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Investigation of the effect of type and source of microcrystalline cellulose on capsule filling

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Abstract

The influence of the type and source of 8 microcrystalline cellulose samples on the capsule filling performance has been investigated. Different sources of fine, medium and coarse grade microcrystalline cellulose have been used. Several properties of the powders such as particle size, packing and flow were determined and related to the capsule filling behaviour and the capsule disintegration time. A fine grade microcrystalline cellulose such as Avicel® PH105 cannot be used in capsule filling because of unsatisfactory flow properties. Medium and coarse grade microcrystalline cellulose can be classified as a good capsule filling excipient, but not all sources are suitable. The Lüdde-Kawakita constant a (Lüdde and Kawakita, 1966) and Hausner's ratio (Hausner, 1967) are good indicators of the capsule filling performance, especially in terms of interchangeability of different sources, possibility of filling above maximum bulk density and flow problems producing large coefficients of fill weight variation.

Keywords: Capsule filling; Flow properties; Microcrystalline cellulose; Principal component analysis

1. Introduction

Microcrystalline cellulose is a very important excipient for oral solid dosage forms. While widely studied in tabletting (Doelker et al., 1987; Whiteman and Yarwood, 1988; Podczeck et al., 1993; Dittgen, 1993), there is little information in the literature about its capsule filling performance. Microcrystalline cellulose exists in several types and can be purchased from different manufacturers. The problem of source variability is well known (Roberts and Rowe, 1987; Parker and Rowe, 1991; Podczeck and Newton, 1992a; Podczeck and Newton, 1992b; Podczeck and Révész, 1993), and there are some common rules about the effect of the type of microcrystalline cellulose on the manufacturing properties of tablets. The relevance of these problems in capsule filling, however, is unknown.

The aim of the present paper was to investigate the effect of type and source of microcrystalline cellulose products on the capsule filling performance. Fine, medium and course grades of microcrystalline cellulose of different sources have been studied, and powder properties such as compressibility, flow, packing and particle size have been related to the coefficient of fill weight variation,

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Table 1
Powder properties of different microcrystalline cellulose products

Source	Ed (μm)	PSR (μm)	ϕ (°)	H	C (%)	a (%)	b	SV (%)
Avicel PH102	86	200	34.3	1.23	18.4	17.8	0.115	22.7
Unimac MG-200	97	250	40.2	1.34	24.0	28.2	0.028	40.0
Avicel PH101	64	145	31.7	1.29	22.4	24.7	0.053	33.3
Microcel	99	220	40.0	1.32	24.5	24.5	0.058	38.1
Emcocel	77	170	25.4	1.26	20.4	23.8	0.114	31.8
Unimac MG-100	71	192	31.3	1.38	28.7	29.6	0.081	38.1
Avicel PH103	60	150	41.8	1.34	25.2	25.4	0.083	30.0
Avicel PH105	41	110	38.3	1.50	31.5	36.2	0.023	27.3

Ed, Edmundson's volume distribution diameter; PSR, particle size range; ϕ, angle of wall friction; H, Hausner's ratio, C, Carr's compressibility; a, b, constants of the Lüdde-Kawakita equation; SV, increase in volume due to swelling.

adhesion and disintegration of the capsules filled using a dosator nozzle filling machine.

2. Materials and methods

Microcrystalline cellulose of the following types and sources has been used: Avicel® PH101, PH102, PH103, PH105 (FMC Corporation, Philadelphia, USA), Microcel® (Blanver Farm. Ltd., Cotia, Brazil), Emcocel® (E. Mendell, Kuopio, Finland) and Unimac® MG-100, MG-200 (Unitika Rayon, Osaka, Japan).

Particle size analysis has been undertaken using image analysis (Solitaire 512, Seescan, Cambridge, UK), suspending the powders in paraffin oil. Edmundson's volume distribution diameter and the particle size range have been determined from 1000 particles.

The minimum and maximum bulk density of the powders were measured in a 200 ml measuring cylinder using a tapping device (B.S. 1800, 1967). Readings were made after every 5 taps up to 50 and then every 10 taps until the volume did not change over 5 consecutive tapping intervals. From these readings the Lüdde-Kawakita constants a and b (Lüdde and Kawakita, 1966; Kawakita and Lüdde, 1970/71) were also calculated. Carr's compressibility (Carr, 1965) and Hausner's ratio (Hausner, 1967) were determined from the minimum and maximum bulk density values.

The angle of wall friction was measured using an annular shear cell as described by Tan and Newton, 1990.

Hard gelatin capsules were filled on an automatic dosator nozzle filling machine (Zanasi AZ5, Industria Macchine Automatiche, Bologna, Italy) using size 0 capsule shells and a target fill weight of 300 mg. The filling was performed at maximum bulk density without further compression. No lubricant was used. For the determination of the coefficient of fill weight variation, 20 capsules were randomly obtained and the BP test of uniformity of fill weight was performed. After each filling the nozzles were inspected for powder coating (adhesion) and the amount of coating was graded as 0.0 (no coating), 0.5 (slight coating) and 1.0 (strong coating).

The disintegration time of the capsules was assessed by the BP test procedure using 6 capsules, whereas the swelling rate of the powders was evaluated as described by Podczeck and Révész, 1993.

3. Results and discussion

Table 1 summarizes the results of the powder properties obtained from the different microcrystalline cellulose products. Avicel PH102 and Unimac MG-200 are both coarse grade powders, but due to the difference in source they vary considerably in their particle size, flow properties (Hausner's ratio, Carr's compressibility and the angle of wall friction), compressibility (Lüdde-Kawakita constant a) and swelling ratio. Avicel PH105 is the only fine grade microcrystalline cellulose tested.

Its very bad flow properties (Hausner's ratio and Carr's compressibility) can be due to its small particle size. The other five batches of microcrystalline cellulose are medium grade products, which again, vary largely in their powder properties.

Table 2 lists the parameters evaluated to describe the capsule filling performance and the disintegration of the capsules. Avicel PH105 did not give filled capsules because of extreme flow problems. An addition of 1.0% magnesium stearate did not improve the flow properties, and hence Avicel PH105 and probably other fine grade microcrystalline cellulose products cannot be recommended for use in capsule filling. The coefficient of fill weight variation for medium and coarse grade microcrystalline cellulose products varies between 1.1 and 3.1% without showing a clear dependence on particle size. Adhesion to the metal surface of the nozzles, quantified as a grade of coating, is also found to occur in both coarse and medium grade products. Jolliffe et al., 1980 proposed a relation between compression of the powder in the nozzle, ease of ejection of the powder plug and coefficient of fill weight variation. They recommended the use of low compressive forces, which assure the formation of a plug but do not hinder the ejection of the plug into the capsule body. Visual inspection of the plugs has shown that the plug formation was satisfactory in all cases, and therefore one could assume that either the adhesion of the plug to the nozzle wall or the difference in flowability might have caused the differences in the coefficient of fill weight variation. However, neither the coating of the nozzle observed nor the flow properties of the powders (angle of wall friction, Hausner's ratio, Carr's compressibility) are simply related to the filling.

Table 2
Capsule filling performance and disintegration time

Source	CV (%)	CO	D (min)
Avicel PH102	1.5	0.5	6.0
Unimac MG-200	3.1	1.0	5.2
Avicel PH101	2.1	0.0	6.0
Microcel	1.1	0.5	10.8
Emcocel	1.2	0.0	6.5
Unimac MG-100	2.0	1.0	11.0
Avicel PH103	2.0	0.0	4.7
Avicel PH105	No capsule filling		

CV, coefficient of fill weight variation; CO, nozzle coating rate; D, disintegration time.

The disintegration time of the capsules made from coarse grade microcrystalline cellulose powders is similarly low, but for medium grade products a wide variability can be reported. Metha and Augsburger, 1981 have shown that the disintegration of capsules depends on the densification of the powder plugs, and they recommended to fill capsules with no or only a small amount of compression. In this study the capsules have been filled at maximum bulk density, hence virtually without compression. Therefore the disintegration time of the capsules filled with different microcrystalline cellulose products should purely be the result of the powder properties. Microcrystalline cellulose acts as disintegrant itself by enhancing the water penetration into the compact. Furthermore microcrystalline cellulose products increase their volume by swelling, when in contact with water, by up to 45% (Podczeck and Révész, 1993). However, there is no relationship between the swelling volume and the disintegration time.

Using the coefficient of fill weight variation as a criterion to group the microcrystalline cellulose products tested, three groups can be identified:
(1) Avicel PH102, Microcel, Emcocel;
(2) Avicel PH103, PH101, Unimac MG-100;
(3) Unimac MG-200.

The first group has the lowest coefficient of fill weight variation, followed by group 2, but the values obtained in group 2 are still below the upper limit for the coefficient of fill weight variation according to the BP. The coefficient of fill weight variation of 3.1% (Unimac MG-200) would, in practice, be regarded as an indication of filling problems. Microcel and Emcocel are claimed to be usable as exchange materials for Avicel PH101. However, this simple approach for evaluation of the results of the experiments suggests their similarity with Avicel PH102. Unimac MG-200 should be equivalent to Avicel PH102, but obviously such an exchange could cause problems in filling.

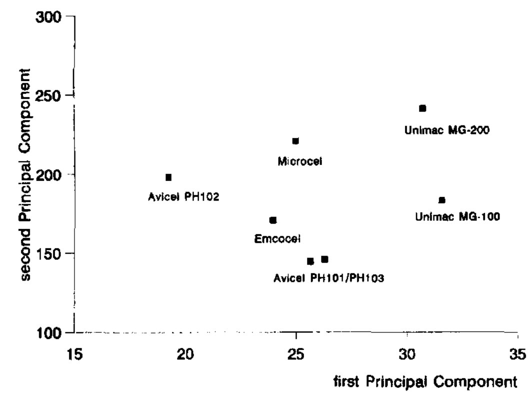

Fig. 1. Principal Component Analysis to cluster different microcrystalline cellulose products according to their powder properties and their capsule filling performance.

Principal Component Analysis reduces a variety of correlated input variables into a usually smaller number of Principal Components, which are uncorrelated (Flury and Riedwyl, 1983). In this paper, it was used to enhance the complex relationship between the powder properties of the microcrystalline cellulose products and the capsule filling performance. Two significant Principal Components, which are able to explain 89.9% of the information contained in the data, were constructed. The first Principal Component is composed of the Lüdde-Kawakita constant a, Hausner's ratio, the coefficient of fill weight variation and the coating level, whereas the second Principal Component consists of the Lüdde-Kawakita constant b, mean particle size (Edmundson's volume distribution diameter) and particle size range. Hence, the latter Principal Component reflects the particulate properties of the microcrystalline cellulose samples, whereas the former Principal Component represents the powder properties. The angle of wall friction and Carr's compressibility are not contained in the Principal Components, because they contained no further information. Using the first Principal Component as a criterion to group the microcrystalline cellulose samples, three clusters appear in the graphical presentation (see Fig. 1), but they are different from the groups obtained using only the coefficient of fill weight variation. Avicel PH102 is a single point cluster, Unimac MG-100 and MG-200 form a second cluster, and Emcocel, Microcel and Avicel PH101 and PH103 are together in a third cluster. Avicel PH102 has comparatively good filling properties (low coefficient of fill weight variation, only slight nozzle coating, good powder flow), but it would not be very useful if the powder requires filling above the maximum bulk density, because the Lüdde-Kawakita constant a is very small. At the other extreme, the Unimac products would be the microcrystalline cellulose products of choice if compression is desired, but the filling behaviour (excessive nozzle coating, high coefficient of fill weight variation) is not very good due to considerable poor flow properties (Hausner's ratio). In fact, Avicel PH101, PH103, Microcel and Emcocel appear to be the most suitable microcrystalline cellulose sources tested for capsule filling. Although they vary considerably in their powder properties, they appear to be exchangeable in terms of capsule filling performance.

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