Report

Measurement of the Particle Size of Tablet Excipients with the Aid of Video Recording

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Received April 15, 1987; accepted July 17, 1987

A method for the determination of the particle size of tablet excipients involving the use of video recording of microscopic examination of powders is described. The projected area of the particle profile was measured, and Feret's diameter and shape factors such as the elongation ratio, bulkiness factor, and surface factor were determined. Starch particles are the smallest among the excipients studied. Primojel particles are two to three times larger (Feret's diameter) and have up to 10 times greater projected areas. Particles of Avicel PH101, Ac-Di-Sol, Nymcel ZSD16 and ZSB10, and Polyplasdone XL have an irregular surface which results in large differences between the projected area diameter and the perimeter diameter. Particles of Nymcel and Ac-Di-Sol have the highest elongation ratio because of their cylindrical shape. Both Primojel and Starch have a low surface factor because of their spherical shape. This video-recording method is a simple system to observe, record, store, and retrieve particle-size data from microscopic examination of tablet excipients.

KEY WORDS: size; tablet excipients; video recording.

INTRODUCTION

Particle shape and size are important properties of powders. Methods to describe particle shape have been developed by Heywood (1). The comprehensive description of the three-dimensional structure of a fine particle with a random shape presents many problems. Several types of geometric descriptions and ratios may be used to describe fine particles (2–4).

Detailed numerical analyses of images are now possible (5–7), and the shape index has found more applications. The role of particle morphology, that is, size, shape, and composition, in making tablets has been recognized. Variations in particle shape have been found to affect markedly the apparent density, flow rate, and Hausner ratio of bulk solids (8). Scanning electron microscopy is able to obtain direct pictures of tableting excipients, and this allows a detailed study of the properties of excipients. Comparison between various tablet excipients has been made in a microscopic study involving the use of a camera, but no quantification of the observations was attempted (9). The purpose of this report is to show the application of video recording of tablet excipient particles examined microscopically. The resultant information is thought to be of use in an ongoing investigation of disintegration and dissolution of tablets formulated with these excipients.

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MATERIALS AND METHODS

Tablet Excipients

The tablet excipients used were microcrystalline cellulose (Avicel PH101, FMC Corp., USA), cross-linked sodium carboxymethylcellulose (Ac-Di-Sol, FMC Corp., USA), low substituted carboxymethylcellulose sodium (Nymcel ZSD16, ZSB10, Nyma BV, The Netherlands), sodium starch glycolate (Primojel, Avebe Veendam, The Netherlands), maize starch (Corn Brand, The Netherlands), crospovidone NF XV (Polyplasdone XL, GAF, USA), and methylcellulose of various viscosity grades, 20–30, 80–120, 350–550, 800–1200, 4000, and 7000–10,000 cp (Tokyo Kasei, Japan). The difference between Nymcel ZSB10 and ZSD16 is that the former has a fine fibrous structure and the latter is finely granulated.

Procedure

A small amount of dry powder sample is spread uniformly in a thin layer on a microscopic slide. A video camera (Hitachi VK-C500, Japan) was linked to the microscope (American Optical, series one-ten MICROSTAR, USA). The particles can be seen on the camera as well as on the monitor screen (Sony Trinitron, KX-14 CP1, Japan). When observed on the monitor screen the particles had a magnification of ×950.

A video recording of the particles was made using a video recorder (JVC VHS professional editing recorder BR-8600E, Japan). In the replay of the recording, a sharply focused image of the particle could be obtained on the mon-

0724-8741/87/1200-0504$05.00/0

Table I. Percentage Frequency Distribution of Feret's Diameter of Particle Profiles of Tablet Excipients

Diameter (μm)	Avicel PH101	Ac-Di-Sol	Nymcel ZSB10	Nymcel ZSD16	Poly-plasdone XL
0–20	2.50	—	—	—	—
20–40	40.00	20.37	—	—	—
40–60	20.00	16.67	6.45	8.89	24.00
60–80	17.50	18.52	16.13	11.11	32.00
80–100	10.00	12.96	29.03	26.67	28.00
100–120	10.00	18.52	16.13	26.67	12.00
120–140	—	5.56	22.58	8.89	4.00
140–160	—	3.70	6.45	15.56	—
160–180	—	—	3.23	2.21	—

Table III. Percentage Frequency Distribution of Feret's Diameter of Particle Profiles of Various Grades of Methylcellulose (MC)

Diameter (μm)	MC 20–30	MC 80–120	MC 350–550	MC 800–1200	MC 4000	MC 7000–10,000
0–20	—	—	—	—	—	—
20–40	7.14	10.00	3.45	—	4.17	2.70
40–60	28.57	27.50	17.24	6.67	8.33	18.92
60–80	32.14	20.00	31.03	20.00	33.33	32.43
80–100	21.43	22.50	10.34	43.33	12.50	8.11
100–120	10.72	15.00	20.69	13.33	20.83	8.11
120–140	—	5.00	17.25	13.33	8.33	2.70
140–160	—	—	—	3.34	4.17	13.51
160–180	—	—	—	—	—	8.11
180–200	—	—	—	—	8.33	—
200–220	—	—	—	—	—	5.41

itor screen by freezing a frame using an editing control unit (JVC RM-86U). There are 25 frames in each second of recording and thus the editing control unit allows a frame-by-frame analysis. Tracings of the image of the particles from the monitor screen can be easily made with the use of transparency sheets.

The area of each particle as exhibited in the particle profile tracings was measured with an electronic digital planimeter (Ushikata Digi-plan 220L, Japan). The perimeter of the particle profile was determined by measuring the length of a thread placed along the outline of the particle tracing. For each material, 120–160 particles were chosen from at least 30 different fields of vision. Measurements of various parameters were carried out for all these particles. A representative sample of the powder was obtained by intermittent sampling of a flowing stream of the powder. The sample so obtained was subdivided into portions suitable for observation under the microscope.

RESULTS AND DISCUSSION

Feret's Diameter

Feret's diameter (10,11) was measured as the longest distance between two tangents on opposite sides of the particle, parallel to a fixed direction. A frequency distribution of the Feret's diameter of the particles of different excipients is shown in Tables I and II. The results show that starch particles are the smallest among the excipients studied, 4–18 μm, with more than 75% of them in the range of 8–14 μm. For Primojel, the particles are much larger, 0–80 μm, and more than 75% were in the range 10–40 μm. The majority of the particles of Avicel PH101 (>75%) measures from 20 to 80 μm. In contrast, the size of Ac-Di-Sol and Nymcel particles is distributed over a wide range, most of them occurring in the range 20–120 and 60–140 μm, respectively. The size distribution of Polyplasdone XL particles is in the range 40–140 μm.

Table III shows the size distribution of MC particles of various viscosity grades. Higher viscosity grades of MC 4000 and 7000–10000 cp have particles measuring up to 220 μm; the lower viscosity grades, on the other hand, have few particles larger than 120 μm. The Feret's diameter seems to be related to the viscosity of the MC. The increase in viscosity of some grades of MC is due to the chain length or degree of polymerization.

Projected Area

The determination of Feret's diameter is affected by the orientation of the particle under measurement. The projected area of the particle can also be used to express particle size, it is not dependent on particle shape. Tables IV and V show the projected areas of particles of tablet excipients studied. It is seen that Primojel particles have projected areas of up to 1600 μm^2, while those of starch particles do not exceed 180 μm^2. Larger projected areas are demonstrated by Avicel PH101, Ac-Di-Sol, Nymcel, and Polyplasdone XL. In the case of MC, the projected areas are

Table II. Percentage Frequency Distribution of Feret's Diameter of Particle Profiles of Primojel and Starch

Diameter (μm)	Primojel	Diameter (μm)	Starch
0–10	4.20	4–6	3.28
10–20	35.29	6–8	9.84
20–30	26.06	8–10	26.23
30–40	16.81	10–12	26.23
40–50	8.40	12–14	24.59
50–60	4.20	14–16	8.20
60–70	2.52	16–18	1.63
70–80	2.52		

Table IV. Percentage Frequency Distribution of Projected Areas of Particle Profiles of Tablet Excipients

Area ($\times 10^2$ μm^2)	Avicel PH101	Ac-Di-Sol	Nymcel ZSB10	Nymcel ZSD16	Poly-plasdone XL
0–5	32.50	18.52	—	—	4.17
5–10	22.50	20.37	12.90	4.44	4.17
10–15	15.00	12.96	19.35	26.69	12.50
15–20	12.50	12.96	19.35	17.78	12.50
20–25	12.50	18.52	22.58	24.44	16.67
25–30	2.50	11.11	12.90	6.67	16.67
30–35	2.50	2.00	9.68	15.56	12.50

Table V. Percentage Frequency Distribution of Projected Areas of Particle Profiles of Primojel and Starch

Area ($\times 10^2$ μm^2)	Primojel	Area ($\times 10^2$ μm^2)	Starch
0–2	33.61	0–0.2	—
2–4	21.85	0.2–0.4	19.67
4–6	14.29	0.4–0.6	24.59
6–8	8.40	0.6–0.8	29.51
8–10	5.04	0.8–1.0	11.48
10–12	4.20	1.0–1.2	4.92
12–14	4.20	1.2–1.4	3.28
14–16	8.41	1.4–1.6	4.92
		1.6–1.8	1.63

larger, as much as 7000 μm^2. A higher proportion of greater particle area is observed with MC of higher viscosity (Table VI).

The marked difference in the range of the particle-size frequency distribution of the Feret's diameter of particles of different tablet excipients (Tables I–III) is not observed in the comparison of the projected areas of corresponding particles (Tables IV–VI). It is probable that Feret's diameter may not be appropriate to describe the size of the particle and that factors such as shape, contour, and orientation may have an influence on particle-size measurement. It also suggests that although the different excipients have particles of various shapes, their projected areas do not vary to a great extent.

Shape Factors

The shape of particles influences the flowability and compression of powders. A qualitative description of the shape of powder particles can be made by the use of terms such as crystalline, fibrous, flaky, and spherical. A quantitative description of the shape characteristics gives a better understanding of the elements that govern powder properties. Shape factors are dimensionless numerical values that assist comparison of different classes of particles. Figures 1 and 2 show the shape and edge texture of samples of the tablet excipients studied. A few particle shapes were chosen of the 120–160 analyzed for each material, in order to facilitate a visual comparison between particles of various materials. After viewing many frames of recording, profiles of individual particles were obtained by tracing the particle shape from the TV monitor screen. These tracings were subsequently reduced in size to yield Figs. 1 and 2.

The projected area diameter (d_a) is the diameter of a circle having the same area as the projected area of the particle, while the perimeter diameter (d_p) is the diameter of a circle having the same perimeter as that of the particle profile (12).

For the determination of the shape factor, each particle profile is enclosed in a rectangle of minimum area (Fig. 3). The length of the rectangle is the Feret's diameter a. A dimension measured at a right angle to a gives b, which is the breadth of the rectangle. The microscopic study described in this paper is essentially a two-dimensional observation. It is not possible to obtain a third dimension, depth of the particle, with the equipment used. Three shape factors have been examined (13,14). The elongation ratio (x) is the ratio of a and b. The value of x would be equal to unity if the particle profiles were to be boxed in a square. Rectangles will have a value greater than unity. The more elongated the particle, the greater is the elongation ratio.

The bulkiness factor (y) is the ratio of the projected area of the particle to the product of a and b. The value y would be equal to unity if the particles were a perfect square or a rectangle.

The surface factor (z) is the ratio of the square of the

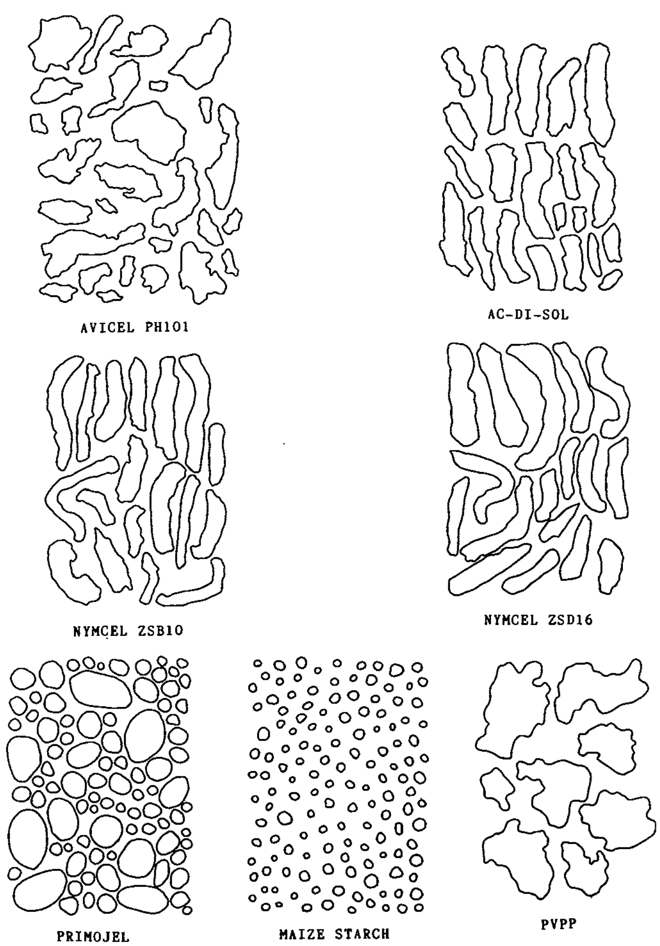

Fig. 1. Particle shape and edge texture of samples of tablet disintegrants (same magnification for all samples).

Table VI. Percentage Frequency Distribution of Projected Areas of Particle Profiles of Various Grades of Methylcellulose (MC)

Area ($\times 10^2$ μm^2)	MC 20–30	MC 80–120	MC 350–550	MC 800–1200	MC 4000	MC 7000–10,000
0–10	14.29	25.00	6.90	—	4.17	11.11
10–20	42.86	22.50	17.24	34.48	25.00	30.56
20–30	32.14	32.50	37.93	34.48	37.50	19.44
30–40	7.14	10.00	—	20.69	4.17	22.22
40–50	3.57	7.50	27.59	—	8.33	5.56
50–60	—	2.50	6.90	10.35	20.83	5.56
60–70	—	—	3.44	—	—	5.56

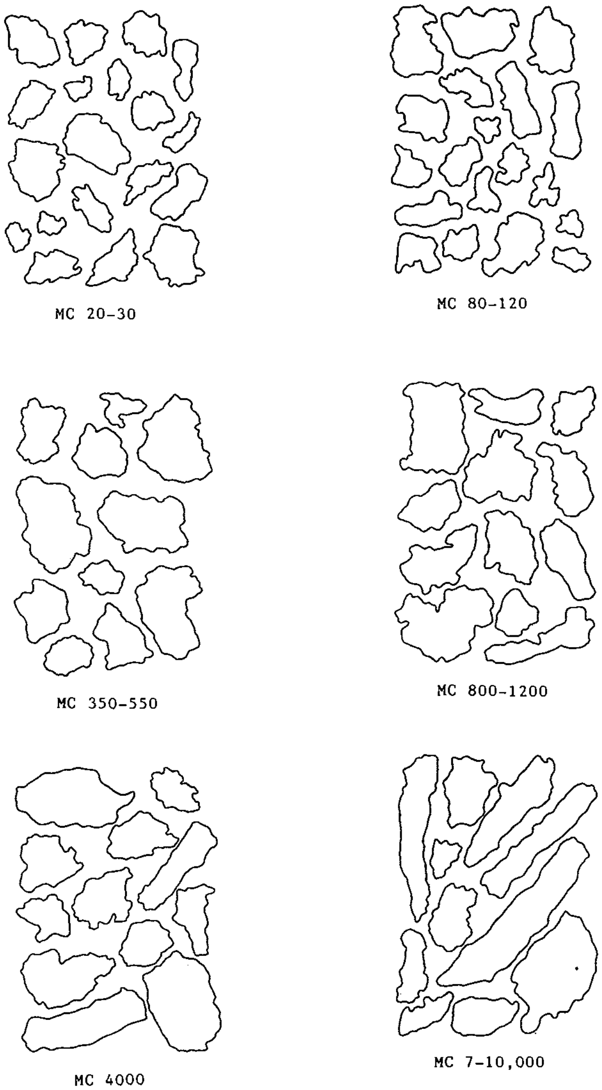

Fig. 2. Particle shape and edge texture of samples of methylcellulose of viscosity grades 20–30, 80–120, 350–550, 800–1200, 4000, and 7000–10,000 cp (same magnification for all samples).

perimeter of the particle profile to 12.6 times its cross-sectional area. For a circle, the relationship between the circumference and the area is

$$C = 12.6\,A$$

where C is the circumference and A is the area. Hence, if the particle were to be perfectly spherical, the value of z would be equal to unity.

There is a large difference between the projected area diameter d_a and the perimeter diameter d_p for Avicel PH101, Ac-Di-Sol, Nymcel, and Polyplasdone XL (Table VII). This is because these particles have an irregular edge which gives rise to an increase in perimeter without a marked enlargement of area. Primojel and starch particles are smaller in comparison. These have a smooth edge unlike that observed for the other excipients. Consequently, there is not much difference between the value of d_a and the value of d_p for Primojel and starch. With an increase in the viscosity of MC, there is an increase in the perimeter diameter (Table VIII) but this trend of behavior is not obvious when the projected area is considered.

Both grades of Nymcel have the highest elongation ratio x, followed by Ac-Di-Sol and Avicel PH101 (Table VII). The excipients are thread-like and cylindrical in shape. In con-

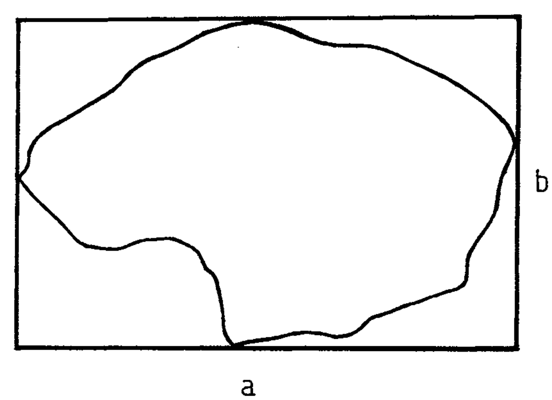

Fig. 3. Length (a) and breadth (b) of a particle profile.

Table VII. Size and Shape Factors of Particle Profiles of Tablet Excipients[a]

	Avicel PH101	Ac-Di-Sol	Nymcel ZSB10	Nymcel ZSD16	Primojel	Starch	Polyplasdone XL
d_a (μm), projected area diam.	39.43 ± 12.86	51.37 ± 8.81	53.68 ± 6.31	53.17 ± 9.37	28.62 ± 9.97	8.92 ± 1.41	57.57 ± 10.01
d_p (μm), perimeter diam.	53.23 ± 18.45	78.13 ± 14.55	84.36 ± 17.04	85.83 ± 16.91	30.83 ± 10.87	10.92 ± 1.82	72.33 ± 12.78
$x = a/b$, elongation ratio	2.02 ± 0.31	3.65 ± 0.59	5.05 ± 1.40	5.00 ± 1.11	1.31 ± 0.14	1.27 ± 0.16	1.67 ± 0.14
$y = A/ab$, bulkiness factor	0.66 ± 0.07	0.75 ± 0.05	0.89 ± 0.06	0.86 ± 0.12	0.82 ± 0.09	0.77 ± 0.14	0.78 ± 0.06
$z = C^2/12.6\,A$, surface factor	1.81 ± 0.25	2.32 ± 0.27	2.46 ± 0.59	2.62 ± 0.46	1.16 ± 0.06	1.50 ± 0.08	1.58 ± 0.15

[a] a and b are the length and breadth of the particle, respectively, as described in the text. A and C are the projected area and perimeter of the particle, respectively.

Table VIII. Size and Shape Factors of Particle Profiles of Various Grades of Methylcellulose (MC)

	MC 20–30	MC 80–120	MC 350–550	MC 800–1200	MC 4000	MC 7000–10,000
d_a (μm), projected area diam.	53.64 ± 9.33	53.14 ± 13.54	60.60 ± 13.13	59.11 ± 13.13	68.89 ± 14.17	65.86 ± 16.22
d_p (μm), perimeter diam.	70.12 ± 11.89	71.43 ± 19.56	76.55 ± 19.56	82.41 ± 20.22	92.03 ± 18.57	99.80 ± 33.64
$x = a/b$, elongation ratio	1.64 ± 0.53	1.80 ± 0.41	1.53 ± 0.24	2.15 ± 0.63	2.15 ± 0.83	3.45 ± 1.62
$y = A/ab$, bulkiness factor	0.75 ± 0.04	0.80 ± 0.06	0.78 ± 0.07	0.78 ± 0.12	0.78 ± 0.06	0.78 ± 0.07
$z = C^2/12.6\,A$, surface factor	1.71 ± 0.10	1.80 ± 0.25	1.59 ± 0.29	1.95 ± 0.34	1.82 ± 0.41	2.25 ± 0.60

[a] *a* and *b* are the length and breadth of the particle, respectively, as described in the text. *A* and *C* are the projected area and perimeter of the particle, respectively.

trast, Primojel and starch have values approximating unity. This is attributed to their spherical shape. Higher viscosity grades of MC have a greater proportion of rod-like long particles and therefore they have larger values of x than the lower viscosity grades of MC. Little discernible difference is exhibited in the bulkiness factor y of the various excipients (Tables VII and VIII). Nymcel has a higher value; because of its cylindrical shape, the cross-sectional area approaches that of a rectangle. As for surface factor z, the smallest value obtained is that for Primojel; this value is close to unity. Ac-Di-Sol and Nymcel have high values. The reason is that they are long and thread-like, thus deviating from the circular form.

Thus, this video-recording method allows easy recording of particle size and shape and, more importantly, easy storage of such data obtained so as to be readily accessible for subsequent size analysis.

ACKNOWLEDGMENTS

The authors wish to thank the staff of the Center for Educational Technology, National University of Singapore, for their assistance and the use of the video equipment.

NOMENCLATURE

- a Length of particle; maximum Feret's diameter
- A Projected area of particle, μm^2
- b Breadth of particle; Feret's diameter at right angles to maximum Feret's diameter
- d_a Projected area diameter; diameter of equivalent area circle
- d_p Perimeter diameter; diameter of equivalent perimeter circle
- C Perimeter of particle profile
- x Elongation ratio; ratio of length to breadth, a/b
- y Bulkiness factor; ratio of projected area to product of a and b, A/ab
- z Surface factor; ratio of the square of perimeter to 12.6 times its projected area, $C^2/12.6A$

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