II
Avicel 301 (a)	II	II	II	II
Avicel 301 (b)	I (14.4 \pm 5.6)	II	II	II
Avicel 301 (c)	I (1.2 \pm 0.3)	I (3.4 \pm 1.7)	I (3.2 \pm 1.5)	I (5.2 \pm 2.2)

^a Criteria: (I) Completely disappears within 30 min; (II) disintegrates to more than five pieces at 30 min; (III) disintegrates to equal or less than four pieces at 30 min; (IV) disintegrates to two pieces within 30 min; (V) one or two small pieces separate from tablet within 30 min; (VI) intact tablet within 30 min.

^b Values in parentheses indicate the time (min, mean \pm SD) required to disintegrate completely.

Table 4

The powder flowability of various MCC products mixed with three different percentages of magnesium stearate: (1) 0.2%; (2) 0.5%; (3) 1.0%^a

	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)
Codried product	39.0 ± 1.0	0.565 ± 0.008	0.644 ± 0.002	12.4 ± 1.4
Codried product (1)	34.7 ± 0.6 ^b	0.693 ± 0.002	0.760 ± 0.002	8.9 ± 0.1 ^b
Codried product (2)	34.7 ± 0.3 ^b	0.686 ± 0.002	0.750 ± 0.002	8.6 ± 0.3 ^b
Codried product (3)	36.0 ± 1.0 ^b	0.691 ± 0.000	0.749 ± 0.001	7.7 ± 0.1 ^b
Avicel 101	44.2 ± 0.8	0.296 ± 0.002	0.427 ± 0.001	30.7 ± 2.1
Avicel 101 (1)	45.3 ± 0.3	0.366 ± 0.002	0.478 ± 0.001	23.4 ± 0.6 ^b
Avicel 101 (2)	44.2 ± 1.0	0.378 ± 0.004	0.482 ± 0.002	21.5 ± 1.1 ^b
Avicel 101 (3)	45.7 ± 0.6	0.386 ± 0.008	0.484 ± 0.001	20.2 ± 1.4 ^b
Avicel 301	44.3 ± 0.6	0.398 ± 0.002	0.541 ± 0.003	26.5 ± 0.7
Avicel 301 (1)	47.5 ± 0.5 ^b	0.532 ± 0.011	0.640 ± 0.007	16.9 ± 2.5 ^b
Avicel 301 (2)	43.8 ± 0.3	0.567 ± 0.001	0.655 ± 0.004	13.5 ± 0.6 ^b
Avicel 301 (3)	43.7 ± 0.8	0.553 ± 0.004	0.648 ± 0.002	14.6 ± 0.8 ^b

^a All values are means ± SD of three determinations.^b *P* < 0.05 vs non-lubricated MCC products.

of all MCC samples decreased after wet granulation, and the extent of reduction was proportional to the increase of particle size. In addition, Carr index decreased with increasing particle size for all MCC samples after wet granulation. The one-way ANOVA test of Carr index demonstrated that powder flowability of the codried product, Avicel PH 101 and 301 changed significantly after wet granulation (*P* < 0.001). Among them, the powder flowability of Avicel PH 301 after wet granulation did not only increase, but also significantly increased with increasing particle size. For Avicel PH 101, only the two bigger size fractions showed a significant improvement of powder flowability. On the contrary, the powder flowability of the smallest size fraction of codried product became statistically worse. Therefore, the powder flowability of codried product and Avicels could be improved after wet granulation by selecting size fractions of particles bigger than 60 μm.

It is well known that powder flowability is size-dependent and can be characterized by the angle of repose and Carr index. As the particle size increased, the total surface area decreased accompanied by a reduction of friction force between particles, thus increasing powder flowability. Correspondingly, the packing of particles into a dense structure was easier for those particles with better flowability, resulting in a higher bulk density and a smaller increase of tapped density. Since that, the decrease of Carr index for all samples is probably due to the increase in bulk density exceeding the increase in tapped density. Therefore, we concluded that the improvement of powder flowability after wet granulation for all samples was mainly due to the change of particle size.

The crushing strengths of tablets produced from original samples of codried product, Avicel PH 101 and Avicel PH 301 and their granules after wet granulation are shown in

Table 5

Crushing strength (Newton) of tablets produced from various MCC products and their lubricated powders with three different percentages of magnesium stearate: (1) 0.2%; (2) 0.5%; (3) 1.0%^a

	Compression force (metric ton)					
	0.25	0.50	0.75	1.00	2.00	4.00
Codried product	282.1 ± 23.6	≥ 300	≥ 300	≥ 300	–	–
Codried product (1)	ND	13.8 ± 1.4 ^b	–	17.7 ± 3.7 ^{b,c}	21.7 ± 3.3 ^{b,c}	24.2 ± 3.7 ^{b,c}
Codried product (2)	ND	0 ^b	–	0 ^b	14.3 ± 1.4 ^{b,c}	14.0 ± 1.7 ^{b,c}
Codried product (3)	ND	0 ^b	–	0 ^b	0 ^b	0 ^b
Avicel 101	189.8 ± 23.1	209.3 ± 23.1 ^c	258.3 ± 16.6 ^c	257.6 ± 26.8 ^c	–	–
Avicel 101 (1)	155.4 ± 14.4 ^b	170.4 ± 5.1 ^{b,c}	202.3 ± 6.1 ^{b,c}	211.2 ± 7.0 ^{b,c}	–	–
Avicel 101 (2)	107.0 ± 5.4 ^b	113.7 ± 3.8 ^b	130.0 ± 7.5 ^{b,c}	134.9 ± 3.7 ^{b,c}	–	–
Avicel 101 (3)	75.4 ± 3.6 ^b	80.7 ± 4.0 ^b	88.5 ± 3.7 ^b	97.6 ± 5.6 ^{b,c}	–	–
Avicel 301	157.2 ± 20.6	169.0 ± 17.0 ^c	203.4 ± 17.9 ^c	203.6 ± 13.5 ^c	–	–
Avicel 301 (1)	78.9 ± 7.5 ^b	92.0 ± 4.5 ^{b,c}	100.3 ± 3.9 ^{b,c}	105.1 ± 6.2 ^{b,c}	–	–
Avicel 301 (2)	40.6 ± 2.1 ^b	43.3 ± 2.7 ^b	48.9 ± 3.9 ^b	51.8 ± 2.9 ^{b,c}	–	–
Avicel 301 (3)	37.9 ± 2.0 ^b	42.7 ± 2.6 ^b	47.2 ± 3.4 ^b	49.0 ± 2.5 ^{b,c}	–	–

^a All values are means ± SD of ten determinations. ND, no available tablets for determination.^b *P* < 0.05 vs. non-granulated MCC products at the same compression force.^c *P* < 0.05 vs. the lowest compression force for each individual sample.

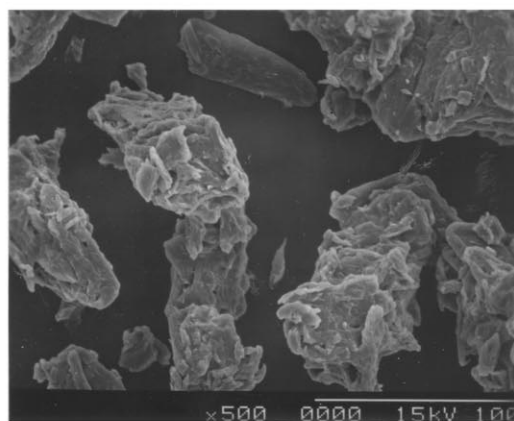
Table 2. According to the results of two-way ANOVA test, both decreasing particle size of granules and increasing compression force significantly increased the crushing strength of tablets ($P < 0.001$) for codried product and Avicels. Compared to Avicels, the original codried sample produced the hardest tablets at each compression force, and tablet strength was relatively strong for the codried sample after wet granulation. The friability being close to 0% for all tablets produced from codried product and Avicels with or without granulation (data not shown) is also a reflection of excellent compactibility.

Since the primary compression mechanism of MCC is plastic deformation, bigger granules provide less bonding surface area and result in weaker tablets [1,9]. Moreover, the compressibility (yield pressure) of a given material deformed plastically does not change by varying particle size fractions [10]. It means that the deformation mechanism of MCC is independent on particle size. The reduction of tablet strength merely comes from the lowering of bonding surface area. As discussed in a previous paper, β -CD might play an important role as a binder in tablet strength [7]. It illustrated that the codried sample made with MCC slurry and β -CD had better compactibility. Therefore, the crushing strength of tablets produced from the biggest particle size fraction (c) of codried sample after granulation was comparable to that from original Avicel PH 101 and was stronger than that from original Avicel PH 301, even that the decrease of tablet strength with increasing particle size was also observed for the codried sample after wet granulation.

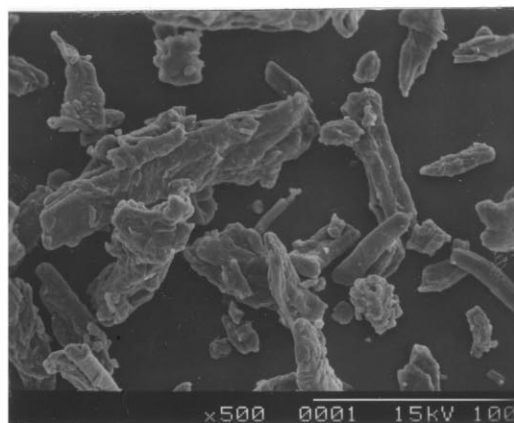
As shown in Table 3, the higher the compression force, the lower the tendency for tablets to disintegrate no matter which type of MCC was used. The disintegration of tablets produced with the codried sample was rapid and was improved after wet granulation by selecting the biggest particle size fraction (c). However, the disintegration of tablets produced with the smallest particle size fraction (a) was worse than the non-granulated codried sample as well as other fractions. On the other hand, the disintegration of tablets produced directly from Avicel PH 101 was very poor. Nevertheless, the disintegration of PH 101 was improved after wet granulation for all three size fractions, and the extent of improvement increased significantly with increasing particle size. The disintegration of tablets produced directly from PH 301 was fairly rapid. It did not change significantly after wet granulation except for the biggest particle size fraction (c).

For a plastically deformed material of MCC, new surface area generated during tableting is limited. Therefore, the total surface area of MCC powder is a determinant factor for crushing strength, and in turn for disintegration of the tablet. The selection of a bigger particle size fraction for tableting provides less bonding surface area. Therefore, the crushing strength of tablets decreased with an increase in the particle size of granulated Avicel PH 101, the same as with the disintegration time of tablets. On the other hand, the crushing strength of tablets produced from PH 301 was

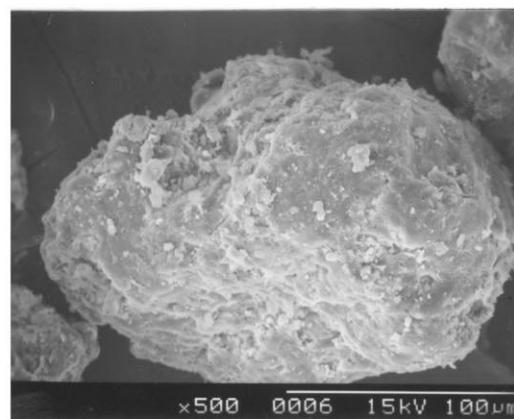
lower than that of tablets from PH 101 making them disintegrate more rapidly. According to preliminary studies of a codried product of MCC slurry with β -CD, the water-solubility property of β -CD combined with the swelling prop-



(A) Avicel PH 101



(B) Avicel PH 301



(C) Codried product

Fig. 1. SEM photographs of granules of individual and codried MCC samples. (A) Avicel PH 101; (B) Avicel PH 301; (C) codried product.

Table 6

Friability (%) of tablets produced from various MCC products lubricated with three different percentages of magnesium stearate: (1) 0.2%; (2) 0.5%; (3) 1.0%

	Compression force (metric ton)					
	0.25	0.50	0.75	1.00	2.00	4.00
Codried product (1)	ND ^a	90.11	–	0.30	0.21	0.00
Codried product (2)	ND	100.00	–	100.00	100.00	70.24
Codried product (3)	ND	100.00	–	100.00	100.00	100.00
Avicel 101 (1)	0.00	0.00	0.00	0.00	–	–
Avicel 101 (2)	0.00	0.00	0.00	0.00	–	–
Avicel 101 (3)	0.10	0.05	0.08	0.01	–	–
Avicel 301 (1)	0.00	0.00	0.00	0.00	–	–
Avicel 301 (2)	0.25	0.15	0.16	0.08	–	–
Avicel 301 (3)	0.24	0.22	0.21	0.24	–	–

^a ND, no available tablets for determination.

erty of MCC made this codried product disintegrate rapidly [7]. Fraction (a), which presented the worst case of disintegration among the granulated codried samples, was an exception and this might be attributed to its smallest particle size. Generally, as the particle size was reduced to the range of fraction (a), the resulting tablets possessed lower porosity. The surface structure of tablets might become so compact that water penetration into tablets for inducing disintegration was hindered.

This study on the wet granulation of MCC confirms results previously reported by other groups [2,3]. The wet granulation of MCC significantly increased the powder flowability and improved the disintegration of the produced tablets but also decreased the compactibility of MCC with the selection of the bigger particle size fractions. However, the codried excipient after wet granulation still had better

compactibility than did the non-granulated Avicel PH 101 and 301, and the powder flowability was significantly improved when the particle size of granules exceeded 60 μm . Therefore, the codried excipient seemed to be a better choice in wet granulation than did the Avicels.

Table 4 shows the flowability of codried product, Avicels, and their lubricated powders. According to the one-way ANOVA test, the addition of magnesium stearate significantly improved powder flowability of codried product and Avicels as indicated by a lower Carr index value ($P < 0.001$). However, the angles of repose of Avicel 101 and 301 were not influenced. On the contrary, the angle of repose of the codried sample was significantly reduced ($P < 0.001$) after lubrication. As shown in Fig. 1, the codried sample displayed more regular particles compared to the irregular shape of Avicels. This may be the reason why the codried excipient was coated more completely by an equal amount of magnesium stearate resulting in a significant reduction in the angle of repose.

The crushing strength of tablets decreased when codried product and Avicels were lubricated with magnesium stearate (Table 5). The reduction of compactibility due to the lubrication of magnesium stearate was especially serious for the codried excipient. Hence, the compression force of 0.25 metric ton was not sufficient enough to produce the tablets for the lubricated codried products. As the percentage of magnesium stearate increased to 1%, all the produced tablets had crushing strengths below the limit of measurement even at 4 metric tons of compression force. Accompanying the decrease of crushing strength, the friability of tablets increased correspondingly when the Avicels were lubricated. Further, as shown in Table 6, the codried excipient was very sensitive to magnesium stearate and resulted in 100% friability when the addition of magnesium stearate exceeded 0.5%.

Table 7

Disintegration of tablets produced from various MCC products and their lubricated powders with three different percentages of magnesium stearate: (1) 0.2%; (2) 0.5%; (3) 1.0%^a

	Compression force (metric ton)					
	0.25	0.50	0.75	1.00	2.00	4.00
Codried product	I (2.3 \pm 0.6) ^b	I (4.6 \pm 1.5)	I (8.8 \pm 1.3)	I (10.9 \pm 1.9)	–	–
Codried product (1)	ND	I (0.6 \pm 0.0)	–	I (1.4 \pm 0.0)	I (1.1 \pm 0.0)	I (1.1 \pm 0.0)
Codried product (2)	ND	I (0.8 \pm 0.0)	–	I (0.9 \pm 0.0)	I (1.0 \pm 0.0)	I (1.1 \pm 0.0)
Codried product (3)	ND	I (2.3 \pm 0.0)	–	I (2.6 \pm 0.0)	I (2.7 \pm 0.0)	I (3.0 \pm 0.0)
Avicel 101	VI	VI	VI	VI	–	–
Avicel 101 (1)	IV	IV	IV	VI	–	–
Avicel 101 (2)	II	II	IV	IV	–	–
Avicel 101 (3)	II	II	III	III	–	–
Avicel 301	I (3.3 \pm 2.5)	I (8.1 \pm 1.8)	I (11.2 \pm 7.6)	II	–	–
Avicel 301 (1)	I (0.6 \pm 0.2)	I (0.5 \pm 0.3)	I (1.2 \pm 0.6)	I (1.6 \pm 0.6)	–	–
Avicel 301 (2)	I (0.1 \pm 0.0)	I (0.3 \pm 0.0)	I (0.4 \pm 0.0)	I (0.5 \pm 0.0)	–	–
Avicel 301 (3)	I (0.3 \pm 0.0)	I (0.5 \pm 0.0)	I (0.6 \pm 0.0)	I (0.9 \pm 0.0)	–	–

^a Criteria: (I) Completely disappears within 30 min; (II) disintegrates to more than five pieces at 30 min; (III) disintegrates to equal or less than four pieces at 30 min; (IV) disintegrates to two pieces within 30 min; (V) one or two small pieces separate from tablet within 30 min; (VI) intact tablet within 30 min.

^b Values in parentheses indicate the time (min, mean \pm SD) required to disintegrate completely. ND, no available tablets for determination.

The dramatic decline in crushing strength of tablets produced from codried samples after lubrication was also attributed to particle morphology. Generally speaking, the irregular particle shape of MCC plays an important role in the mechanical interlocking between particles during tableting. Furthermore, the irregular particle shape also means a large particle surface which is important for interparticular bonding. The more regular particles of codried excipient, however, cannot provide such efficient bonding mechanisms. Instead, the bonding between the surfaces of particles of codried product might be attributed to the adhesion provided by β -CD as discussed in a previous report [7]. We expected the formation of a hydrophobic film on the surface of particles by magnesium stearate during lubrication to be easier for rounded particles of the codried sample than the irregularly shaped ones of Avicels. Therefore, the hindrance of bonding by the formation of a hydrophobic film after lubrication resulted in reduced crushing strength and increased friability of tablets to a greater extent in codried excipient than in Avicels.

The disintegration of tablets (Table 7) also reflected the change of crushing strength of tablets. The lower crushing strength made tablets disintegrate more rapidly. The disintegration of tablets for all Avicels and codried excipient increased after lubrication with magnesium stearate as well. Since the bonding between particles of MCC was significantly hindered by the hydrophobic film, the decrease of tablet strength led to the promotion of the disintegration of tablets.

In conclusion, wet granulation significantly increased powder flowability and disintegration of the codried excipient. In addition, the compactibility of the codried excipient after granulation was still better than the non-granulated Avicel PH 101 and 301. Therefore, the codried excipient seemed to be a better excipient of choice in wet granulation.

On the other hand, the lubrication method by addition of magnesium stearate also improved powder flowability of the codried excipient. However, due to the rounder shape of particles, the codried excipient was more sensitive to magnesium stearate and produced weaker tablets than did Avicels.

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