DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(6), 643-661 (1995)

RESEARCH PAPERS

MORPHOLOGICAL, PACKING, FLOW AND TABLETING PROPERTIES OF NEW AVICEL TYPES

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ABSTRACT

The six Avicel products designed for compression - the classical grades PH-105, PH-103, PH-101 and PH-102, and the new Avicels PH-112 and PH-200 - have been submitted to a comparative investigation for both their basic and tableting properties. According to the manufacturer all these products differ by their nominal particle size and moisture content.

Basic properties of the powders were first determined, namely moisture content (loss on drying and Karl Fischer titration), particle size and shape (sieving and image analysis), densities (true bulk and tap densities, Hausner ratio) and flow properties (vibratory hopper technique).

As tableting properties, the compactibility of the powders and the effect of adding a hydrophobic lubricant (0.5% magnesium stearate) on the compact strength were evaluated by preparing compacts at a given applied pressure using a hydraulic press. Weight and dimensional variations were assessed by

Note: The symbols for registered names and trademarks have been systematically omitted for sake of simplicity.

preparing tablets at a target crushing strength of 70 Newtons on a high speed machine.

The comparison of the conventional Avicel PH grades showed that Avicel PH-105 differed markedly in its properties (high compressibility on tapping, high compactibility, inacceptable tablet weight variability and very poor disintegrating properties) from the other grades.

As to the two new Avicel PH grades, conflicting results with the literature were obtained with the low-moisture product Avicel PH-112. We observed, like other authors but in contrast to manufacturer's data, values of compactibility and strength reduction ratio upon lubrication as well as of the coefficient of tablet weight variation similar to those of the standard Avicel PH-102, of comparable particle size.This can be certainly explained by an uptake of moisture of the Avicel PH-112 powder as proved experimentally. This would limit the use of this material to an air-conditioned room.

The large particle size product Avicel PH-200 displayed a compactibility close to that of all the other Avicel PH grades (except PH-105), but the highest susceptibility to magnesium stearate. As expected, because it is free-flowing, Avicel PH-200 gave the lowest tablet weight variability. Additionnally, the two new grades showed disintegrating properties similar to those of Avicel PH-103, PH-102 and PH-101. Finally, one should bear in mind that the small differences reported here may not be significant because of substantial inter-batch variability.

INTRODUCTION

The preparation of microcrystalline cellulose (MCC) has been patented in the beginning of the 1960s by Battista and Smith of the American Viscose Company (1) and MCC has been put on the market as a pharmaceutical tableting excipient in 1963 under the trade name Avicel® (it is now sold by the FMC Corp.). Since then, its tableting properties, especially as a dry binder for direct compression, have been extensively investigated. Some of these studies compare the standard Avicel product with other types of Avicel and since the 1980s with generic products (see ref. 2 for a complete review of the subject).

For more than 20 years, only four Avicel grades were available for direct compression. These four grades were obtained by varying the hydrolysis, shearing and drying conditions :

- Avicel PH-101 has typically an average particle size of 50 µm and a maximum moisture content of 5%,
- Avicel PH-102 has a larger average particle size (100 µm) than that of Avicel PH-101 but a similar moisture content,
- Avicel PH-103 has an average particle size similar to that of Avicel PH-101 (50 µm) but a lower moisture content (max. 3%),
- Avicel PH-105 has a smaller average particle size (20 µm) than Avicel PH-101 but a similar water content.

Precise particle size distributions of these products can be found for instance in references 3 to 6. Though a controversial subject, all these Avicel PH products, with perhaps the exception of Avicel PH-102, suffer from poor flow properties. Further, and with the exception of Avicel PH-103, their water content is too high for making tablets containing water-sensitive drugs.

To remedy these drawbacks, two new Avicel PH grades were launched these last years :

- Avicel PH-112, having the typical particle size specifications of Avicel PH-102 (100 µm) but very low moisture content (max. 1.5%) which makes it an ideal excipient for moisture-sensitive substances (for this reason Avicel PH-112 was first named Avicel PH-102 SLM, Special Low Moisture),
- Avicel PH-200 having a larger average particle size (200 µm) than Avicel PH-102, but a similar moisture content, was designed for improved flow.

The aim of this work was to examine the properties of these new excipients (moisture content, morphology, packing, flowability) of importance for tableting and to relate these properties to the tableting performance of these new excipients (compactibility, susceptibility to hydrophobic lubricants and tablet weight variation). As MCC is known to possess disintegrating properties, the disintegration time of the tablets was also determined. The four conventional Avicel PH products were included in the study to judge the significance of the differences observed with the two new grades.

MATERIALS

The six Avicel PH grades were used as received from the supplier (FMC Corp., Brussels, Belgium) : Avicel PH-101 (lot N° 1715), Avicel PH-102 (lot N° 7236), Avicel PH-103 (Lot N° 8036), Avicel PH-105 (lot N° 5005), Avicel PH-112 (lot N° 9111) and Avicel PH-200 (lot N° X129). Magnesium stearate was purchased from Siegfried (Zofingen, Switzerland).

METHODS

Basic powder characteristics

Moisture content was checked by two methods. The loss on drying was determined according to the NF monograph on microcrystalline cellulose (3 hrs at 105°C) and the water content was measured by the Karl Fischer method (Metrohm type 633, Herisau, Switzerland) using the one-component Hydranal Composite 5 reagent (Riedel-de-Hahn, Hannover, Germany).

Size parameters were assessed using sieving, optical microscopy and scanning electron microscopy. Particle size distribution was first checked in duplicate using air-jet sieving (Alpine 200, Augsburg, Germany). The weight geometric mean diameter, d_{gw}, and geometric standard deviation, σ_g, were obtained from log-normal plots, and the arithmetic volume-surface mean diameter, d_{vs}, was calculated using the appropriate Hatch-Choate equation to facilitate comparison with published data.

Both size and shape of the particles were determined using a Wild M3Z macroscope (Heerbrugg, Switzerland) coupled to a MicroScale TC image analyzer (Digithurst, Royston, U.K.). Four parameters were calculated :

- the average projected area diameter, d_p
- the elongation ratio, defined as the quotient of the maximum diameter to the minimum diameter (7)
- the circularity, K, defined as (8) : $K = 4\ \pi\ \text{area} / (\text{perimeter})^2$ (Eq. 1)
- the circularity, C, defined as (9) : $C = 4\ \text{area} / (\pi\ d^2_{max})$ (Eq. 2)

where d_{max} is the maximum diameter.

Scanning electron micrographs of the powders coated with gold were taken at a magnification of 600 X with a Jeol JSM-6400 apparatus (Tokyo, Japan) using an accelerating voltage of 15 kV.

The true density was measured with the model 930 air comparaison pycnometer Beckman (Fullerton, USA). Determination of the bulk density and tap density was carried out in a 25-ml graduated cylinder using 6.0 g of material. The bulk density was calculated from the volume of powder after turning over the cylinder and the tap density was obtained from the volume after 100 tamps in the JEL volumenometer, model STAV 2003 (Engelsmann, Ludwigshafen, Germany). The Hausner ratio (10) was calculated from the quotient of tap to bulk density.

As only Avicel PH-200 was a free-flowing material, a vibratory hopper technique was used. A DIN 12445 glass funnel with an efflux tube of 8 mm internal diameter and 10 cm length was fixed to a vibratory sieving apparatus (Fritsch Analysette, Idar-Oberstein, Germany).

When set on intensity 6, a regular flow was observed for all Avicel grades except Avicel PH-105 which did not pass through the orifice. The flow rate was calculated from the time necessary for 50 g to pass through the funnel. Packing and flow properties were determined at least in triplicate.

Tableting and tablet characteristics

The study was carried out in two parts. Firstly, the compactibility of the powders and their sensitivity to a model hydrophobic lubricant were examined by preparing flat 12-mm diameter compacts with a hydraulic press (Specac, Sidcup, U.K.). A quantity of powder corresponding to a 2-mm thick compact at zero theoretical porosity was manually filled into the unlubricated die and compressed at 100 MPa during 10 seconds.

The same operation was repeated with the powders mixed with 0.5% magnesium stearate for 5 min (Turbula type T2A, W.A. Bachofen, Basle, Switzerland) at 25 r.p.m.

The diametral crushing force of those compacts was measured with a universal testing machine (Schenck-Trebel, type RM 50, Darmstadt, Germany) at a strain rate of 3 mm/min. The result are the mean values of 10 compacts. As index of the lubricant sensitivity a strength reduction ratio was calculated, defined as the quotient of the compact tensile strength with and without the magnesium stearate addition (11).

The second part of the study consisted in preparing flat bevel-edged 8 mm diameter tablets with a breakline on a high speed 27-station rotary tableting machine (Manesty Unipress, U.K.), equiped with a forced feeding system and a compaction force monifor, and operating at 1400 tablets/min (12). A weight of 160 mg and a diametral crushing force of 70 N were targeted and the force necessary to prepare the tablets was estimated with the compaction force monitor.

The mean weight and the coefficient of weight variation of the tablets were determined by weighing 30 tablets (Mettler AE163, Greifensee, Switzerland). The same tablets were also characterized for their uniformity of thickness and diameter. Porosity of the tablets was calculated from their dimensions at ejection and from the true density of the materials.

The mean diametral crushing force and its coefficient of variation were measured on 10 tablets using the Heberlein hardness tester (Schleuniger, Zürich, Switzerland).

The friability was determined from the weight loss of 20 tablets trumbled 100 revolutions in a TAB Erweka friabilator (Heusenstamm, Germany). As a complement, disintegration testing was performed at 37°C in water using the EP/USP apparatus (Sotax DT-3, Basle, Switzerland). Six tablets were examined with the disks and six others without the disks. The reported disintegration times are the times when the sixth tablet of the test disintegrated. For all tests a delay of at least 24 hrs was respected before any measurement.

RESULTS AND DISCUSSION

Basic powder characteristics

The parameters related to the particle size and shape of the six Avicel PH grades tested are given in Table 1. Grades are listed by increasing order of particle size.

As expected, big differences in particle size, both by sieving and microscopy, were found between the various Avicel PH grades. Some discrepancies are also noticeable with published data obtained using the same analytical methods but the data obtained are either unreliable or the experimental conditions were inadequately described. Thus, values of "median" particle size were calculated from air jet sieving for Avicel PH-105 (17.5 µm), Avicel PH-101 (40 µm) and Avicel PH-102 (83 µm) by Roberts and Rowe (5). Excessively high values of weight geometric mean diameter were published for the Avicel grades PH-105, PH-103, PH-101 and PH-102 (6) and for Avicel PH-112 (181 µm) and Avicel PH-200 (213 µm) (13). This was obviously due to the sieving technique used. Median diameters were also given by Pande and Shangraw (14) for Avicel PH-103 (79 µm), Avicel PH-102 (83 µm) and Avicel PH-112 (98 µm) using a Bradley Sonic Sifter apparatus. Finally an "average" particle size of 94 µm was found for Avicel PH-102 and 188 µm for Avicel PH-200, when using a Ro-Tap sieve shaker (15).

It is well established that the sieving method much affects the results. For instance we obtained in another study (16) d_{VS} values as different as 69 and 108 µm for Avicel PH-101, 85 and 144 µm for Avicel PH-102 and 118 and 161 µm for Avicel PH-200 when using respectively air jet sieving (Alpine) and

TABLE 1
Micromeritic Data of the Various Avicel PH Grades

Material	Sieving			Microscopy				
	d_{gw} (µm)	σ_g	d_{vs} (µm)	d_p (µm)	d_{max} (µm)	Elongation ratio	Circularity K	Circularity C
Avicel PH-105	37	1.25	36	-[1]	-[1]	-[1]	-[1]	-[1]
Avicel PH-103	64	1.46	60	25	40	1.94	0.73	0.74
Avicel PH-101	60	1.61	54	41	7	2.39	0.74	0.55
Avicel PH-102	87	1.63	77	42	66	2.07	0.70	0.70
Avicel PH-112	85	1.59	77	30	48	1.90	0.77	0.73
Avicel PH-200	145	1.95	116	65	96	2.02	0.80	0.60

[1] Could not be determined because the powder could not be properly disaggregated.

vibratory sieving (Fritsch). In the authors' opinion, only carefully selected sieving methods (such as air jet sieving or possibly Ro-Tap) can provide "clean" size fractions and consequently reliable results. When examining d_{gw} or d_{vs} values pesented in Table 1, only Avicel PH-105 and Avicel PH-200 differ significantly from the other grades. Additionnaly, Avicel PH-200 shows the widest size distribution of all samples, as evidenced by the highest σ_g value calculated.

Optical microscopy gives size parameters related to the projected diameter which of course differs from the equivalent sieve diameter (Table 1). It also provides information on the shape of the particles. In this respect, all grades have close elongation ratios and circularity values, with Avicel PH-101 having slightly the highest asymmetry as demonstrated by the SEM pictures shown on Figure 1. Incidentally, note that the circularity as defined by Eq. 2 seems more discriminating than when calculated using Eq. 1.

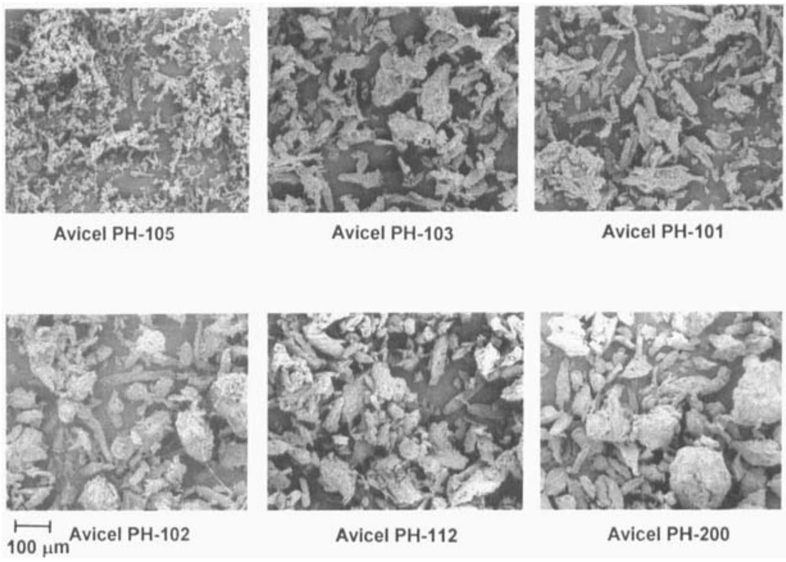

FIGURE 1

Scanning electron micrographs of the Avicel PH grades

Table 2 presents the moisture contents, densities and flow rates of the various powder samples. Loss on drying values comply with the NF requirement (max. 5%), but the two "low-moisture" grades were beyond the manufacturer's specifications, namely Avicel PH-103 (LOD > 3%) and Avicel PH-112 (LOD > 1.5%). Karl Fischer data confirmed the loss on drying values, suggesting that all bound and free water was probably measured. Note that the values quoted for these two materials by the two batch certificates of analysis comply with the manufacturer's specifications. This discrepancy, which is due to the hygroscopicity of MCC, certainly comes from the fact that the moisture content was measured at the time of compression and not directly at the opening of the container.

True densities are in agreement with published values and are quite close. In contrast, packing and flow properties differ significantly among products. Quite logically, the order of flow rates inversely rank that of Hausner ratios, with Avicel PH-105 and Avicel PH-200 showing extreme values.

TABLE 2

Moisture Contents, Densities and Flow Rates of the Various Avicel PH grades

Material	Moisture content		True density (g/cm^3)	Bulk density (g/cm^3)	Tap density (g/cm^3)	Hausner ratio	Flow rate (g/s)
	LOD[1] (%)	K.-F.[2] (%)					
Avicel PH-105	2.0	1.9	1.52	0.308	0.545	1.77	-[3]
Avicel PH-103	3.6	3.0	1.57	0.316	0.480	1.52	2.4
Avicel PH-101	4.9	5.0	1.54	0.293	0.461	1.57	2.2
Avicel PH-102	4.1	4.3	1.52	0.324	0.480	1.40	9.6
Avicel PH-112	2.9	2.5	1.52	0.343	0.480	1.40	9.6
Avicel PH-200	3.2	3.3	1.54	0.375	0.480	1.28	13.3

[1] Loss on drying (the manufacturer's certificates of analysis give respectively 2.8, 2.0, 3.6, 4.0, 1.2 and 2.8% for these six Avicel PH samples); [2] Karl-Fischer, [3] No flow at all in the condition used.

Compactibility and sensitivity to lubricant

Porosities and tensile strengths of the compacts prepared with pure Avicel or added with 0.5% magnesium stearate using the hydraulic press are presented inTable 3.

To better visualize the effect of the lubricant, Figure 2 shows histograms of the crushing forces of the same compacts together with numbers, which are the strength reduction ratios as proposed by Duberg and Nyström (11).

When looking first at the compactibility of pure materials (both crushing forces and tensile strengths), the strongest compacts were obtained with the finest powder (Avicel PH-105). Differences between other grades were so small that they can be considered of identical compactibility when taking into account for instance the well-known inter-batch variability or the inaccuracy when measuring the true density of the materials, which conditions the weight of powder used. Anyway, a general effect of the particle size could not be observed, because other factors may play a role in compactibility, some of

TABLE 3

Porosities and Tensile Strengths of the Compacts Prepared at 100 MPa Using Pure and Lubricated Materials

Material	Without lubricant		With 0.5% magnesium stearate	
	Porosity (%)	Tensile strength (MPa)	Porosity (%)	Tensile strength (MPa)
Avicel PH-105	17.5	7.00	16.1	7.03
Avicel PH-103	21.1	4.73	20.3	4.39
Avicel PH-101	17.1	5.04	16.7	4.92
Avicel PH-102	16.7	5.40	15.5	4.53
Avicel PH-112	17.8	5.29	16.7	4.43
Avicel PH-200	18.8	4.97	17.7	2.48

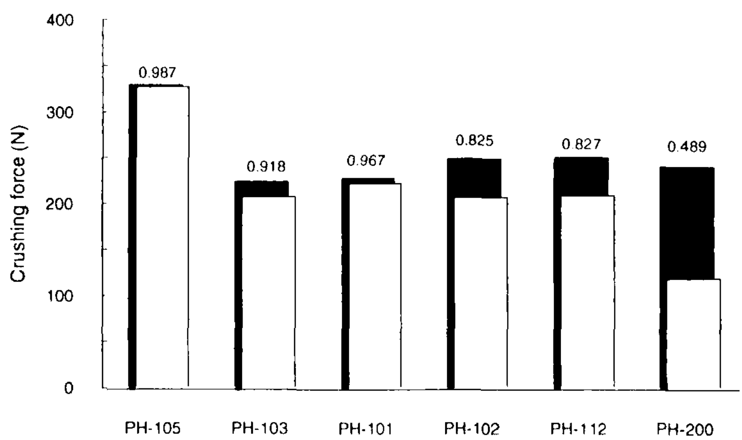

FIGURE 2
Diametral crushing force values for compacts prepared at 100 MPa from unlubricated (shaded areas) and lubricated (unshaded areas) Avicel PH powders. Numbers are for strength reduction ratios.

them being related to the material itself and others to the operating conditions. In the first category of factors for example, the effect of the degree of crystallinity has been demonstrated (17). Moisture content also influences the compactibility of MCC as noted by many authors (18-21) which report varying optimal water contents, but moisture levels measured in this work are not as different as those obtained by these authors. Actually, these factors and others may contribute to the variability of a given grade. In fact, inter-batch variability has been observed for MCC. For instance, we noted very important differences in compactibility between batches of Avicel PH-101 or Avicel PH-102 as well as for other generic materials (12).

The second type of factors influencing the compactibility of materials to consider, are those related to the compaction procedure, i.e. the magnitude and rate of applied load, which, together with the inter-batch variability, makes it difficult to compare our results with those obtained by other authors. As far as we know, no work actually reports on the six materials studied here. Sixsmith (3) compared the four basic types and found superior compactibility for Avicel PH-105, the other materials being quite similar but showing some small inversions of rank order, depending on the pressure applied. At 37.5 MPa, Vromans et al. (22) also obtained harder compacts with Avicel PH-105, Avicel PH-101 being slighthy better than Avicel PH-102. As far as the two new grades are concerned, Pande and Shangraw (14) observed the rank order Avicel PH-102 > Avicel PH-103 > Avicel PH-112 at four different applied loads. In this case, the loss on drying of Avicel PH-103 was very low (1.07%), in conformity with the manufacturer's specifications. Erkoboni et al. (15) found no significant differences between Avicel PH-102 and Avicel PH-200 at four compression forces. Finally, Munoz-Ruiz et al. (13) observed at a 3 kN applied force very close compactibilities for Avicel PH-112 and Avicel PH-200. Thus, both series of results (13,15) are in accordance with our data for Avicel PH-200. In contrast, our data and those of Munoz-Ruiz et al. (13) concerning Avicel PH-112 contradict those of Pande et al. (14). Munoz-Ruiz et al. (13), like us, certainly used a sample with a moisture content (no value is given) above the manufacturer's limit (1.5%). Avicel PH-112, when exposed to ambiant air (say 43% relative humidity), regains water (14). Two conclusions may be drawn from this first part of the work and from other published data: i) Avicel PH-101, Avicel PH-102, Avicel PH-103 and Avicel PH-200 have similar compactibilities, particularly when taking into account the inter-batch variability; ii) Avicel PH-112, when used at the manufacturer's moisture specifications (< 1.5%) has low compactibility because water is not at optimum level for hydrogen bonding.

A reduction of the tensile strength of the compacts was observed when magnesium stearate was added to MCC, the extent of which depend on the Avicel PH grade (Figure 1, Table 3). The sequence of susceptibility was the following : Avicel PH-200 >> Avicel PH-112 = Avicel PH-102 > Avicel PH-103 = Avicel PH-101 > Avicel PH-105 as assessed from the strength reduction ratios. Avicel PH-105 was shown to be the least sensitive and the new Avicel PH-200 by far the most sensitive material. The differences between some grades were not very big at 5 min mixing time but were confirmed by conducting parallel experiments using a 15 min mixing. At this time for instance, Avicel PH-105 was again not sensitive to magnesium stearate in contrast to Avicel PH-103 and PH-101. The higher susceptibility of Avicel PH-102 compared to that of Avicel PH-101 was confirmed (12). Vromans et al. (22) found a similar order of strength reduction ratio for the PH-105, PH-102 and PH-101 grades but the differences they noted were much more pronounced because they used a 1% magnesium stearate concentration and a 30 min blending time. Using the same lubricant level, Pande and Shangraw (14) showed that the sequence depends on the operating conditions and at a 5 min mixing time, these authors observed that Avicel PH-112 was much more sensitive to magnesium stearate than Avicel PH-102 and Avicel PH-103. Here, identical strength reduction ratios were found for Avicel PH-112 and Avicel PH-102. The reason could have been that we used a different mixer and 0.5% magnesium stearate, but we are of the opinion that the discrepency between both data is firstly due to the difference in flowability of the two Avicel PH-112 samples. In fact, Vromans et al. (22) first suggested that the susceptibility of a material to magnesium stearate is a complex function of its surface area, its mechanism of consolidation, and also of the distribution and quantity of lubricant. As the latter is the same for all MCC products, the relative susceptibility is determined by the completeness of the lubricant surface film formation and thus the flowability characteristics of the powders, which depend on both particle size and moisture content. It is to be mentioned that the Avicel PH-112 sample used by Pande and Shangraw (14) had a much lower moisture content (1.07 %) and that the particles were coarser compared to their Avicel PH-102 sample, whereas our Avicel PH-112 sample had a moisture content around 3% and a mean diameter lower than that of the Avicel PH-102 sample. On the whole, these observations strongly support the opinion of Vromans et al. (22), that the ability to form a film is a major contributing factor. Here, particle size plays a double role, i.e. on the surface area available for coating by the magnesium stearate and on the flowability of the powders. Moisture influences mainly the flowability, although it cannot be excluded that the water present at the particle surface may alter the magnitude and nature of the attractive forces between excipient and lubricant.

Tablet weight variation and other tablet characteristics

Mean values and coefficients of variation of several characteristics of the tablets prepared industrially on a rotary machine are listed in Table 4.

The rank order of compaction force monitored on the machine, i.e. the force applied to the powder bed to obtain a tablet with a nominal crushing strength of 70 N, did not follow that of the compactibility observed for the compacts prepared manually (Table 3, Fig. 2). On the contrary, the lowest force monitored was for Avicel PH-101 and the highest for Avicel PH-105. Two reasons can be put forward for this difference : the pressure range used (here approximately 200 to 450 MPa) and more specifically the compaction kinetics.

Tablet weight variability (as assessed by the weight coefficient of variation) followed the logical order : Avicel PH-200 < Avicel PH-112 = Avicel PH-102 < Avicel PH-103 < Avicel PH-101 << Avicel PH-105.

The superiority of Avicel PH-102 over Avicel PH-101 on lubricated tablets was noted in a previous study conducted identically (12) and by other authors (23-26). Avicel PH-112 was slightly better that the equivalent (in terms of particle size) Avicel PH-102 because of its lower moisture content and its more rounded particles (Tables 1 and 2, Figure 1). For the same reasons,

TABLE 4

Properties of the Tablets Prepared on a Rotary Machine at a Target Crushing Force of 70 Newtons

Material	Comp-action force (kN)	Weight mean (mg)	Weight C.V. (%)	Thickness mean (mm)	Thickness C.V. (%)	Diameter mean (mm)	Diameter C.V. (%)	Porosity (%)	Crushing force mean (N)	Crushing force C.V. (%)	Friability (%)	Disintegration time (min) with disks	Disintegration time (min) without disks
Avicel PH-105	22.6	164.2	3.37	3.38	0.53	8.11	0.16	38.1	73	21.6	0.16	>120	>30
Avicel PH-103	21.6	160.0	1.34	3.58	0.92	8.11	0.21	44.9	65	8.2	0.06	0.83	1.03
Avicel PH-101	10.3	159.5	1.68	3.43	0.35	8.05	0.52	40.7	79	8.7	0.01	0.33	1.67
Avicel PH-102	14.2	159.5	0.88	3.42	0.61	8.07	0.22	40.0	76	6.3	0.07	0.75	1.98
Avicel PH-112	21.6	161.2	0.83	3.61	0.64	8.13	0.12	43.4	63	7.8	0.09	0.33	1.00
Avicel PH-200	18.6	157.9	0.56	3.47	0.35	8.10	0.12	42.7	64	4.3	0.07	0.13	0.58

Avicel PH-103 was also slightly better than Avicel PH-101. Being too fine, Avicel PH-105 did not give acceptable tablets when used alone and the best grade was definitely Avicel PH-200. Data illustrating the better weight reproductibility of placebo tablets made with Avicel PH-200 over Avicel PH-102 or Avicel PH-112 tablets can be found elsewhere (13,15). A low speed and a high speed rotary machine without force feed were used by Erkobani et al. (15), whereas the tablets prepared by Munoz-Ruiz et al. (13) were obtained on a single punch machine. Additionally, a similar variability was noted for Avicel PH-103, PH-102 and PH-112 tablets prepared on a slow rotary machine (14).

A perfect correlation was found between the coefficients of tablet weight variation and the Hausner ratios for powders but not with flow rates through an orifice. The reason is probably the use of force-feed delivery employed in the tableting procedure. More reliable data on flow properties determined using the Jenike shear cell can be found in the literature (3,27) for the classical Avicel PH grades.

The variability in thickness and in diametral crushing force quite logically paralleled that of weight. Friability values were very low for all grades, whereas apparent porosities were quite high, but very close. Finally, tablets disintegrated very rapidly both in presence and absence of disks, except the Avicel PH-105 tablets. The poor disintegrating properties of Avicel PH-105 tablets, both pure (3) or added to spray-dried lactose (3,28), have already been reported. Note that in Sixsmith's work (3) tablets made with pure Avicel PH-103, PH-101 and PH-102 also disintegrated very quickly. In contrast, Bolhuis and Lerk (23) found satisfactory disintegration times for Avicel PH-101 and PH-102 tablets only when lubricated.

CONCLUSIONS

Taking into account that some of the small differences observed may be simply due to the inherent inter-batch variability, Table 5 compares the performance of the six Avicel PH grades. Here the main properties were evaluated relatively to the standard Avicel PH-101 product. This evaluation

TABLE 5
Evaluation of the Basic and Tableting Properties of the Avicel PH Grades Relatively to Avicel PH-101
(+, ++ : better; = : not significantly different; -, -- : worse)

Material	Hausner ratio[1]	Compactibility[2]	Sensitivity to lubricant[3]	Regularity of weight	Disintegration[4]
Avicel PH-105	--	+	+	--	--
Avicel PH-103	=	=	-	=	=
Avicel PH-102	=	=	-	+	=
Avicel PH-112	+	=	--	+	=
Avicel PH-200	++	=	--	++	=

[1] Compressibility on tapping; [2] Based on the compact crushing strength; [3] Strength reduction ratio on adding 0.5% magnesium stearate; [4] Both with or without disks.

should not be put in parallel with other published evaluations where the operating conditions were generally different.

In many aspects Avicel PH-105 differs from the other grades: high compressibility on taping indicating very poor flow properties, with the result of an inacceptable tablet weight variation when used without a diluent, a high insensitivity to hydrophobic lubrication, and very poor disintegrating properties. The other conventional types are very similar in their performance, except that a lower coefficient of weight variation of the tablets and a higher strength reduction ratio were obtained for Avicel PH-102. Some of our data concerning the new low moisture material Avicel PH-112 conflict with the literature regarding its compactibility and susceptibility to added magnesium stearate. For instance, we found similar compactibilities for all grades, as Munoz-Ruiz et al. (13) had found for Avicel PH-112 and PH-200. In contrast, for Pande and Shangraw (14) the compactibility of Avicel PH-112 was inferior to those of Avicel PH-103 and PH-102. These authors also noted that Avicel PH-112 demonstrates a higher sensitivity to magnesium stearate than Avicel PH-102, while we found close values for both materials. Obviously, the discrepency may be related to the fact that our Avicel PH-112 sample apparently - and probably the one used by Munoz-Ruiz et al. (13) -regained moisture during use, to the point of exceeding the manufacturer's specifications. Consequently, the assessment of this product made here may be dubious in some respects.

The large particle size Avicel PH-200 shows a compactibility similar to that of other grades, but is very sensitive to magnesium stearate, as already reported elsewhere (13,14). Being a free flowing powder, it gives tablets with improved weight reproducibility. Furthermore, like Avicel PH-112, its disintegrating properties are similar to those of the other grades, except Avicel PH-105.

To conclude, the two recently commercialized MCCs offer some advantages over conventional grades. In particular, Avicel PH-112 is indicated for moisture-sensitive drugs, but should be utilized in air-conditionned rooms and special packaging has to be envisaged. Avicel PH-200 will reduce weight variation of many direct compression formulations but some decrease in compactibility in presence of hydrophobic lubrication can be anticipated. Likewise, the dilution potential (not studied here), i.e. the capacity of the excipient to act as a dry binder when blended with a diluent and/or drug, may not be as good as that of other materials (say Avicel PH-102) because its coarser particles may not provide an adequate contact area for bonding.

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