Physical Aspects of Wet Granulations I: Distribution Kinetics of Water

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Abstract ☐ The kinetics of wetting during the process of making tablet granulations were studied; the process progresses through an intermediate (overwetted) nonequilibrium granule to a final, equilibrated granule. In systematic formulation changes, there is an optimum composition from the point of view of hardness and content of equilibrium granules.

Keyphrases ☐ Kinetics, distribution—wetting during process of making tablet granulations ☐ Distribution kinetics—wetting during process of making tablet granulations ☐ Granulations, tablet—distribution kinetics of wetting during preparation ☐ Tablet granulations—distribution kinetics of wetting during preparation ☐ Dosage forms—tablet granulations, distribution kinetics of wetting during preparation

Granulation technology has been employed for close to a century in pharmacy (1), yet many aspects are still confined to what is considered art. The primary purposes of granulating material in general are to: (a) enlarge particle sizes to improve flow and uniformity of solid dosage forms, (b) make hydrophobic surfaces hydrophilic to improve bioavailability (2), (c) improve homogeneity of low dosage level dosage forms, (d) improve cohesion during and after compression of tablets, and (e) overcome adverse electrostatic properties of a powder blend (3).

In "wet" granulation operations, fine powders are agglomerated; the agglomerates attain their strength by formation of solid bridges (3–5). Improved binder distribution in the agglomerate improved the strength (5–8) when agglomerates were made by chemical reaction, hardened by melting, and hardened by crystallization of dissolved materials. In general, the agglomerate (ball) diameter, d, had a crushing strength, l, given by:

$$l = kd^n \qquad \text{(Eq. 1)}$$

where k and n are parameters particular to the solid and condition under study. When sodium chloride (or another inorganic salt) is the bridging (granulating) agent (9), then k increases with increasing drying temperature and depends on the concentration of salt in the granulating liquid since k reaches a maximum close to (but somewhat below) the saturation concentration. The value of n simply increased (from 1.5 to 2) with increasing temperature.

The quoted references concern the heavy and fine chemical industries. Unlike studies of this type, granulations in pharmacy are made either by adding the bridging agent to a mixture of finely subdivided pharmaceutical powders or by adding water to the powder containing the bridging agent in dry state. In both cases, the granulation goes through several stages:

1. At first, part of the mixture is wetted excessively and forms large aggregates. The remaining powder stays dry.

2. Distribution of water or the granulation liquid is then effected, and both large and small granules are present.

3. Finally, the granules equilibrate and attain a fairly uniform size (provided "proper" amounts of water or granulating fluid are present).

4. A granulation can be kept in a kneading mixer too long, and the equilibrium granular structure can be destroyed. Steps 1–3 are studied here.

EXPERIMENTAL

Powders of the following composition were used: $(29 - y)$ kg of lactose USP, y kg of sucrose USP, and 4 kg of starch USP (cornstarch). They were blended for 2 min in a chopper-ribbon mixer[1] with blades rotating at 140 rpm and chopper blades rotating at 3500 rpm. Four 750-ml portions of distilled water were added at 15-sec intervals, and the mixer was stopped at t min after addition of the first portion of water. Then the material was passed through an oscillating granulator[2] using a No. 6 screen. The material was then dried in a fluid bed drier[3] using air at an inlet velocity of 380 cfm and 42°. The drying end-point was about 20 min after the initial drying time, and the end-point was established by a rise in the outlet air temperature (35°).

The dried powders were subjected to sieve analysis with standard U.S. sieves; the density of the granulation was determined by pycnometry, using ethyl acetate as the displacement liquid. The hardness of the granules was estimated by the method of Harwood and Pilpel (10).

Experiments at mixing intensities lower than those obtained in the chopper-ribbon blender were performed in a planetary mixer[4]; 1150 g of lactose USP was mixed with 120 g of corn starch and granulated with 400 ml of a 1:10 starch paste (40 g of corn starch and 400 g of water) at low agitation speed (50 rpm), using a shield-type agitator blade in the following fashion. Forty grams of corn starch was suspended in 100 ml of water at 25° and added to 300 ml of boiling water, and the ensuing gel was cooled to 60°. The paste was placed in a plastic bag with a pinhole. When the temperature of the paste reached 50°, the paste was forced through the hole into the lactose–corn starch mix in the mixer. At the same time, a timer was started. The time for completion of addition was noted, and the mixing was stopped at a predetermined time.

The powder mass was poured out on a six-mesh screen, and the dry powder and/or the smaller wet granules were passed through by shaking. The retained and passed fractions were weighed, dried, and reweighed. The moisture balance was assured by checking the loss on drying, showing that the coarse fraction had the higher water content.

RESULTS AND DISCUSSION

The purposes of this study were to describe the initial granulation process and to follow the amount of granulation that is of a larger size than the equilibrium granule which eventually ensues. Therefore, granulations were mixed for the various times, t, indicated in Fig. 1 and subjected to screen analysis.

A convenient measure of the powder is its geometric surface area. Surface areas can, of course, be measured in many fashions (e.g., gas

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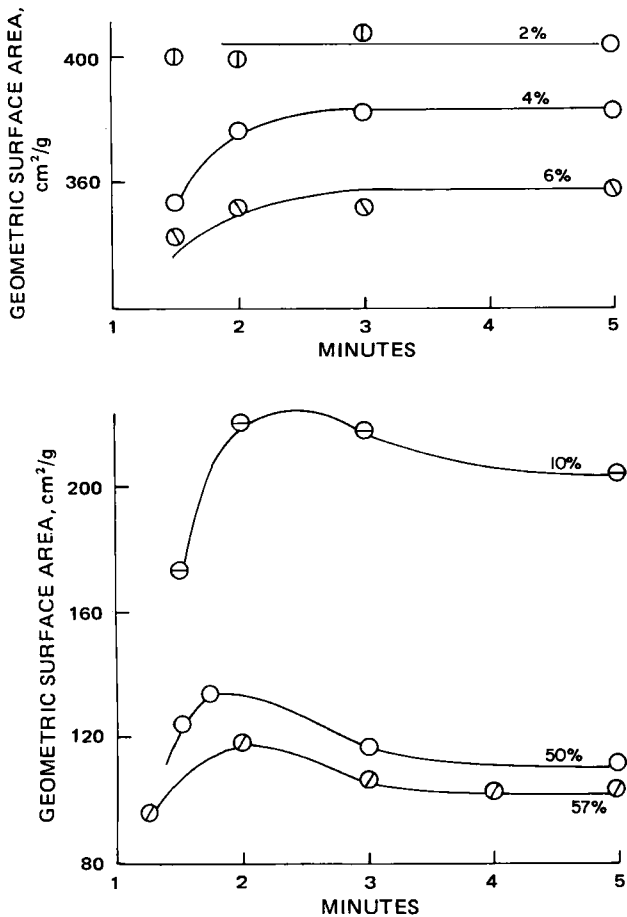
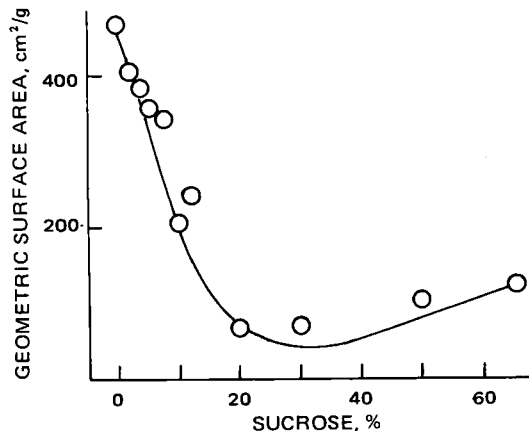Figure 1—*Geometric surface areas as a function of kneading time for various y values.*

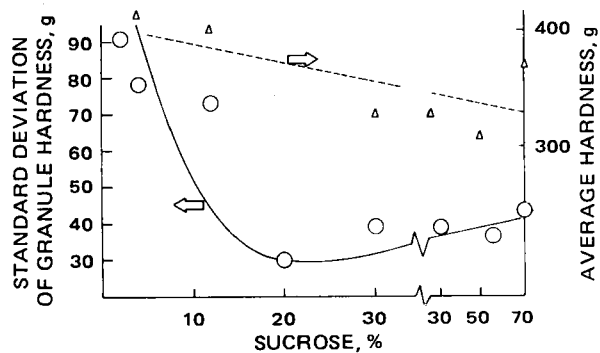Figure 2—*Equilibrium geometric surface area as a function of the amount of sucrose.*

Figure 3—(Δ) *Average Pilpel hardness (grams) of final granules (right scale) as a function of percent sucrose in formulation. The final granulations were kneaded for 5 min. The points represent data set of 10.* (O) *Left scale represents standard deviation.*

adsorption). In this study, however, the important characteristic was the external surface of agglomerates and not the internal surface of the pore space. For this reason, screen analysis was an appropriate tool.

The screen analysis data were converted to geometric surface areas in the following fashion. A mesh fraction is defined by a maximum size (the upper screen) and a minimum size (the lower screen). The particles are assumed to be spherical and of a size of the mean of the confining sieve openings; e.g., a powder of fraction −20/+40 would be considered to consist of spheres of diameter (840 + 420)/2 = 630 μm = 0.063 cm, since the wire mesh openings of the two screens are

840 and 420 μm, respectively[5].

If p g of density $ρ$ (grams per milliliter) is retained by confining screens of q and s cm, then $d = (q + s)/2$ cm and the solid volume is $p/ρ$. Therefore, the number of particles in the mesh fraction is:

$$n = 6p/(ρd^3π)$$ (Eq. 2)

i.e., the surface area of the fraction is (11):

$$O' = \frac{6p}{πd^3ρ} πd^2 = 6p/(ρd)$$ (Eq. 3)

The total area is $(6/ρ) [Σ(p/d)]$ cm²/(Σp) g, so that the area (square centimeters) per gram is:

$$O = \frac{6Σ(p/d)}{ρΣp}$$ (Eq. 4)

For −20/+40-mesh granules with 2% sucrose, $ρ$ was found to be 1.50 ± 0.01. For −20/+40-mesh granules with 30% sucrose, it was 1.51 ± 0.01 g/ml. Therefore, $ρ$ was estimated at 1.5 g/ml in all cases. There was a slight increase in density in the finer fractions (up to 1.53 g/ml), so the denominator in Eq. 4 more properly should be $Σ(ρp)$. The error in factoring out $ρ$ is, however, less than 2%.

Surface areas obtained *via* Eq. 4 are shown in Fig. 1. Equilibrium seems to be established after 5 min, and the surface areas at equilibrium were plotted *versus* the sucrose to lactose ratio (expressed in percent as 100y/29) in Fig. 2.

The hardness (Pilpel) of the granules estimated by the method of Harwood and Pilpel (10) is shown graphically in Fig. 3. The granule-to-granule variation decreased and became level at sugar concentrations above 20%.

The crushing strength of a granule as a function of its weight was determined by taking granules after 5 min of mixing (and subsequent drying), weighing various granules individually, and determining their Pilpel hardness (Fig. 4). There was a good correlation ($r = 0.96$) at granule weights of 4 mg or less. The effect of mixing time on Pilpel hardness is shown in Fig. 5.

A 10% sugar granulation was mixed for 1.5 min, dried granules were sampled randomly, and Pilpel hardness was checked (Fig. 6). The same procedure also was repeated for a granulation kneaded for 3 min.

It is apparent from Fig. 1 that O passes through a maximum in many cases and then approaches an equilibrium value. This finding is in accord with the introductory description of the granulation process (Steps 1–3). As shown schematically in Fig. 7, when the powder mass consisting of N particles of diameter d is "wetted," a fraction, f, of the particles is going to be overwet and a fraction, $(1 − f)$, is not wet at all[6]. Eventually the moisture distributes itself evenly over the powder mass. If it is assumed that a wet agglomerate can

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[5] The rationale and limitations of this approach were described previously (12, 13); the validity of the approximations made here were tested with the larger screen sizes by weighing granules. The ensuing error in geometric surface area is about 5%. As opposed to crystalline solids, granules are fairly "spherical."

[6] This assumes that there is only one equilibrium size in the "equilibrium" granule. The more realistic case of several sizes present at the final stage is somewhat complex and is treated in the *Appendix*.
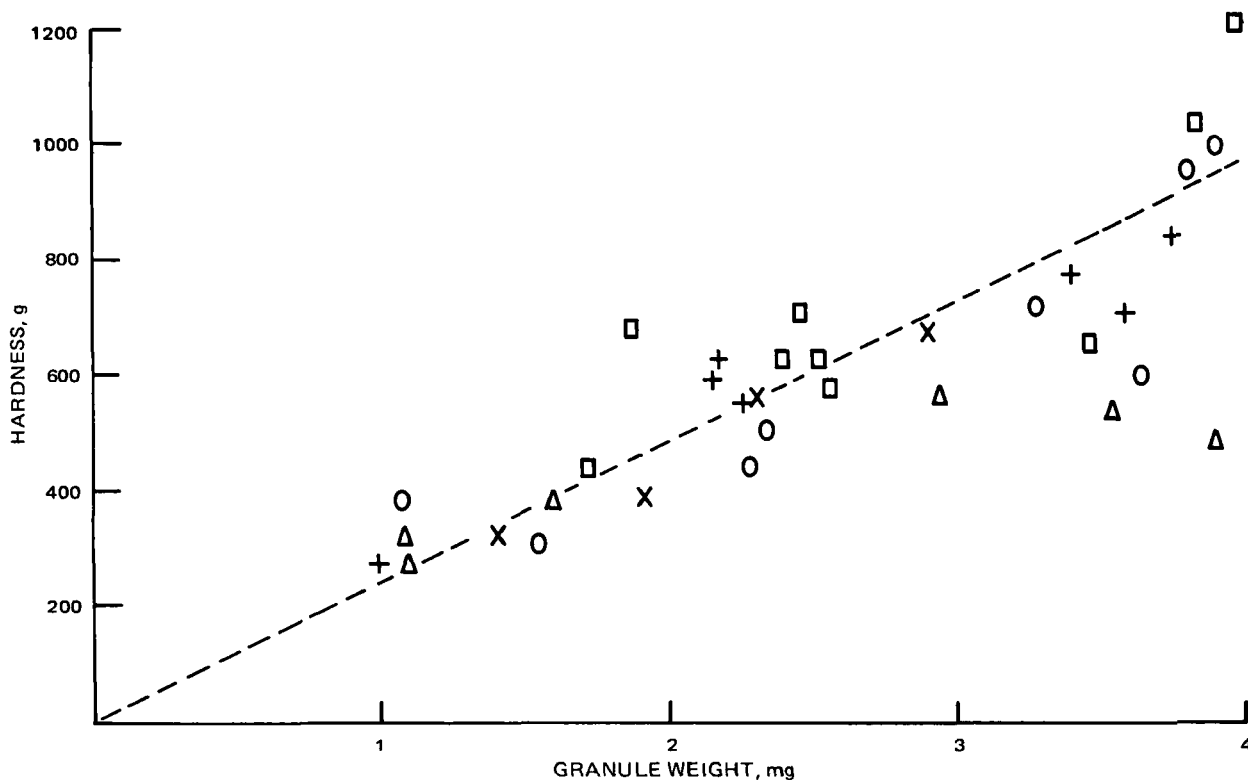
Figure 4—*Pilpel hardness (grams) as a function of granule weight. Key (percent sucrose):* O, 2; +, 6; ✕, 12; □, 10; and △, 30.

accommodate at most an amount of water w^* in an agglomerate of diameter d^* and at the end will accommodate an amount of water w' in an agglomerate of diameter d' and, furthermore, that a total of W g of water is added, then at first, there are W/w^* agglomerates with a total volume of $[W/w^*]\pi(d^*)^3/6$, which (in all) contain the Nf wetted particles.

If the amount of water in an agglomerate at time t is denoted w, then the geometric surface area, O, is a function of w and f, i.e., $O = \phi[w,f]$. This function is defined for all values of w and f, where $w^* > w > w'$ and $0 < f < 1$. Not all of the w and f values occur in practice; e.g., a high w value and a high f value will not occur simultaneously. A process, essentially, defines a set of w and f values as a function of time, so that the geometric surface area as a function of time is a *curve* defined by $O = \phi[w,f]$, $w = \psi_1(t)$, and $f = \psi_2(t)$.

For the sake of simplicity, it is assumed that $w = w^*$ until the entire mass is wetted (i.e., $f = 1$). At higher time values, the nonequilibrium granule of diameter d^* containing w^* g of water decreases in size to a diameter of d' and a water content of w' g/granule.

If, as shown in Fig. 7, it is assumed that the individual particles in the agglomerates form cubic assemblages (14, 15), i.e., that the spheres touch at the poles and at four points of their equator, then they have coordination number six and a porosity of 0.475[7]. Each particle oc-

cupies a virtual volume of d^3 in this configuration, so the volume of the agglomerates in total is Nfd^3. This leads to:

$$Nfd^3 = W(d^*)^3\pi/(6w^*) \qquad (\text{Eq. 5})$$

and, therefore:

$$d^* = d\,[6w^*Nf/(\pi W)]^{1/3} \qquad (\text{Eq. 6})$$

The geometric surface area, then, is:

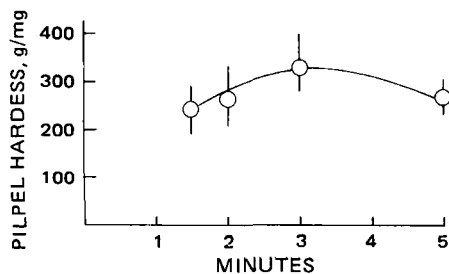$$O = N(1-f)\pi d^2 + \frac{W}{w^*}\,\pi(d^*)^2 \qquad (\text{Eq. 7})$$

Figure 5—*Pilpel hardness of granules of less than 4 mg as a function of time (10% sucrose).*
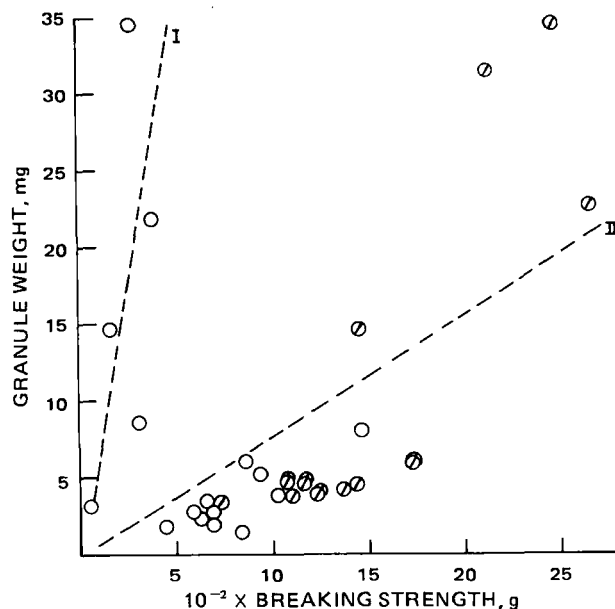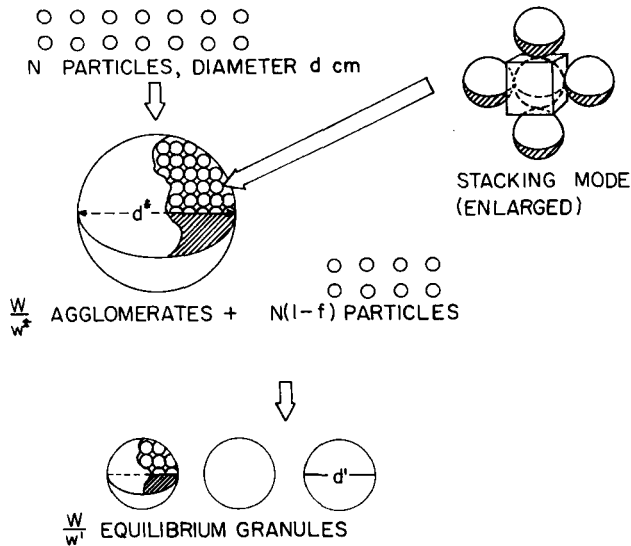

Figure 6—*Pilpel hardness and granule weights of a granulation kneaded for 1.5 min (⊘) and of a granulation kneaded for 3 min (O).*

[7] The volume of the sphere is $\pi d^3/6$ and that of the cube enclosing it is d^3, so the fraction of the void is $[1 - (\pi/6)] = 0.476$.

Figure 7—*Schematic drawing of the formation of agglomerates from prime particles plus water and the formation of equilibrium granules from the agglomerates. The curved lines indicate wedge-shaped cuts into spheres; the insert at the top right is an enlargement of the six-coordinated stacking within agglomerates and granules.*

From Eq. 6, it is seen that:

$$d* = d \left(\frac{6w*Nf}{\pi W}\right)^{1/3} \qquad \text{(Eq. 8)}$$

which, when inserted in Eq. 7, gives:

$$O = N(1 - f)\pi d^2 + \frac{W}{w*}\left(\frac{6w*N}{W\pi}\right)^{2/3}(f^{2/3}\pi d^2) \qquad \text{(Eq. 9)}$$

It is seen that:

$$\partial O/\partial f = \pi d^2\left\{-N + \frac{2W}{3w*}\left(\frac{6w*N}{\pi W}\right)^{2/3}(f^{-1/3})\right\} = 0 \quad \text{(Eq. 10)}$$

when:

$$f = 1.08\frac{1}{N}\frac{W}{w*} \qquad \text{(Eq. 11)}$$

$W/w*$ is the number of particles wetted, and when $(W/w*)/N < 0.93$ then $f < 1$; *i.e.*, under such conditions, there will be an extremum. This inequality is quite reasonable for "good" granulations.

The extremum is a maximum because:

$$\partial^2 O/\partial f^2 = -\frac{1}{3}\frac{2}{3}\frac{W}{w*}\left(\frac{w*N}{\pi W}\right)^{2/3}(f^{-4/3}) < 0 \qquad \text{(Eq. 12)}$$

for $0 < f < 1$.

The maximum refers to the initial stage where the powder is eventually all wetted at time t_1. The granule, at this point, contains $w*$ g of water/agglomerate of diameter $d[6w*N/(\pi W)]^{1/3}$; this is obtained by inserting the value $f = 1$ in Eq. 8. Therefore the geometric surface area at time t_1 is:

$$O_1 = (w*/W)(\pi)d^2[6w*N/(\pi W)]^{2/3} \qquad \text{(Eq. 13)}$$

After time t_1, the agglomerate becomes smaller. At time t_2, it attains an equilibrium size of diameter d' containing w' g of water. Then w' and d' are related by an equation similar to Eqs. 8 and 13:

$$d' = d[6w'N/(\pi W)]^{1/3} \qquad \text{(Eq. 14)}$$

The geometric surface area at time t_2 is:

$$O_2 = (w'/W)(\pi)d^2[6w'N/(\pi W)]^{2/3} \qquad \text{(Eq. 15)}$$

The maximum referred to in the initial stage is an overall maximum if $O_1 > O_2$, *i.e.*, if:

$$(w*/W)(\pi)d^2[6w*N/(\pi W)]^{2/3} > (w'/W)(\pi)d^2[6w'N/(\pi W)]^{2/3}$$

$$\text{(Eq. 16)}$$

i.e., if $w* > w'$, which is true by definition. Therefore, with the as-

Table I—Amounts of Equilibrium and Nonequilibrium Granules as a Function of Kneading Time

| Kneading Time, min	Number of Equilibrium Granules	Number of Nonequilibrium Granules
1.5	2[a]	14[a]
2	3	13
3	5[a]	11[a]
5	5	10

[a] These figures are shown in Fig. 6.

sumptions made, the geometric surface area curve has a maximum in time under the conditions given by $[(W/w*)/N] < 0.93$.

This relationship and Eqs. 5–16 are reflected in the final surface areas as well. A plot of O after 5 min is shown in Fig. 2. It is noted that O drops to a (fairly) constant value at the 20% sucrose concentration. In this respect[8], these experiments actually define an optimum formulation, *i.e.*, a sucrose concentration at or above 20%. Such optima have been reported in other systems under other circumstances (16).

Figure 4 shows that a −12/+20-sieve fraction shows consistent Pilpel hardness *versus* weight relations if one considers weights below 4 mg only. At higher weights, consistency disappears. Figure 6 shows the situation after 1.5 and 3 min of kneading; there seem to be two distinct lines in the graph. If there is a decrease in the hardness of the granule (through better distribution of water) as time progresses, more and more points should shift from line II to line I, *i.e.*, from non-equilibrium to equilibrium granules.

If one considers the points that have shifted away from the high load–weight ratio, this may, indeed, represent the fraction of granules that have acquired equilibrium conditions. The data in Table I are the fractions of equilibrium granules in randomly selected granules in a −12/+20-sieve fraction as a function of time. The slopes of the equilibrium load *versus* weight plots are shown in Fig. 5 and appear to be somewhat independent of time, since the slope of the line in Fig. 5 equals the slope of line II in Fig. 6.

The experiments in the planetary blender were performed to demonstrate the principle of equilibrium *versus* nonequilibrium granules and to test one step in the large-scale experimental procedure that might have affected the previous results. As a necessary step, the wet granulations from the ribbon-chopper mixer were processed through an oscillating granulator; the smaller scale experiments in the planetary blender did not include the oscillator step. The results (Fig. 8) demonstrate that the amount of wetted (nonequilibrium) material first increased (as the wetting progressed and more and more of the powder was wetted) and then decreased at the expense of
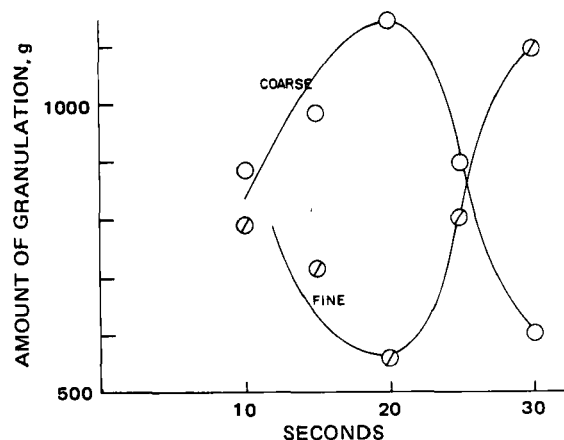
Figure 8—*Amount of wetted and nonwetted material of a corn starch–lactose granulation as a function of kneading time in a planetary mixer.*

[8] This is optimum with regard to hardness- and surface-area-related properties only. Other qualities (*e.g.*, disintegration) may not be optimum at this point.

Table II—Sieve Analysis Data[a] of a Granulation with y = 16.57 kg

Screen Cut	t = 1.25 min	t = 2 min	t = 3 min	t = 4 min	t = 5 min
+12	41	27.5	25	17.5	16
−12/+20	17	16	17.5	16	16.5
−20/+40	12.5	13	15.5	18.5	21
+40	70.5	56.5	58	52	53.5
−40/+60	11	17.5	22	31.5	31
−60/+80	8.5	15	13.5	12	11.5
−40/+80	19.5	32.5	35.5	43.5	42.5
−80/+100	4.5	6	4	3	2.5
−100/pan	6.5	7	5	3	3.5
−80/pan	11	13	9	6	6

[a] Values are in grams.

"finer" equilibrium granules. If one considers this process as $(p + w)$ $\xrightarrow{k_1} n$ and $n \xrightarrow{k_2} m$, where p denotes the amount of powder, n is the amount of nonequilibrium granulation, w is the amount of water, and m is the amount of equilibrium granule, then:

$$n = Q\,(1 - e^{-k_1 t})e^{-k_2 t} \qquad \text{(Eq. 17)}$$

and:

$$m = p_0 - n \qquad \text{(Eq. 18)}$$

qualitatively describe the curves in Fig. 8. No attempts were made here to test k_1 and k_2 as a function of the operating conditions.

APPENDIX

Table II (and Fig. 9) lists the actual sieve mesh data ($y = 16.57$ kg) used in Fig. 1. It is obvious from the data that more than just one size granule was left after 5 min. The model suggested is, therefore, somewhat oversimplified. The following argument (although tedious) will show that a first-order improvement in the model considering three sizes will lead to maxima in the geometric surface area within certain limits.

The data in Table II show the amounts (per 100 g) retained by 12, 20, 40, 60, 80, and 100 mesh and pan. If it is assumed that the material above 40 mesh is nonequilibrium granules, the material between 40 and 80 mesh is equilibrium granules and the material below 80 mesh is prime particles (i.e., nongranules), then the disappearance of the coarse and fine fractions at the expense of the middle fraction will have the appearance of the curves in Fig. 9.

This argument has the more realistic features, compared to the previous argument, that: (a) the equilibrium granules start being formed immediately and (b) some fine and some coarse fractions are always present.

In the terms of the established nomenclature, there are originally, prior to wetting, N particles of diameter d. After wetting, there are: n_1 large nonequilibrium granules of diameter d^*, and each granule contains P original particles; n_2 equilibrium granules of diameter d' and each granule contains q particles; and n_3 nonwetted particles of
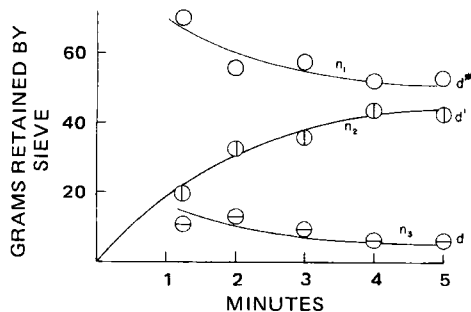
Figure 9—*Amounts of fractions larger than 40 mesh (O), between 80 and 40 mesh (⊕), and finer than 80 mesh (⊖). The data correspond to the cumulative figures in Table II.*

diameter d, and each particle contains one particle. It follows from the definitions that $P > q$.

At any time t, the following number balance must hold:

$$N = n_1 P + n_2 q + n_3 \qquad \text{(Eq. A1)}$$

That is:

$$n_2 = \frac{1}{q}\,[N - n_1 P - n_3] \qquad \text{(Eq. A2)}$$

The curves in Fig. 9 suggest that n_1 and n_3 decrease by exponential decay; i.e.:

$$n_1 = n_\infty' + (n_0' - n_\infty')e^{-\alpha t} \qquad \text{(Eq. A3)}$$

and:

$$n_3 = n_\infty'' + (n_0'' - n_\infty'')e^{-\beta t} \qquad \text{(Eq. A4)}$$

The diameter of the overwet granule, d^*, is given by:

$$P d^3 = (\pi/6)(d^*)^3 \qquad \text{(Eq. A5)}$$

so that the area of the overwet granule is:

$$O^* = \pi(6P/\pi)^{2/3}d^2 = \eta P^{2/3}d^2 \qquad \text{(Eq. A6)}$$

where:

$$\eta = \pi(6/\pi)^{2/3} \qquad \text{(Eq. A7)}$$

And d' and O' in a similar fashion give:

$$O' = \eta q^{2/3}d^2 \qquad \text{(Eq. A8)}$$

The total surface area at time t is given by:

$$O(t) = n_1\eta P^{2/3}d^2 + n_2\eta q^{2/3}d^2 + n_3\pi d^2 \qquad \text{(Eq. A9)}$$

Rearranging and introducing Eq. A2 then give:

$$O(t)/(\eta d^2) = P^{2/3}n_1 + q^{-1/3}[N - n_1 P - n_3] + n_3(\pi/\eta) =$$
$$n_1(P^{2/3} - Pq^{-1/3}) + n_3\left[\frac{\pi}{\eta} - q^{-1/3}\right] + Nq^{-1/3} \quad \text{(Eq. A10)}$$

The surface area will have an extremum when the derivative with respect to time vanishes, i.e., when:

$$\frac{1}{\eta d^2}\frac{\partial O}{\partial t} = [P^{2/3} - Pq^{-1/3}](\partial n_1/\partial t) + \left[\frac{\pi}{\eta} - q^{-1/3}\right](\partial n_3/\partial t) =$$
$$\alpha(Pq^{-1/3} - P^{2/3})(n_0' - n_\infty')e^{-\alpha t} -$$
$$\beta\left(\frac{\pi}{\eta} - q^{-1/3}\right)(n_0'' - n_\infty'')e^{-\beta t} = Ae^{-\alpha t} - Be^{-\beta t} \quad \text{(Eq. A11)}$$

vanishes. It is noted that $(\pi/\eta) \sim (0.25)^{1/3}$, so the last preexponential term is positive when $q > 5$. Since $P > q$, $q^{-1/3} > P^{-1/3}$ or, by multiplying by P on both sides of the inequality sign, $Pq^{-1/3} > P^{2/3}$, so the first preexponential term is positive. Therefore, there is a solution to the equation:

$$Ae^{-\alpha t'} = Be^{-\beta t'} \qquad \text{(Eq. A12)}$$

when A and α are larger than B and β, respectively ($A > B$ and $\alpha > \beta$) or when A and α are smaller than B and β, respectively ($A < B$ and $\alpha < \beta$). The extremum occurs at $t = t'$. This extremum will be a maximum if the second derivative is smaller than zero:

$$\frac{1}{\eta d^2}\frac{\partial^2 O}{\partial t^2} = B\beta e^{-\beta t'} - A\alpha e^{-\alpha t'} < O \qquad \text{(Eq. A13)}$$

The time of extremum, t', is defined by Eq. A12. Introducing it into Eq. A13 gives:

$$\frac{1}{\eta d^2}\frac{\partial^2 O}{\partial t^2} = \beta Ae^{-\alpha t'} - A\alpha e^{-\alpha t'} = Ae^{-\alpha t'}(\beta - \alpha) \quad \text{(Eq. A14)}$$

which is smaller than zero when $\alpha > \beta$; i.e., when $\alpha > \beta$, there is a maximum in the O versus t curve with the assumptions made here.

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Comparative Serum Prednisone and Prednisolone Concentrations following Prednisone or Prednisolone Administration to Beagle Dogs

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Abstract ☐ The relative serum prednisone and prednisolone concentrations were determined following the administration of prednisone or prednisolone as 5-mg tablets to male beagle dogs. Serum prednisone concentrations were significantly greater following prednisone administration than they were following prednisolone administration. Serum prednisolone concentrations were significantly greater following treatment with prednisolone than with prednisone. The combined prednisone and prednisolone areas under the serum concentration–time curves were similar for the two treatments.

Keyphrases ☐ Prednisone—serum concentration after administration of prednisone or prednisolone, radioimmunoassay, dogs ☐ Prednisolone—serum concentration after administration of prednisolone or prednisone, radioimmunoassay, dogs ☐ Bioavailability—prednisone and prednisolone, serum radioimmunoassay, dogs ☐ Glucocorticoids—prednisone and prednisolone, serum radioimmunoassay, dogs

With the advent of radioimmunoassays for both prednisone and prednisolone (1, 2), a unique opportunity arose to investigate the interconversion of prednisone and prednisolone in many experimental animals and in humans. In the present study, male beagle dogs were chosen as the test animal.

Previously, the conversion and interconversion of prednisone and prednisolone had been studied by tedious, time-consuming, and often difficult methods (3–7). With radioimmunoassays, the analyses could be conducted in just days without chromatography or separation steps.

The present study was conducted to investigate the interconversion of prednisone and prednisolone fol-

lowing the administration of 5-mg compressed tablets of prednisone[1] or prednisolone[2] to male beagle dogs.

EXPERIMENTAL

Materials—The buffers used were: tromethamine, 0.2 M and pH 8.0 (I), and sodium phosphate (monobasic and dibasic), 0.2 M and pH 6.5 (II). The tritiated steroids[3] were 6,7-^{3}H-prednisone at 40.0 Ci/mmole and 6,7-^{3}H-prednisolone at 45.4 Ci/mmole. The primary antiserums were rabbit antiprednisolone 21-hemisuccinate–bovine serum albumin (III) and rabbit antiprednisone 21-hemisuccinate–bovine serum albumin (IV).

Goat antirabbit serum or ammonium sulfate solution (80% saturated) was used as the precipitant. Analytical grade toluene-based liquid scintillation counting solution[3,4] was used, and the high capacity liquid scintillation spectrophotometer had a 4° refrigeration unit[5]. Other materials consisted of 1-ml adjustable automatic pipets and 100-, 200-, and 500-μl pipets with disposable tips[6,7]; 7-ml glass disposable miniature liquid scintillation counting vials with glass minivial holders[8]; 10 × 75-mm disposable culture tubes[9]; and a moderate speed refrigerated centrifuge[10].

Methods—*Animal Study*—Sixteen male beagle dogs, 9.5–17.2 kg, were placed in a randomized two-way crossover design. Blood samples were withdrawn from the jugular vein immediately prior to drug ad-

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[1] Deltasone, 5-mg compressed tablet, The Upjohn Co.
[2] Delta-Cortef, 5-mg compressed tablet, The Upjohn Co.
[3] Bio-Solv, Beckman Instrument Co.
[4] Liquifluor, New England Nuclear Corp.
[5] Model 2450 Tri-Carb liquid scintillation spectrophotometer, Packard Instrument Co.
[6] Biopette, Bioschwartz.
[7] Microliter pipets, Eppendorf.
[8] Miniature holder and vials, Demuth Glass Co.
[9] Disposable culture tubes, Kimble Glass Co.
[10] Refrigerated centrifuge, International Equipment Co.