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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.

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