Drying Rates of Tablet Granulations II: Effect of Particle Size and Granular Densities

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Abstract □ The effects of the granule size and density on the drying rate kinetics of tablet granulations were studied using lactose and sulfathiazole granules prepared with acacia mucilage and povidone solution. The drying rate kinetics consisted of three distinct phases of drying when the drying rate was plotted against remaining moisture content: constant rate, first falling rate, and second falling rate periods. The effect of various statistical diameters and granular density on the drying rate during the first falling rate period was analyzed, and the mechanism of moisture migration during this phase of drying was identified.

Keyphrases □ Tablets—granulations, drying rates, effect of particle size and granular densities □ Granulations, tablet—drying rates, effect of particle size and granular densities □ Drying rates—tablet granulations, effect of particle size and granular densities, lactose and sulfathiazole granules prepared with acacia mucilage and povidone □ Particle size—effect on drying rates of tablet granulations □ Densities, granular—effect on drying rates of tablet granulations

In a preliminary investigation (1), a satisfactory technique was developed to study the kinetic rates of drying and to evaluate the effect of certain granulating adjuvants and fillers on the drying rates of tablet granulations.

It was observed that drying of granulation occurs through three distinct phases, as has been reported (2–6) for various materials in the chemical industry. The drying rate kinetic data vividly showed this drying as three straight lines when the drying rate (grams of moisture evaporated per hour per gram of dry solid) was plotted *versus* moisture content based upon dry solid. The first phase, generally termed the constant rate period, corresponded to the phase of drying during which the drying rate remained unchanged.

As long as the drying surface remained saturated with liquid moisture, the constant rate period existed. However, when the rate of drying exceeded the rate of moisture migration to the drying surface, the drying rate started falling, which initiated the first falling rate period. During this period, the drying rate depended more upon the physicochemical nature of the granulation and less on the external drying conditions such as temperature and air flow rate. During the second falling rate period, drying occurred by moisture evaporation within the granulation, followed by diffusion of water vapor from the interior of the granules to the drying air.

A major portion of the granulation drying takes place during the first falling rate period, so the drying rate during this phase has significant influence on the total drying time. Drying during the second falling rate period is usually extremely slow and utilizes proportionally larger amounts of energy. Thus drying during both falling rate periods can be significant in terms of the cost of the drying operation and the prolonged exposure of the active ingredients to heat.

This investigation is a detailed study of the effect of granule size on the drying rate. This parameter is related to other physical characteristics of granules such as density and porosity. An attempt was made to establish a relationship between the size and the density of granules and the drying rate during the first falling rate period. The first falling rate period was selected since the drying rate during this period is most affected by granulation properties and least by drying conditions. The effect of granules size and density has never been studied quantitatively for this phase of drying.

Lactose and sulfathiazole granules, prepared with acacia mucilage and povidone solutions as granulating agents, were selected as test substances.

EXPERIMENTAL

Equipment Design—The rates of drying of prepared granules were studied under standardized conditions. For each type of material, the temperature of inlet air, the velocity of air flow, and the method of granulation were kept constant. The apparatus developed by Bhutani and Bhatia (1) was used, but some modifications were made to enhance the reproducibility of the results obtained. The insulation of the heating chamber was improved by initially lining the outside of the chamber with glass wool followed by two layers of foam padding. This insulation kept the inlet air temperature more stable by eliminating heat loss. The second modification was related to the placement of the wet granulations in the drying tray. The bed thickness was reduced from 1.27 to 0.64 cm, and the granules were placed in the middle of the tray in the form of a square, 20 × 20 cm. This modification provided more direct and uniform contact between the granules and the drying air.

Granulating Process—On the basis of preliminary experiments, a standard granulating procedure was selected such that the variations in particle-size distribution due to variations in wet mixing time during granulation were completely avoided. A standard batch of granulation was prepared by granulating the test substance in a Glen mixer, using a definite quantity of concentrated solution of the binder and adding sufficient quantities of distilled water to obtain the wet mass. By keeping the amount of binder (dry weight) constant for a test substance, the particle-size distribution could be varied for a batch of granules by varying the amount of distilled water. The wet mass was then forced through a standard No. 8 mesh screen. Each granulation was prepared in quadruplicate, and the average results of the four batches were considered.

Lactose Granulation Studies—The drying chamber was preheated to about 42° with an inlet air temperature of 65° and the heating coil placed inside the dryer appropriately set to give the

Table I—Statistical Diameter[a], Granular Densities, Slopes for the First Falling Rate Period, and the Moisture Content of the Granulation at the First Critical Point for Batches of Test Granules

System	Batch	d_{geo}, μm	d_v, mm	d_s, mm	d_{vs}, mm	Density[b], g cm^{-1}	Slope[c]	σ_s[d]	Percent Moisture Content at First Critical Point
Lactose granulations with acacia mucilage	A	1600	0.778	0.612	1.25	1.37	2.95	0.26	7.8
	B	1050	0.482	0.371	0.82	1.42	3.99	0.25	7.9
	C	810	0.310	0.221	0.58	1.47	5.36	0.00	7.2
	D	640	0.239	0.170	0.46	1.51	6.02	0.41	4.0
	E	560	0.160	0.107	0.37	1.52	6.86	0.28	4.5
Lactose granulations with povidone aqueous solution	A	1580	0.588	0.436	1.13	1.36	2.43	0.06	11.1
	B	1050	0.490	0.380	0.82	1.43	3.48	0.03	10.1
	C	870	0.259	0.166	0.58	1.47	4.83	0.38	8.2
	D	680	0.197	0.130	0.45	1.51	6.54	0.00	5.1
	E	465	0.084	0.040	0.26	1.52	7.88	0.15	4.0
Sulfathiazole granulations with acacia mucilage	A	1180	0.436	0.313	0.86	1.43	2.17	0.12	22.0
	B	980	0.370	0.269	0.71	—	3.08	0.17	16.0
	C	720	0.260	0.190	0.52	1.52	3.80	0.16	14.0
	D	680	0.250	0.180	0.49	1.57	5.10	0.24	9.5
	E	610	0.230	0.160	0.44	1.59	6.30	0.50	7.0

[a] d_{geo} = geometrical mean diameter = 50% size from the logarithmic probability plot, d_v = mean volume diameter, d_s = mean surface diameter, and d_{vs} = mean volume surface diameter. [b] Densities represent average of three determinations. [c] Slopes of the first falling rate period calculated as g of moisture lost, g of dry solid × 100/hr, kg of dry solid, g of moisture still present. [d] σ_s = standard deviation for the slope of the first falling rate period obtained with 90% confidence limit.

desired temperature. The chamber was equilibrated at this temperature for 15 min prior to the introduction of granules. The initial moisture content of the granules was determined using a moisture balance[1] at 80° for 15 min. Sufficient sample of the wet granules was then spread uniformly to provide a 20 × 20-cm square bed of 0.64-cm thickness in a sample tray.

The tray was suspended inside the dryer from the weighing device and a thermocouple placed on the surface of the granules bed. The placement of the tray in the drying chamber requires the opening of the chamber door, which usually led to a slight drop in the drying chamber temperature. However, placement of the tray was done very quickly so that the drop in temperature was about 2° and the test granulations were immediately exposed to a temperature of 40 ± 1°.

The initial weight of the suspended system, *i.e.*, the weighing assembly and granules, was recorded along with the inlet air, granule surface, and outlet air temperatures every 30 min until the weight of the granulations became constant. At this point, the dryer was opened and the final moisture content of the granules was determined using the moisture balance.

Sulfathiazole Granulation Studies—The same procedure as described for lactose was used, except that the drying chamber was initially heated to about 53° with an inlet air temperature of 85°. The drying chamber was then equilibrated at 53° for 15 min. When placed in the dryer, the sulfathiazole granules were immediately exposed to a temperature of 50 ± 1°.

Determination of Mean Volume Diameter, d_v, Mean Surface Diameter, d_s, and Mean Volume-Surface Diameter, d_{vs}, of Granules—The statistical diameters were determined because of their physical significance and close relationship to the process of drying. Sieve analyses were performed on each of five batches of granules using standard U.S. sieve numbers 8, 10, 20, 40, and 60. Plots of the logarithm of sieve size against cumulative percent less than stated size (percent undersize) on a probability scale were obtained for each batch from sieve analysis data.

From log-probability plots, the geometric mean diameter, d_{geo}, and standard deviation, σ_{geo}, were calculated. Since a weight distribution was involved in this plot, the definitions of the statistical diameters in terms of weight distribution as derived by Hatch (7) were used for their determination:

$$\log d_v = \log d_{geo} - 3.4539 \log^2 \sigma_{geo} \quad \text{(Eq. 1)}$$

$$\log d_s = \log d_{geo} - 4.6052 \log^2 \sigma_{geo} \quad \text{(Eq. 2)}$$

$$\log d_{vs} = \log d_{geo} - 1.1513 \log^2 \sigma_{geo} \quad \text{(Eq. 3)}$$

[1] Model 6000, Ohaus Scale Corp., Union, N.J.

Determination of Granular Densities—Accurately weighed samples of dried granules (about 5 g) were placed in a known volume of xylene, and the volume of xylene displaced was carefully determined. The granular density was then calculated from the weight of the sample and the granular volume.

Determination of Slopes of First Falling Rate Period—The drying rate (grams hour^{-1} kilogram^{-1} of dry solid) was plotted against the percent moisture content of granules on a dry basis for each drying run. The drying rate curves followed three distinct linear drying phases, as previously reported for tablet granulation (1). For the present investigation, the slopes of the first falling rate period were of particular interest and were determined by linear regression (3). Four runs were made for each formulation, and four slopes were determined from them. The averages of the slopes were calculated and used in this study. The standard deviations for the slopes were determined with a 90% confidence limit for each batch of granulations.

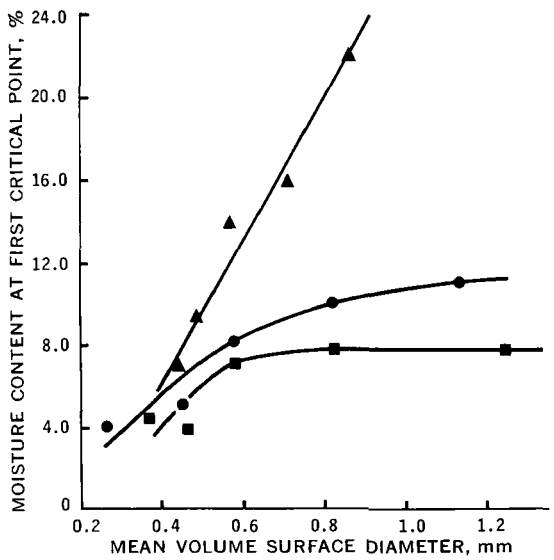

Figure 1—*Plot of the percent moisture content at first critical point* versus *mean volume-surface diameter of sulfathiazole and lactose granulations. Key:* ▲, *sulfathiazole granulations prepared using acacia mucilage as binder;* ●, *lactose granulations prepared using aqueous povidone solution as binder; and* ■, *lactose granulations prepared using acacia mucilage as binder.*

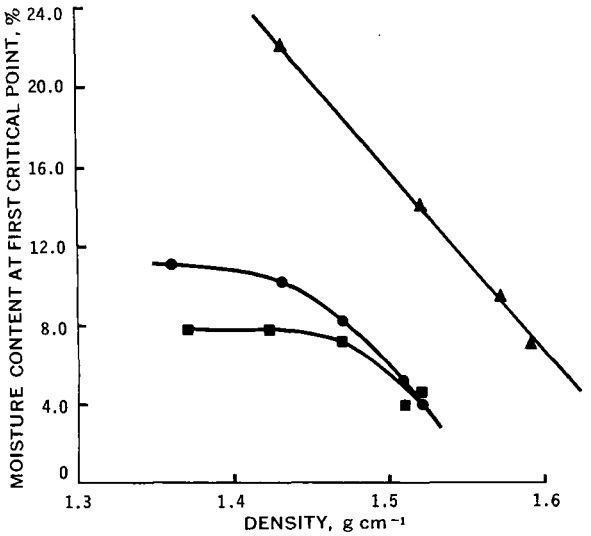

Figure 2—*Plot of the percent moisture content at first critical point* versus *density of sulfathiazole and lactose granulations. Key:* ▲, *sulfathiazole granulations prepared using acacia mucilage as binder;* ●, *lactose granulations prepared using aqueous povidone solution as binder; and* ■, *lactose granulations prepared using acacia mucilage as binder.*

RESULTS AND DISCUSSION

The various physical parameters for lactose and sulfathiazole granules, prepared using acacia mucilage and povidone solutions, are presented in Table I along with their corresponding values for the slopes of the first falling rate period and the moisture contents at which the first falling rate period started (first critical point). The statistical diameters of the granules affected the first critical points for these batches (Fig. 1). As the mean volume–surface diameters of the granules increased, the first critical point occurred at a higher moisture content. Since the moisture movement within a larger size granule would be more restricted, whether by diffusion or capillary flow, unsaturation of the granulation surface occurs at higher moisture content. Therefore, for larger granulations, more drying occurs during the falling rate periods and more time is needed to dry them to a given final moisture content.

There was a marked difference in the shape of the curves for lactose and sulfathiazole granules. For sulfathiazole granules, which are mostly porous and the moisture present is unbound since the material is water insoluble, the relationship was linear; for lactose granules, the curve indicated an apparent logarithmic relationship. This observation suggests that the moisture movement during this phase of the drying rate is directly proportional to the moisture content of the sulfathiazole granules and thus basically due to a

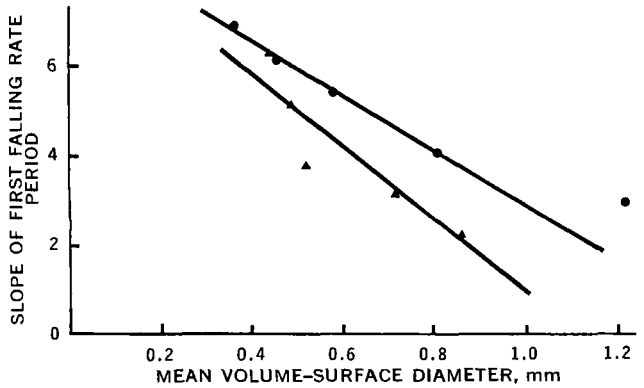

Figure 3—*Plot of the slope of first falling rate period* versus *mean volume–surface diameter of sulfathiazole and lactose granulations. Key:* ▲, *sulfathiazole granulations prepared using acacia mucilage as binder; and* ●, *lactose granulations prepared using acacia mucilage as binder.*

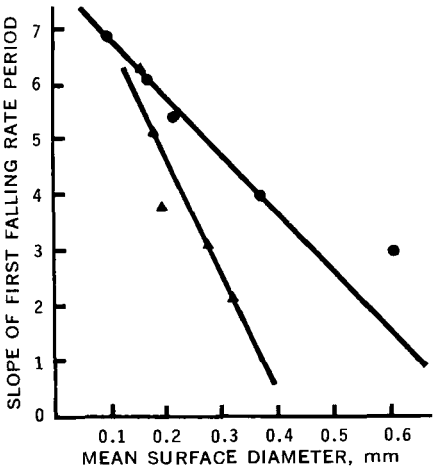

Figure 4—*Plot of the slope of first falling rate period* versus *mean surface diameter of sulfathiazole and lactose granulations. Key:* ▲, *sulfathiazole granulations prepared using acacia mucilage as binder; and* ●, *lactose granulations prepared using acacia mucilage as binder.*

capillary flow mechanism as reported for sand beds (6) and porous ceramic plates (5). For lactose granules, the moisture movement is due to a diffusion mechanism or to diffusion and a capillary flow mechanism, both occurring simultaneously as in the drying of clays and paper pulp (2).

Pitkin and Carstensen (9), while studying the final moisture content of sucrose granulations as a function of granule size, concluded that granules dry by a diffusional process. This conclusion is probably true for sucrose granules. However, in the present study, the mechanism of drying differed depending upon the nature of the ingredients present in the granulations.

The curves for the percent moisture content at the first critical point *versus* the mean volume diameter and the mean surface diameter were observed to be similar, and it was difficult to conclude if one statistical diameter gave a better correlation than the other two studied.

The density of the dried granules varied inversely with the granular size. Thus, opposite relationships were observed with densities of the granules compared with those observed with various statistical diameters. The curves for the percent moisture content at the first critical point *versus* densities of the granulations are shown in Fig. 2. As the granular density increased, the first critical point occurred at lower moisture contents. This relationship was linear for sulfathiazole granules; for lactose granules, an apparent logarith-

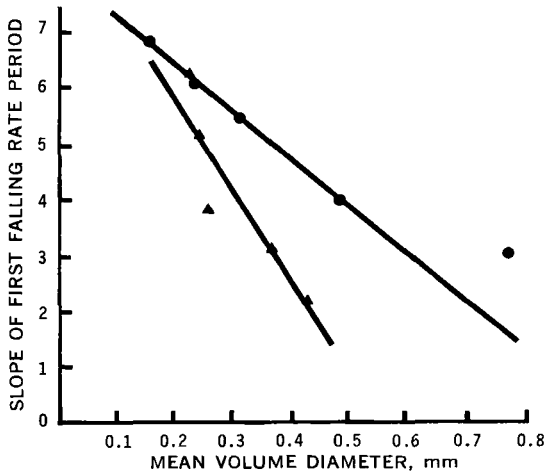

Figure 5—*Plot of the slope of first falling rate period* versus *mean volume diameter of sulfathiazole and lactose granulations. Key:* ▲, *sulfathiazole granulations prepared using acacia mucilage as binder; and* ●, *lactose granulations prepared using acacia mucilage as binder.*

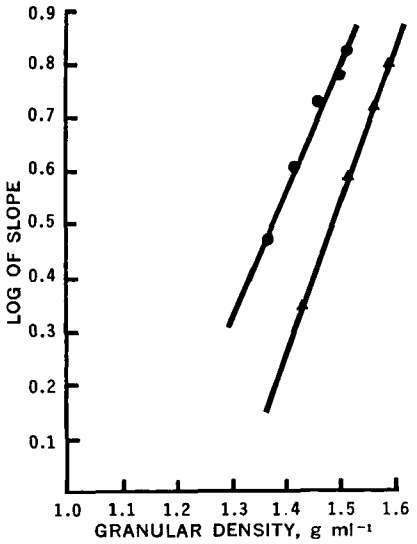

Figure 6—*Plot of logarithm of slope of first falling rate period* versus *granular density of sulfathiazole and lactose granulation. Key:* ▲, *sulfathiazole granulations prepared using acacia mucilage as binder; and* ●, *lactose granulations prepared using acacia mucilage as binder.*

mic-type relationship existed. This phenomenon could be easily explained based upon mechanism of moisture movement within the granules during this phase of drying.

Linear relationships were also observed between the slopes of the falling rate period and the statistical diameters of granulations prepared using the same binding agent (Figs. 3–5). A reduction in the size of the granules led to an increase in the slope because for smaller granules the first falling rate period starts at a lower moisture content so moisture is depleted at a faster rate and, furthermore, the moisture movement to the surface of the granules occurs faster.

A logarithmic linear relationship was observed between the slopes of the first falling rate period and the granular density for both lactose and sulfathiazole granules (Fig. 6). As the granular density decreased, the moisture movement within the granules became more restricted and the rate of moisture depletion from the surface increased. The granular density affects the first critical points as well as the slope of the first falling rate period and, therefore, the drying rate curve of the granulations. Having established the effect of physical parameters upon the drying rate during the constant rate period, falling rate periods, and critical points, one could draw a drying rate curve for a given formulation and determine the drying time from the initial to a desired final moisture content.

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Automated Method for Determining Calcium Disodium Edetate in Iodinated Contrast Media Parenterals

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Abstract □ An automated method, based on the chelating reaction of calcium disodium edetate with zirconium and the subsequent determination of excess zirconium reacted with xylenol orange, was developed. The procedure is applicable to parenterals consisting of iodinated contrast media. Familiar modules of an automated analyzer were used, but the method can be performed manually if the sample load does not warrant automation. The pH should be controlled between 0.3 and 0.5. No interferences were encountered. Twenty samples per hour can be run on prepared sample solutions. The precision of a single determination, at the 95% confidence level, was ±0.008 mg/ml with a limit of detection near 0.40 mg/ml.

Keyphrases □ Calcium disodium edetate—automated analysis in iodinated contrast media parenterals □ Sequestering agents—automated analysis of calcium disodium edetate in iodinated contrast media parenterals □ Automated analysis—calcium disodium edetate in iodinated contrast media parenterals

Calcium disodium edetate USP (I) is commonly added to iodinated contrast media parenterals (*e.g.*, sodium and meglumine iothalamates USP) as a sequestering–stabilizing agent. It is also used as an antioxidant in some foods and beverages such as salad dressings, margarine, barbecue sauce, beer, and wine. As a sequestering agent, it is added to complex traces of metals, thus preventing oxidation (catalyzed by trace metals) or possible discoloration.

Several colorimetric methods have been reported