DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(6), 921-933 (1990)

A STUDY OF THE SWELLING OF TABLET EXCIPIENTS USING VIDEO RECORDING

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ABSTRACT

A video recording technique was used to study microscopically the swelling characteristics of individual tablet disintegrant particles in water. Feret's diameter, projected area and dimensionless shape factors such as elongation ratio, bulkiness factor and surface factor of various particle profiles were determined. Hydrated particles of cross-linked sodium carboxymethylcellulose (Ac-Di-Sol) and low substituted sodium carboxymethylcellulose (Nymcel ZSB10 and ZSD16) had high Feret's diameter and projected areas. Swelling in their case was due to the hydration of macromolecules. Hydrated microcrystalline cellulose (Avicel PH101) particles had a narrow distribution of both Feret's diameter and projected area. The low degree of swelling in these particles was due to entry of water into particle pores. Fibrous particles of Nymcel ZSB10 retained their elongated shape even after swelling fully. Ac-Di-Sol and Nymcel ZSD16 particles however swelled appreciably along their breadth also and assumed a less elongated

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profile than when dry. The order for increase in projected area diameter after hydration was Ac-Di-Sol > Nymcel ZSB10 > ZSD16 > Avicel PH101.

INTRODUCTION

Powders are composed of individual fine particles and their agglomerates. An investigation of the size and shape characteristics of fine particles is essential for understanding the various properties of powders such as flowability, compactability, cohesiveness, etc.

Tablets are prepared by compressing agglomerates of powders called granules which are made by wet [1] and dry [2] methods. Excipients such as binders and disintegrants are added at various stages in the manufacture of tablets. Wetting of excipients can bring about changes in the morphological and structural composition of excipient particles. Water is often used as a wetting agent in the preparation of tablet granulations and hence a study of the hydration of tablet excipient particles is of interest. Swelling is generally thought to be one of the mechanisms by which disintegration of tablets takes place [3, 4]. Gums, clays and some cellulose derivatives swell on contact with water, creating pressures between particles of the tablet and bringing about disintegration.

Most methods used for direct measurement of the dimensions of fine particles consist of the viewing of elongated images of particles either directly, as in an optical microscope or indirectly, as using a cathode ray tube projection. Recording of the images is done by photographing or image analysis using digital computers. A video recording technique developed by Prasad and Wan [5] was found to be suitable for determining the size and shape of dry tablet excipient particles.

Swelling of tablet excipient particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particle or hydration of macromolecules. The liquid enters the particles through pores and binds to large molecules, breaking hydrogen bonds and resulting in the swelling of the particle. The disintegration action of microcrystalline cellulose [6], cross-linked sodium carboxymethylcellulose [6, 7] and low-substituted sodium carboxymethylcellulose [8, 9] in tablets containing methylcellulose as a binder has been studied earlier. This study was undertaken with the view to understanding the swelling behaviour of individual particles of these disintegrants upon contact with water, using the video technique of Prasad and Wan [5]. It is hoped that the data generated will help to explain the action of these disintegrants in tablet formulations.

EXPERIMENTAL

Material

The tablet excipients used were microcrystalline cellulose (Avicel PH101, FMC Corp., USA), cross-linked sodium carboxymethylcellulose (Ac-Di-Sol, FMC Corp., USA) and low-substituted carboxymethyl cellulose sodium (Nymcel ZSB10, ZSD16, Nyma B.V., The Netherlands).

Microscopic Examination of Tablet Excipients

The experimental set-up for the determination of the size and shape characteristics of tablet excipient particles has been described earlier [5]. It consists of a video camera (Hitachi VK-C500, Japan) linked to a microscope (American Optical, series one-ten Microstar, USA). The images of the particles when observed on a monitor screen (Sony Trinitron, KX-14 CP1, Japan) had a magnification of x950. A video recording of the particles was made using a video recorder (JVC VHS-Professional editing recorder BR-8600E, Japan). A sharply focussed image of the particle was obtained on the screen in the replay of the

recording by freezing a frame using an editing control unit (JVC RM - 86 U, Japan). Each second of recording had 25 frames of picture and using the editing control unit, a frame-by-frame analysis could be carried out.

Tracings of the images of the particles displayed on the screen were made on transparency sheets. The area of each particle profile tracing was determined using an electronic digital planimeter (Ushikata Digi-Plan 220L, Japan). The perimeter of the particle image was determined by measuring the length of a thread placed along the outline of the particle tracing. About 120-160 particles were chosen from at least 30 different fields of vision for each material.

Swelling of Excipient Particles

A representative sample of the powder was obtained by intermittent sampling of a flowing stream of powder. The sample so obtained was subdivided into portions suitable for microscopic observation. The powder was spread uniformally in a thin layer on a microscope slide and a cover slip was placed on it. Special care was taken to ensure that particle agglomerate formation was avoided. Hydration of the powder was undertaken by introducing water in sufficient quantity below the cover slip using a microsyringe. Timing was carried out from the moment water was introduced. The swelling phenomena was observed on the video monitor and recorded. The field of vision was not changed once swelling of particles was initiated. An arrangement of light bulbs placed around the microscope ensured that the temperature of the immediate surrounding air was maintained at 37 $\pm$ 1°C.

RESULTS AND DISCUSSION

Feret's Diameter

The maximum Feret's diameter, a was measured as the longest length of the particle profile taken with respect to a specific direction. In the case of particles that swelled gradually, sufficient time was

TABLE 1

Percentage frequency distribution of Feret's diameter of hydrated tablet excipient particles

Diameter (μm)	Avicel PH101	Ac-Di-Sol	Nymcel ZSB10	Nymcel ZSD16
0 - 20	6.57	-	-	-
20 - 40	21.17	2.38	1.96	-
40 - 60	20.44	9.52	3.92	7.69
60 - 80	18.98	40.48	15.69	30.77
80 - 100	16.06	23.81	21.57	23.08
100 - 120	8.03	7.14	13.73	23.08
120 - 140	5.84	7.14	13.73	7.69
140 - 160	1.46	4.76	13.73	7.69
160 - 180	1.46	-	1.96	-
180 - 200	-	4.76	3.92	-
200 - 220	-	-	1.96	-
220 - 240	-	-	1.96	-

allowed to lapse before determining their dimensions. This ensured that the value measured was that of the maximum size attainable by the particle or at least close to it.

A frequency distribution of the maximum Feret's diameter values for various tablet excipients in the hydrated state is shown in Table 1. Swollen Ac-Di-Sol, Nymcel ZSB10 and ZSD16 particles measured 20-200 μm, 20-240 μm and 40-160 μm respectively. Avicel PH101 particles also swelled but to a lesser degree. Slightly over 75 % of the hydrated particles measured 20-120 μm (Table 1).

Projected Area

Feret's diameter could be misleading in the case of elongated particles and in such cases the projected area gives a better idea of

TABLE 2

Percentage frequency distribution of projected areas of hydrated tablet excipient particles

Area (x 10^2 μm^2)	Avicel PH101	Ac-Di-Sol	Nymcel ZSB10	Nymcel ZSD16
0 - 10	40.71	4.76	6.12	-
10 - 20	26.43	7.14	10.20	7.14
20 - 30	16.43	35.71	14.29	14.29
30 - 40	10.00	11.90	14.29	21.43
40 - 50	3.57	11.90	24.49	21.43
50 - 60	2.14	9.52	6.12	21.43
60 - 70	0.71	4.76	4.08	-
70 - 80	-	4.76	8.16	-
80 - 90	-	4.76	4.08	7.14
90 - 100	-	2.38	4.08	7.14
100 - 110	-	2.38	4.08	-

particle size. Table 2 shows the projected area distribution of hydrated particles of various tablet excipients. Ac-Di-Sol and Nymcel particles had larger projected areas.

The frequency distribution of Feret's diameter and projected areas of hydrated excipient particles were similar (Tables 1 and 2). A class of particles which had a wide range of distribution of Feret's diameter also followed a similar trend in case of the projected area. Avicel PH101 particles had a narrow distribution of both Feret's diameter and projected area. This was unlike the trend observed during the measurement of dimensions of dry particles of tablet excipients whence the frequency distributions of Feret's diamter and projected area were found to be dissimilar [5].

Wetting caused the expansion of elongated particles preferentially along the breadth component. As a consequence, the differences in the order of the Feret's diameter and projected area were not large and any one of these measurements can reflect the size of the particle. The breadth of the particle, b, is the Feret's diameter taken at right angles to a the maximum Feret's diameter. The particle is enclosed in a minimum area rectangle whose length and breadth are a and b respectively. Figures 1 and 2 show the edge profiles of particles of different tablet excipients in the dry and wet states. Upon hydration, Ac-Di-Sol paricles swell to a greater extent in comparison to Avicel PH101. The particle edges stretch and smoothen and the surface loses its detailed texture. Ultimately, the particle assumes a cross-sectional shape which is closer to a regular geometric figure. Avicel PH101 particles on the other hand expand much less and retain part of their original dry texture form. Ac-Di-Sol has been said to absorb and swell many times its weight in water without dissolving [10]. Its disintegrant action when used at low concentrations in tablets is thought to be due to its fibrous nature, which allows wicking of water into tablet matrices [11].

Wet Nymcel ZSD16 particles have lesser a values and greater b values than Nymcel ZSB10 (Table 1). It appears that wet Nymcel ZSB10 particles, although swollen, still retain their fibrous structure to some extent (Fig 2). Nymcel ZSD16, on the other hand swelled equally along breadth and length. For particles with about the same projected area, Nymcel ZSD16 had a smaller perimeter than ZSB10.

Shape Factors

The projected area diameter (d_a) and the perimeter diameter (d_p) are the diameters of circles having the same area or perimeter as that of the particle respectively. The values for d_a and d_p for different tablet excipients are presented in Table 3. The large differences between d_a and d_p values as observed in dry particles of Avicel PH101,

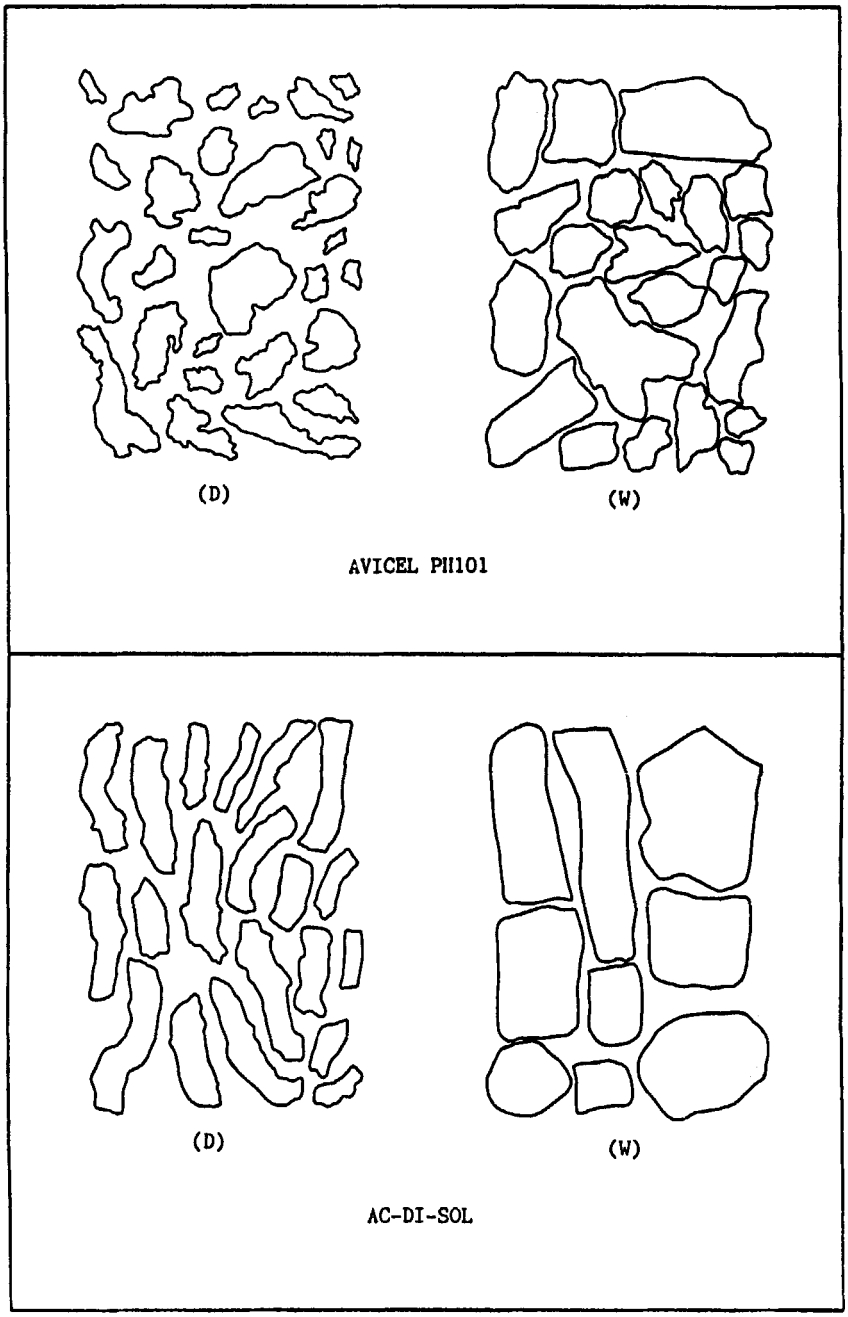

FIGURE 1

Particle shape and edge texture of samples of Avicel PH 101 and Ac-Di-Sol : (D), dry; (W), hydrated.

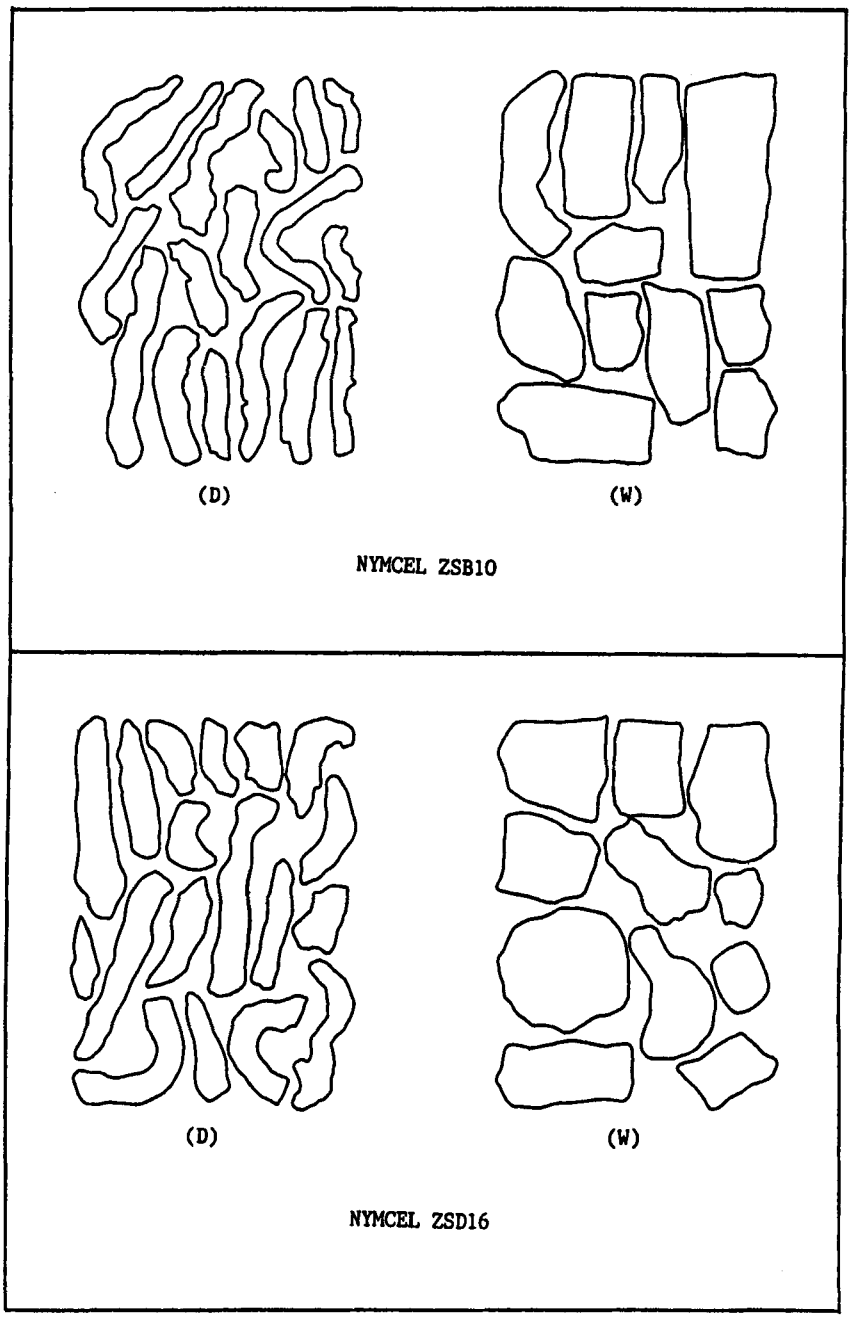

FIGURE 2

Particle shape and edge texture of samples of Nymcel ZSB10 and ZSD16 : (D), dry; (W), hydrated.

TABLE 3

Size and shape factors of hydrated tablet excipient particles

	Avicel PH101	Ac-Di-Sol	Nymcel ZSB10	Nymcel ZSD16
d_a (μm)	52.67 ± 11.73	86.47 ± 18.43	86.25 ± 15.92	81.19 ± 25.63
d_p (μm)	65.70 ± 16.27	96.05 ± 20.75	120.37 ± 22.99	91.39 ± 25.61
x	1.84 ± 0.37	1.47 ± 0.37	3.61 ± 1.50	1.52 ± 0.41
y	0.73 ± 0.05	0.85 ± 0.08	0.81 ± 0.06	0.87 ± 0.09
z	1.55 ± 0.17	1.24 ± 0.14	1.99 ± 0.50	1.30 ± 0.16

Ac-Di-Sol and Nymcel [5] were absent in case of wet systems (Table 3). Swelling caused a smoothening of the particle edges as a result of which the perimeter length per unit area decreased.

Different dimensionless numerical values called shape factors x, y and z are given in Table 3. Elongation ratio (x) is the ratio of a and b. Bulkiness factor (y) is the ratio of projected area to product of a and b. The surface factor (z) is the ratio of the square of the perimeter of the particle to 12.6 times its projected area.

In the dry state the order of x was Nymcel ZSB10 > ZSD16 > Ac-Di-Sol > Avicel PH101 [5]. In the hydrated state however, the order changed to Nymcel ZSB10 > Avicel PH101 > ZSD16 > Ac-Di-Sol. As discussed earlier, Nymcel ZSB10 particles reatain their elongated profile even after being hydrated. Ac-Di-Sol and Nymcel ZSD16 particles swell along their breadth appreciably and appear less

TABLE 4

Percentage change in size and shape factors of tablet excipient particles after hydration

	Avicel PH101	Ac-Di-Sol	Nymcel ZSB10	Nymcel ZSD16
d_a (μm)	+ 33.58	+ 68.33	+ 60.67	+ 52.70
d_p (μm)	+ 23.43	+ 22.94	+ 42.69	+ 6.48
$\underline{x}$	- 8.91	- 59.73	- 28.51	- 69.60
$\underline{y}$	+ 10.61	+ 13.33	- 8.99	+ 1.16
$\underline{z}$	- 14.36	- 46.55	- 19.11	- 50.38

elongated. In numerical terms, all excipients other than Nymcel ZSB10 have $\underline{x}$ values less than 2. Particles having $\underline{x}$ values closer to 1 can be boxed in a minimum area rectangle with both sides equal i.e. a square.

The bulkiness factor ($\underline{y}$) of wet Ac-Di-Sol and Nymcel ZSD16 particles were the closest to unity among the excipients studied. These particles swelled in all directions and appeared to have a near rectangular shape. Nymcel ZSB10 particles had the highest $\underline{z}$ value meaning that their cross-section deviates the most from a circle.

An idea of the extent of change in size and shape factors for various tablet excipient particles that have undergone hydration can be obtained from Table 4. The order for the increase in projected area diameter was Ac-Di-Sol > Nymcel ZSB10 > ZSD16 > Avicel PH101. In the case of increases in the perimeter diameter, the order was Nymcel ZSB10 > Avicel PH101 > Ac-Di-Sol > ZSD16. Although Ac-Di-Sol particles

swelled considerably as indicated by increases in the projected diameter, swelling resulted in the particles losing their rough edge texture and hence the increase in perimeter diameter was relatively less. The change in elongation ratio was negative or zero in all instances signifying that the change along the smaller dimension b upon wetting is higher than that along the larger dimension a.

Changes in the bulkiness factor were positive for Avicel PH101, Ac-Di-Sol and Nymcel ZSD16 and negative for ZSB10. Negative changes would mean that hydration did not result in the particles assuming a shape closer to a rectangle. The change in the surface factor was negative in all instances, meaning that wetting caused the particles to swell and deviate from their sphericity. The change was the highest for Nymcel ZSD16 (-50%) followed by Ac-Di-Sol (-47%).

The video recording method used in this study facilitated the observation of the hydration phenomena. Each frame occupied 1/25 sec of recording and a frame-by-frame search could be carried out using the editing control unit. Avicel PH101 particles underwent slow swelling on contact with water. Swelling was complete in about 3 min and there was no marked change in the shape of swollen particles compared to the dry ones. In the case of Ac-Di-Sol, swelling was complete in 5-6 sec. Upon hydration, smaller particles developed a smoother edge while cylindrical particles and fibres grew in size assuming larger cylindrical shapes. In about 45 sec time, large swollen particles were formed. Some merged together, others dissolved, while still others remained unchanged. The dissolving portions could be the non-crosslinked components of the sodium carboxymethylcellulose polymer.

Swelling of Nymcel ZSB10 particles extended up to about 30 sec although most of it occurred in the first 4 sec after contact with water. The particles became transparent, enlarged in size yet retained their general shape characteristics. Smaller fragments of the material

however dissolved or integrated with other swollen masses in their vicinity. In the case of Nymcel ZSD16, the increase in size continued to 60 sec, the wet particles being largely deformed in shape.

In conclusion, the video recording technique was applied usefully to study the swelling phenomena of individual tablet excipient particles. Most tablet disintegrants swelled almost instantaneously on contact with water, the degree of swelling being different for different disintegrants. Swelling of Avicel PH101 particles was of a lower magnitude in comparison to that of Ac-Di-Sol and Nymcel particles. Swelling resulted in a smoothening of the particle edge profile and a deformation of shape.

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