

Physical Aspects of Wet Granulations II: Factors Involved in Prolonged and Excessive Mixing

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Abstract □ Evidence is presented that excessive blending in a wet granulation process shifts the packing arrangement of the wet granule, causing it to become dense and nonporous. With prolonged kneading, a larger amount of the water-soluble excipients dissolves in the granulating fluid, and these two factors make the drying slower. This result, coupled with the previous finding that a certain time is required to attain an equilibrium size granule, explains why there exists an optimum kneading time for a wet granulation from a mechanical performance point of view.

Keyphrases □ Granulations, wet—physical aspects, effect of prolonged and excessive mixing □ Hardness, granule—effect of prolonged and excessive mixing □ Dissolution rate—wet granulations, effect of prolonged and excessive mixing

It has been shown (1) that the initial steps in wet granulation processes are (a) moisture distribution and (b) formation of an equilibrium size granule. It has also been pointed out (1) that kneading (mixing) beyond a certain time point decreases the quality of the ensuing granule. The purpose of this study was to elaborate this latter point.

EXPERIMENTAL

A wet granulation was made of the composition denoted A in Table I. This formula is identical to the optimal formula described previously (1); other lactose-sucrose ratios cause less uniformity in granule hardness and lower overall granule hardness per granule weight.

The granulation procedure was as described elsewhere (1), except that the kneading times were varied; *i.e.*, granulations were kneaded 3, 5, 7, 9, 11, and 13 min. The wet granulation mass was processed through an oscillating granulator¹ with a No. 6 screen and then dried in a fluid bed drier² with an incoming air stream at a velocity of 380 ft³/min and a temperature of 42°.

The dried granulations were subjected to sieve analysis and Karl Fischer moisture determinations. Pilpel hardness determinations (1-3) of the +20 and the -6/+14-mesh fractions were performed. The drying rates of Formulation A kneaded for 2 and 10 min were determined by checking the weight of the granulations as a function of time.

A starch-lactose granulation was made³ with the following composition: 1150 g of lactose USP, 160 g of starch USP, and 6 g of FD&C Yellow No. 5. A premix of the dye and 100 g of lactose was made, and this premix was blended³ with the remaining lactose and 80 g of starch. It was then granulated with a paste made with the remaining starch in 300 ml of water. The granulation was passed through a No. 6 hand screen and dried in a forced air oven for 3 hr at 65°. The dried granulation was sieved, and the -20/+40 and -40/+60 fractions were isolated.

Ten tablets, each weighing 300 mg, were made by hand on a single-punch tablet machine⁴ using a 0.9-cm (0.37-in.) standard concave punch. Six tablets were subjected to thickness and hardness determinations; the remaining four tablets were subjected to the USP dissolution rate test at 27.5°, using 0.1 N HCl as the dissolution medium. Each mesh fraction was then made into 500 tablets with the machine run at the same punch levels. The fill weights were recorded,

Table I—Formulas of Granulations Used^a

Ingredient	Formulation	
	A	B
Lactose USP (dry mix)	23.2	22.6
Sucrose USP (dry mix)	5.8	—
Starch USP (dry mix)	4.05	4.05
Starch USP (dissolved)	0.15	0.15
Sucrose USP (dissolved)	—	5.8
Lactose USP (dissolved)	—	0.6
Water	3.0	3.0

^a Amounts are in kilograms or liters.

which show the flow rates of each fraction under actual running conditions.

RESULTS AND DISCUSSION

It was shown previously (1) that, at kneading times less than 5 min in a chopper-ribbon mixer, the wet screening through a No. 6 mesh screen does not affect the granulation. At higher kneading times, it is obvious from visual observation that the screen starts acting as an extruder. The mesh analyses are shown in Table II, and the distribution eventually (13 min) reaches one dictated by a 6-mesh extruder.

Table III shows the Karl Fischer moisture contents and the Pilpel hardnesses of the granulation as a function of kneading time. As seen from Fig. 1, the hardness *versus* weight curves are of the type described earlier (1, 4). Capes's equation (4) states that $L = qd^n$, where L is the crushing strength, d is the diameter of the granule, and q and n are characteristics for the material crushed. Values of n for sodium chloride are 1.7-2.6. Since mass, m , is proportional to d^3 , it follows that L is proportional to $m^{n/3}$, where $n/3 = 0.6-0.9$ for sodium chloride. It is apparent in this study that $n/3 = 1$, since the L *versus* m plots (Fig. 1) are linear.

Figure 2 shows that the hardness to weight ratio increases with drying time. It is seen from Table III that the ratio goes through a maximum at 7 min. With the -6/+14-mesh fraction, the moisture values vary and the hardness-weight ratios are not actually directly comparable; with the -14/+20-mesh fraction, however, the moisture contents are close and the maximum at 7 min is quite apparent.

The drying curves of Formulation A, kneaded for 2 and 10 min, are shown in Fig. 3. The drying is strictly monophasic as opposed to the

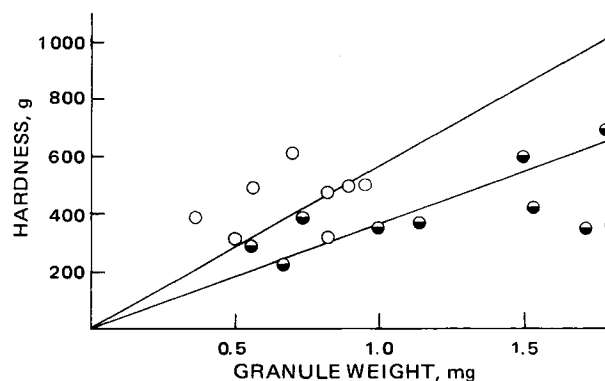


Figure 1—Pilpel hardness as a function of granule weight for 14/20-mesh granules produced by 5 min of kneading and 45 min of drying (O) and by 11 min of kneading and 25 min of drying (●).

¹ F. J. Stokes Machine Co., Philadelphia, Pa.

² Aeromatic A.G., Basel, Switzerland.

³ Hobart mixer, Hobart Manufacturing Co., Troy, Ohio.

⁴ Stokes model E, F. J. Stokes Co., Philadelphia, Pa.

Table II—Amounts of Material^a on the Indicated Mesh after Various Kneading Times

Screen	Minutes					
	3	5	7	9	11	13
14	19	10	10	19	40	73
20	16	18	25	44	37	12
40	25	43	42	31	19	13
60	27	25	19	6	4	2
80	10	3	3	—	—	—
100	2	1	1	—	—	—
Pan	1	—	—	—	—	—

^a Values are percentages.

Table III—Moisture Contents and Hardness to Weight Ratios (x) of Granulations Kneaded for Different Lengths of Time (t)

t , min	x , 10^{-5} , g/g, -6/+14	SD of x	Mois- ture, % by Weight	x , 10^{-5} , g/g, +20	SD of x	Mois- ture, % by Weight
3	0.18	0.04	4.9	2.18	1.15	5.3
5	0.83	0.65	5.1	3.22	1.27	5.7
7	1.02	0.68	5.3	2.75	1.40	5.9
9	0.62	0.25	6.2	1.34	0.27	5.4
11	0.49	0.21	6.8	0.73	0.15	6.6

granulations reported by Opankunkle *et al.*⁵ (5); this finding signifies that no surface moisture is present and that the drying is not carried past the point of bound moisture. As shown in Fig. 3, the drying follows the conventional relationship (6):

$$\ln \frac{W - W_{\infty}}{W_0 - W_{\infty}} = -\Gamma t \quad (\text{Eq. 1})$$

where W is the moisture retained, the subscripts denote initial and final time, Γ is a drying rate constant, and t is time. The drying rate constants are 0.12 and 0.06 min^{-1} for the material kneaded 2 and 10 min, respectively. It is, therefore, apparent that drying becomes slower at increased kneading times. The effect of kneading time described up to this point suggests a mechanism of wet granulation such as is outlined in Fig. 4. It was shown previously (1) that the initial granule is a loosely stacked arrangement of particles; these data imply that, as kneading continues, the configuration changes to a more closely packed arrangement and this change, in turn, means that the proportion of fine capillary pores in the granule increases, causing the

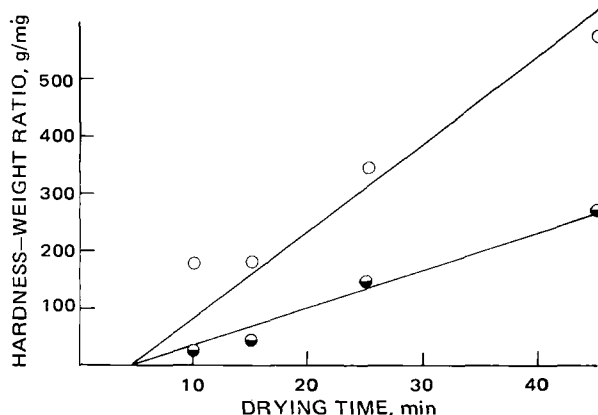


Figure 2—Hardness to weight ratio of granules produced by 5 min of kneading as a function of drying time of 14/20- (O) and 6/14- (●) mesh fractions.

⁵ In the data reported by Opankunkle *et al.*, surface (unbound) moisture gives rise to linear drying curves, whereas diffusional drying phases are log-linear (as in Eq. 1). There is no conflict between the views stated here and those reported by Opankunkle *et al.* (5).

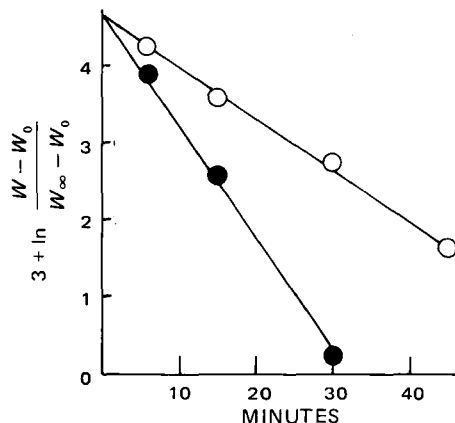


Figure 3—The σ^- -drying plot of tray drying of granules produced by 2 (●) and 10 (O) min of kneading.

granule to dry more slowly. The Kelvin equation (7) states that:

$$\ln(P/P_0) = \frac{2M\gamma}{RT\rho r} \quad (\text{Eq. 2})$$

where P is the vapor pressure over a capillary of radius r , P_0 is the equilibrium vapor pressure, M is the molecular weight, γ is the interfacial tension, R is the gas constant, T is the absolute temperature, and ρ is the density of the liquid. According to Eq. 2, the vapor pressure is lower over the smaller pores in the granule produced by the longer kneading time, explaining why it dries more slowly; it also may explain why a larger granule may not equilibrate with a smaller granule, as reported (8).

To test further the concept of dissolution contributing to the mechanical structure of the granule in excessive kneading, Formulation B (Table I) was made. The sucrose was dissolved in the starch gel; the results from this experiment are shown in Table IV and show that the hardness to weight ratio did not change much as a function of kneading time. The granules have hardness to weight ratios and particle-size distributions that are fairly close to the results obtained from granulations kneaded for 13 min (Table III). It appears, therefore, that the end result of progressively longer kneading times can be simulated to some extent by first dissolving the solubles in the granulating liquid.

Results from the studies in the planetary blender are shown in Table V and in Fig. 5. The dissolution is by a σ^- -curve, showing that the diffusion of liquid into the granule and diffusion of drug out of the granule are the rate-limiting steps⁶ (9). At low kneading times, the dissolution rates are high and they decrease with increased kneading time. This result can be due to the granule becoming more

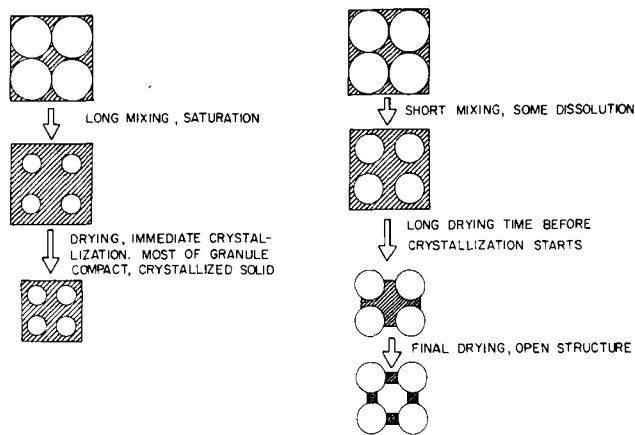


Figure 4—Schematic diagram of the steps in drying of a granule kneaded for a long (left) and a short (right) time.

⁶ The lag times, t_i , of all five curves in Fig. 5 are of comparable magnitude (0.7 min). This length of time represents disintegration plus penetration times. The former values are of the order of 0.5 min.

Table IV—Characteristics of Granules Made by First Dissolving the Sucrose

Kneading Time, min	Hardness—Weight		Sieve Analysis				
	$x, 10^{-5}, \text{g/g}, -6/+14$	$x, 10^{-5}, \text{g/g}, -14/+20$	6/14	14/20	20/40	40/60	60/Pan
2	0.23 ± 0.1	1.14 ± 0.2	—	—	—	—	—
3	0.40 ± 0.15	0.86 ± 0.2	—	—	—	—	—
4	0.20 ± 0.1	1.05 ± 0.2	—	—	—	—	—
5	0.17 ± 0.1	0.93 ± 0.2	—	—	—	—	—
10	0.25 ± 0.1	1.01 ± 0.2	81	10	5	2	1
15	—	—	78	14	6	1	1

Table V—Characteristics of Tablets Made from Starch—Lactose Granulations Prepared in a Planetary Mixer

Kneading Time, min	20/40-Mesh				40/60-Mesh			
	Hardness, kg	Thickness, mm	k^a, min^{-1}	Weight ^b , mg	Hardness, kg	Thickness, mm	k^a, min^{-1}	Weight ^b , mg
3	6.7	4.05	0.28	293 ± 0.5	6.5	4.04	1.2	292 ± 0.5
5	8.1	4.04	0.10	307 ± 2.0	6.5	4.03	0.30	308 ± 1.5
8	8.1	4.04	0.06	330 ± 0.5	7.2	4.03	0.15	332 ± 1.0
10	8.1	4.03	0.07	332 ± 0.8	6.5	4.03	0.20	328 ± 1.5

^a Based on (9): $\ln\{(C - C_\infty)/(C_0 - C_\infty)\} = -k[t - t_i]$, where C is the concentration at time t , k is the dissolution constant in minutes⁻¹, and t_i is the lag time in minutes. ^b Weights are from the sustained run. The other figures correspond to 300.0-mg tablets made by hand on the tablet machine. Figures are averages of 15 measurements, and limits are 95% confidence limits of the averages.

homogeneous (in the sense that less and less dye is found on the outside of the granule). This assumption was substantiated by experiments where the dye was dissolved in the starch paste (Fig. 5). Here the dissolution rate constant was $k = 0.07 \pm 0.005 \text{ min}^{-1}$ for tablets made with a 20/40-mesh cut of a granulation kneaded for 5 min as compared to $k = 0.072 \pm 0.008 \text{ min}^{-1}$ for a granulation kneaded for 10 min where the dye (as in the remaining experiments) had been added to the dry powders prior to addition of paste.

In Table V, the column denoted "Weight" (which is the only figure relating to the tablets not run by hand) reflects the flow rates and consolidating rates of the granules in the die. The test was conducted by having one particular punch setting on the tablet machine; *i.e.*, the tablets were made with a fixed die volume. From the first two lines, it is obvious that a granulation kneaded for 5 min will flow into the die in larger amounts (*i.e.*, have better flow) than one kneaded for 3 min, since, *e.g.*, $307 \pm 2 \text{ mg}$ is significantly larger than $293 \pm 0.5 \text{ mg}$ (on the 99% level). The tablet hardness in this case increases with tablet weight since the volume is fixed. The granulations kneaded for 8 and 10 min, however, flowed so well that the tablets were too hard to make in the volume used.

Tablets could be made by increasing the height of the upper punch (*i.e.*, keeping the die volume constant but increasing the tablet volume and decreasing the tablet hardness), and the fill weights after 8 and 10 min of kneading (330 ± 0.5 and $332 \pm 0.8 \text{ mg}$) are comparable, but

higher, than after the shorter kneading times. Hence, the flow characteristics under actual tableting conditions increased with increasing kneading time. The model outlined in Fig. 4 is consistent with this finding, since the granule surface is smoother and the shape is closer to spherical the longer the kneading time; both these qualities aid in flow and consolidation of the granules.

SUMMARY

1. In a wet granulation process, there appears to be an optimum kneading time for mechanical properties (here 5–7 min). This time appears to be a function of (a) the time required to attain the equilibrium granule size and (b) the amount of solid (here sucrose and lactose) dissolved. With longer kneading times, the granules are more consolidated in structure and smoother because more material dissolves at the time of drying. This causes a finer pore structure, which, in turn, makes the granule dry more slowly.

2. The optimum in mechanical performance criteria is not the optimum point for some other important parameters. Dissolution rates, for instance, are higher the lower the kneading time. Flow and consolidation characteristics are associated with smoothness of granule surface and optimize at high kneading times and at points where large-scale manufacture would not be feasible. At the point of optimum granule hardness, however, drying rates, flow rates, and dissolution rates are in acceptable ranges in the formulas studied here. Prudent process design should make possible the best possible combination of all important variables in wet granulation in general.

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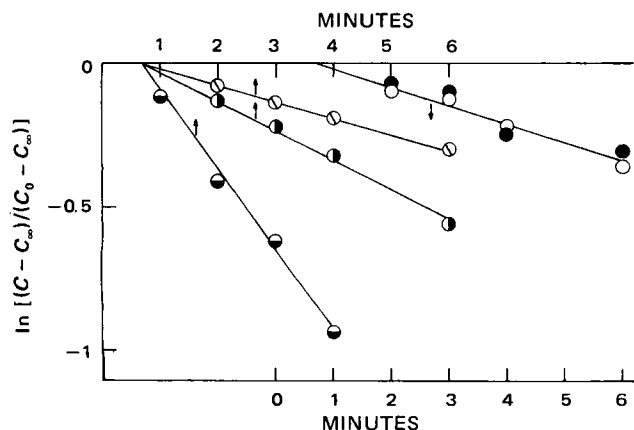


Figure 5—USP dissolution rate test (27°, 50 rpm) of lactose—starch tablets of FD&C Yellow No. 5. Kneading times were 3 (●), 5 (●), 8 (○), and 10 (○) min. The solid circles (●) indicate the sample where dye was dissolved in the starch paste.

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Spectrofluorometric Determination of Hydroflumethiazide in Plasma and Urine

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Abstract □ A rapid, accurate, sensitive, and reproducible assay for hydroflumethiazide in plasma and urine was developed after studies of its UV and fluorescence spectral properties and partitioning behavior. The assay is based on initial extraction from acidified plasma or urine into ether, back-extraction into basic solution followed by acidification to about pH 1, and measurement of the fluorescence derived from the unionized molecule. Analysis of variance indicated no significant differences in assays performed on the same day. The mean recovery was $98.8 \pm 7.4\%$ for plasma over a concentration range of 0.2–2.0 $\mu\text{g/ml}$. The method is convenient for routine clinical use and has sufficient sensitivity to quantify hydroflumethiazide levels after administration of therapeutic doses.

Keyphrases □ Hydroflumethiazide—spectrofluorometric analysis, plasma and urine □ Spectrofluorometry—analysis, hydroflumethiazide, in plasma and urine □ Diuretics—hydroflumethiazide, spectrofluorometric analysis, plasma and urine

Attempts to describe the comparative pharmacokinetics of diuretic agents in various species of animals and in humans have comprised a major research effort in these laboratories. The paucity of pharmacokinetic information on this class of compounds is due in part to the lack of sensitive analytical methods for their determination in biological fluids. Generally, diuretics are given at relatively low doses and have short half-lives; thus, the blood levels obtained are relatively low a short time after administration.

A proposed study of the pharmacokinetics of the diuretic hydroflumethiazide (I) prompted interest in analytical methodology for this compound. A fluorometric TLC procedure was reported for the quantitative analysis of hydroflumethiazide in urine and plasma (1). This method involved extraction and TLC followed by fluorometric determination of hydroflumethiazide utilizing a scanning spectrodensitometer; hydroflumethiazide fluoresced below 400 nm, but no specific emission or excitation maxima were given. Other quantitative or qualitative procedures for benzothiazine diuretics in urine or dosage forms principally involved hydrolysis and colorimetric determination of the diazotized amino degradation products (2, 3).

Since hydroflumethiazide fluoresces strongly, it was proposed that a direct fluorometric determination in biological fluids might prove possible. This technique would decrease assay time and markedly simplify rou-

tine clinical determination by eliminating the necessity for TLC and scanning spectrodensitometry. Based on the fluorescence and partitioning properties of hydroflumethiazide, the present work reports the development of a sensitive, accurate, precise, and convenient procedure for its determination in both plasma and urine.

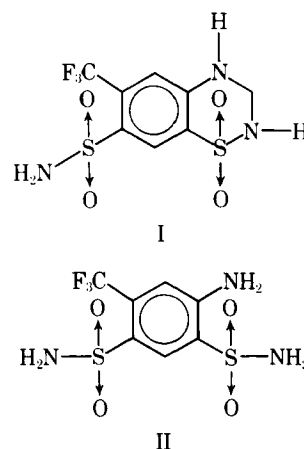
EXPERIMENTAL

Equipment—A scanning spectrofluorometer¹ and a recording UV-visible spectrophotometer² were utilized for spectral measurements.

Materials—Hydroflumethiazide³ powder was used in the analytical procedures without further purification. All chemicals and solvents were of analytical reagent grade. Standard solutions were prepared by dissolving hydroflumethiazide in enough methanol to solubilize the drug and then diluting to the desired volume with pH 7.0 phosphate buffer.

UV Spectral Measurements—The UV spectra of 2.53×10^{-5} M hydroflumethiazide solutions were recorded at various pH values in the 1–12 range. The following buffer solutions (4) were used: potassium chloride-hydrochloric acid (pH 1.0–2.0), glycine buffers (pH 2.4–3.4), acetate buffers (pH 4.0–5.4), phosphate buffers (pH 6.0–7.2), borate buffers (pH 8.0–9.0), carbonate buffers (pH 9.4–10.4), and potassium chloride-sodium hydroxide (pH 11.0–12.0).

Fluorescence Spectral Measurements—The fluorescence spectra of 2.53×10^{-6} M hydroflumethiazide solutions were recorded



¹ Turner model 430, G. K. Turner Associates, Palo Alto, Calif.

² Coleman model 124, Perkin-Elmer Corp., Maywood, Ill.

³ Bristol Laboratories, Syracuse, N.Y.