Powder Flow Studies III

Factors Affecting the Flow of Lactose Granules

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In an attempt to provide a better understanding of the variables affecting the flow of tablet granulations, the effects of different granulating agents and techniques, particle size distribution, fines, and glidants on the flow of lactose granules were studied. Flow rates were measured with a recording powder flowometer. In binary mixtures the addition of increasing proportion of finer particles to 10/20 mesh granules increased the flow rate to a maximum followed by a decrease. Flow rates of granulations were found to vary considerably, depending upon the particular granulating agent used. For granulations and blended systems of various particle size distributions, a strong negative correlation existed between flow rate of granules and proportion of particles less than 100 mesh in size. The particle size of the granules influenced considerably the effect of glidants.

An important requirement of tablet formulations is that the powder or granular material possess uniform and free flowing properties. The ability of particulate matter to flow into the dies in a reproducible manner results in uniform tablet weights and uniform doses of active ingredients, as well as increased production rates (1). Using an instrumented rotary tablet machine, Knoechel *et al.* (2) reported that when good flowing formulations were tableted, compression and ejection force levels became more uniform and weight deviations decreased. To achieve better flowability and desirable compression characteristics, it is often necessary to use a granulating technique in the manufacturing procedure. The most common granulating method is wet granulation which involves the moistening of a powder mixture with a granulating solution containing a binder to form a plasticized mass. The mass is then forced through a sieve, dried, and resieved. The finished granulation is a mixture of various size particles and contains some finely powdered material often referred to by industrial pharmacists as "fines." Some finer particles are necessary in limited amounts for producing smoother tablets and for proper functioning of the tablet press. While 10–20% fines has occasionally been set as the maximum amount permissible, it has been pointed out that there is no general limit to the amount of fines that can be present in a granulation and that excessive fines should be determined for each specific formulation (3). Usage of the term fines is rather widespread, yet there is no general agreement as to what mesh size constitutes fines and much confusion exists in the literature due to varying usage of this term.

Hammerness and Thompson (4) observed that the flow rate, ascertained by timed delivery through an orifice, of a tablet granulation increased with added fines to an optimum flow rate, after which additional fines caused the flow rate to decrease. However, fines in this study were particles smaller than 40 mesh. An increase in the amount of lubricant also increased the flow rate, and the combination of fines and lubricant appeared to have a synergistic action. Crosby (5) reported that surface roughness may be reduced by the presence of fines which serve to fill in the depressions or irregularities in the surface of the particles and, thereby, increase the rate of flow. Nelson (6), using angle of repose measurements, found that the addition of fines smaller than 100 mesh to sulfathiazole granules caused an increase in repose angle and concluded that fines increase interparticle friction and are responsible for difficulty in granulation flow. According to Neumann (7) stickiness is produced by the presence of particles smaller than 10 μ. When these "fines" are removed or adsorbed onto larger particles, the powder becomes free flowing.

In many literature reports (8–10) dealing with investigations concerning flow of solid materials, angle of repose measurement was used with assumed correlation to flow. A recent report including a statistical evaluation from this laboratory (11) indicated that angle of repose measurement was not a reliable method to evaluate flow of materials. In view of this and the lack of reports in the literature dealing with factors affecting the flow of tablet granulations, the present work was undertaken in an effort to evaluate the variables

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TABLE I—EFFECT OF GRANULATING AGENTS AND TECHNIQUES ON FLOW RATE

Formulation	Granulating Solution	Method[a]	Flow Rate (Gm./sec.) Complete Formulation	Flow Rate (Gm./sec.) 10/20 Mesh Fraction	Free H_2O %	Mesh Analysis % 10/60	Mesh Analysis % 60/100	Concn. <100
1	10% Starch	A	4.82	6.95	0.30	31	10	59
2	10% Starch	B	5.59	7.69	0.05	36	17	47
3	10% Starch	C	5.72	7.45	0.03	36	15	49
4	Water	A	6.13	7.66	0.30	34	17	49
5	2% Methylcellulose 15 cps.	A	6.83	7.70	0.00	44	9	47
6	10% PVP	A	7.22	7.32	0.10	45	26	29
7	10% Gelatin	A	8.55	7.18	0.07	50	20	30
8	10% Methylcellulose 15 cps.	A	8.90	8.40	0.24	45	16	39
9	Water	D	9.24	9.22	0.23	77	6	17
10	2% Methylcellulose 15 cps.	D	9.71	8.18	0.13	84	4	12
11	Water	E	9.92	8.03	0.30	72	16	12

[a] A, Standardized method as indicated in *Experimental* using 1,000 Gm. granulating solution. B, Starch added to lactose as dry powder and 1,000 Gm. water added. C, Starch added half as dry powder and remainder as 1,000 Gm. of 5% starch paste. D, Additional 2,000 Gm. of water added. E, Additional 1,000 Gm. of water added.

affecting the flow of granules. Lactose granules were used as the model system and the effects of finer particles were ascertained by adding various size particles to 10/20 mesh granules. The effects of different granulating agents and techniques on the flow rate of the resultant granules were also determined. A final objective was to study the effects of commonly used glidants on the flow of lactose granules of varying particle size distribution to ascertain similarities or differences in effects between glidants and granule fines.

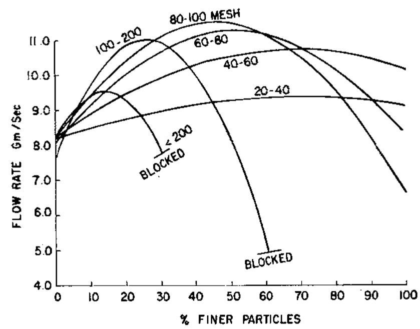

Fig. 1—The effect of finer particles on the flow rate of 10/20 mesh lactose granules.

EXPERIMENTAL

Materials—Methylcellulose,[1] cornstarch, polyvinylpyrrolidone,[2] gelatin, magnesium stearate, talc, and fumed silicon dioxide[3] were either USP or pharmaceutical grade materials. Glidants were used as supplied by the manufacturers and were finer than 100 mesh. However, cornstarch, when used as a glidant, was dried at 140° F. for 24 hr.

Lactose granulations were prepared in 15 Kg. batches by the following standard procedure: USP lactose powder was passed through a No. 12 screen on an oscillating granulator and placed in a 1.8 cubic foot total capacity Stokes' mixer. The granulating solution, at room temperature, was added in three equal volumes at 2-min. intervals until 1,000 ml. was added. The wet mass was mixed for 20 min., wet sieved through a No. 6 screen on an oscillating granulator, dried at 120° F. for approximately 20 hr., and dry sieved through a No. 12 screen. Moisture content of the granules was determined by the Karl Fischer method and all granules were found to contain moisture corresponding to 1 mole of water of hydration (5.00%) for lactose and 0.3% or less free moisture.

Particle Size Separation and Analysis—Separation of granules into different particle size ranges was accomplished by a Ro-Tap testing sieve shaker with U. S. standard sieves in series 20, 40, 60, 80, 100, and 200 mesh sizes. For particle size analysis of granulations, a 100-Gm. sample was placed in the shaker for 5 min.

Flow Rate Determinations—The Recording Powder Flowometer described in a previous report (12) was modified to contain four strain gauges and a built-in transistorized power supply. The potential across the bridge circuit was adjusted so that each horizontal chart division represented 6.25 Gm. of powder. Flow rates, expressed in Gm./sec., were calculated from the recorder tracing resulting from the flow of 300 Gm. of material passing through a conical stainless steel hopper which measured 20 cm. top diameter, 30 cm. in length, and 10 mm. orifice diameter.

RESULTS AND DISCUSSION

A 2% methylcellulose granulation (formulation 10—Table I) was sieved into 7 fractions and the effect of finer particles added to 10/20 mesh granules was determined in 5% increments up to 50% and 10% increments thereafter. The flow rates of each system, Fig. 1, are shown in a multiple regression plane (13). From Fig. 1, it will be noted that, as the proportion of the smaller particle sizes increased, the flow rate of 10/20 mesh granules attained a maximum and then decreased. This maximum flow rate was specific for each binary component system and varied with the concentration and size of the added particles. The data indicate that the smaller the particle size, proportionately less was necessary to reach the maximum flow rate. Also, the maximum flow rates did not reflect the flow rates of the individual sieve fractions but did indicate synergistic effect from their combination. The effect of 100/200 and <200 mesh particles was rather surprising, especially in

[1] Marketed as Methocel 15 cps. by the Dow Chemical Co., Midland, Mich.
[2] Marketed as Plasdone by the General Aniline and Film Corp., New York, N. Y.
[3] Marketed as Cab-O-Sil by the Cabot Corp., Boston, Mass.

view of the fact that neither would flow through the funnel orifice used in the study. High concentrations of the 100/200 and <200 sieve fractions did adversely affect flow as concentrations exceeding 30% for <200 and 60% for 100/200 mesh stopped the flow of powder. Jones and Pilpel (14) in evaluating the flow of binary systems of granular magnesia also noted that the percentage of fine component required to produce the maximum flow rate, increases with the size of the fine component. With granular magnesia, however, increased concentrations of 300/350 mesh granules did not block the flow of either 22/36 or 52/72 mesh granules through an 8.98 mm. orifice.

Few guidelines are available for developing tablet granulations having good flow characteristics. Experiments were, therefore, devised to determine the effects of the granulating process on the flow rate. Table I lists the granulating agents and techniques that were evaluated. By using the 1,000 Gm. aqueous granulating solution as the standard for comparing the effectiveness of the various binders and comparing flow rates for significant differences by the method of analysis of variance (15), it may be concluded that the flow rate decreased with the use of 10% starch paste and increased with 2% methylcellulose, 10% PVP, 10% gelatin, and 10% methylcellulose. A significant increase resulted when the concentration of methylcellulose increased from 2–10%. Maximum flow rates were obtained by increasing the quantity of water. However, free moisture content of the resulting granules indicated no relationship between flow rate and free moisture. Flow rates of the 10/20 mesh sieve fractions are also indicated in Table I and suggest that it is risky to characterize the flow properties of a granulation with a separated sieve fraction. It is evident from the mesh analysis data in Table I that increased flow rates are associated with higher concentrations of 10/60 mesh and lower concentrations of <100 mesh particles. The coefficient of correlation (16) has been used to statistically measure the extent of the linear relationship between flow rates and 10/60, 60/100, and <100 sieve sizes. A correlation coefficient close to 0 indicates a weak or nonexistent relationship; whereas, a value close to +1 or −1 indicates a strong relationship between the two variables. The percent dependence (17), a measure of the percentage of the variation in flow rate related to variation in concentration of mesh sizes, has also been calculated. These statistics (Table II) indicate a fairly strong positive correlation between flow rate and proportion of 10/60 mesh particles ($r = +0.88$). A weak or nonexistent correlation exists for the 60/100 size (−0.20) and a strong negative correlation for <100 mesh granules (−0.92). Increasing the degree of wetness was effective in reducing the concentration of <100 mesh particles and, consequently, produced a faster flowing granulation.

To study the effects of particle size distribution, 5 formulations were prepared with varying concentrations of the 7 sieve fractions used in the binary system study. Table III gives the composition of each formulation and its corresponding flow rate. It will be noted that the flow rates ranged from a low of 4.07 Gm./sec. to a high of 10.19 Gm./sec. A high negative correlation coefficient (Table II) was obtained between flow rate and concentration of particles smaller than 100 mesh (−0.99). The 10/60 mesh fraction had a lower positive correlation coefficient of +0.77 while 60/100 particles had a weak correlation (+0.24). The data obtained from this experiment indicate that the proportion of particles smaller than 100 mesh is the main factor influencing the flow rate.

It was noted in binary mixtures that a linear relationship existed on each side of the composition of maximum flow; whereas, the relationship was nonlinear over the entire range. A negative linear relationship between flow rate and proportion of particles less than 100 mesh was obtained in the concentration range of 12–59% for granulations and 13–44% for blended systems. This negative linear relationship is, therefore, apparently representative of mixtures to one side of the composition of maximum flow.

Various materials commonly referred to as glidants are fine particles. As such, the effects of cornstarch, magnesium stearate, fumed silicon dioxide, and

TABLE II—CORRELATION COEFFICIENTS AND PERCENT DEPENDENCE VALUES SHOWING RELATIONSHIP BETWEEN FLOW RATES AND SIEVE SIZES

	Granulations[a]		Blended Granules[b]	
Sieve Size	Correlation Coefficient	% Dependence	Correlation Coefficient	% Dependence
10/60	+0.88	77.33	+0.77	58.65
60/100	−0.20	3.52	+0.24	5.64
<100	−0.92	83.48	−0.99	96.81

[a] Eleven formulations prepared using different granulating solutions and techniques. [b] Five formulations blended from different sieve fractions of 2% methylcellulose granules.

TABLE III—EFFECT OF PARTICLE SIZE DISTRIBUTION ON THE FLOW RATE OF LACTOSE GRANULES

	Formulations				
	A	B	C	D	E
10/20	14.3%	5.0%	23.6%	23.6%	5.0%
20/40	14.3	8.1	20.5	15.0	13.5
40/60	14.3	11.2	17.4	8.9	19.7
60/80	14.3	14.3	14.3	5.0	23.6
80/100	14.3	17.4	11.2	8.9	19.7
100/200	14.3	20.5	8.1	15.0	13.5
<200	14.3	23.6	5.0	23.6	5.0
Flow rate (Gm./sec.)	7.54	4.07	10.19	5.62	8.58

talc were also studied for comparative purposes. These glidants were added to the following lactose granule fractions: 10/60 mesh; 50% 10/60, 50% 60/100; and 50% 10/60, 25% 60/100, and 25% <100. To compare flow rates, a flow factor "f" (18) which is the ratio of the flow rate of discharged granulate and glidant to the flow rate of the discharged granulate without glidant was calculated. A "f" value greater than 1.0 indicates increased flow; whereas, a value below 1.0 indicates decreased flow. It can be seen from Figs. 2–6 that the effectiveness of added particles is dependent upon the particulate size of the granules to which they are added. For example, lactose fines (Fig. 2) and cornstarch (Fig. 3) were effective when added to 10/60 mesh granules, but their effectiveness

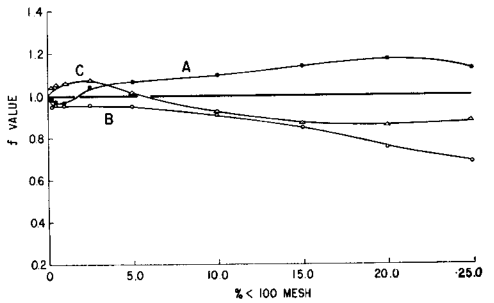

Fig. 2—The effect of <100 mesh particles of the same material on the flow rate of lactose granules. Key: A, 10/60 mesh granules; B, 50% 10/60, 50% 60/100; C, 50% 10/60, 25% 60/100, 25% <100.

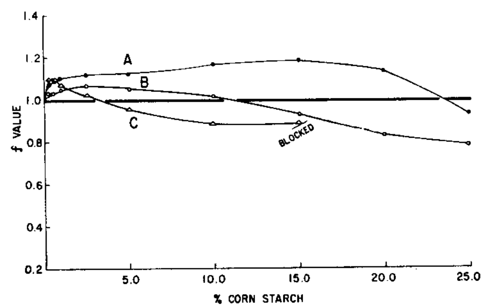

Fig. 3—The effect of cornstarch on the flow rate of lactose granules. Key: A, 10/60 mesh granules; B, 50% 10/60, 50% 60/100; C, 50% 10/60, 25% 60/100, 25% <100.

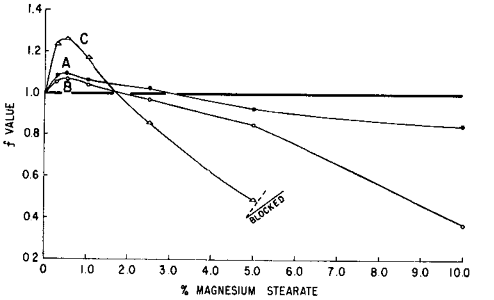

Fig. 4—The effect of magnesium stearate on the flow rate of lactose granules. Key: A, 10/60 mesh granules; B, 50% 10/60, 50% 60/100; C, 50% 10/60, 25% 60/100, 25% <100.

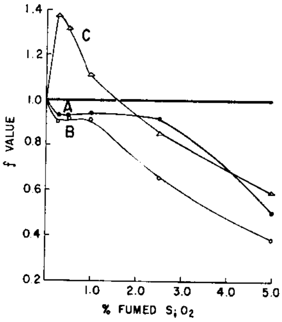

Fig. 5—The effect of fumed silicon dioxide on the flow rate of lactose granules. Key: A, 10/60 mesh granules; B, 50% 10/60, 50% 60/100; C, 50% 10/60, 25% 60/100, 25% <100.

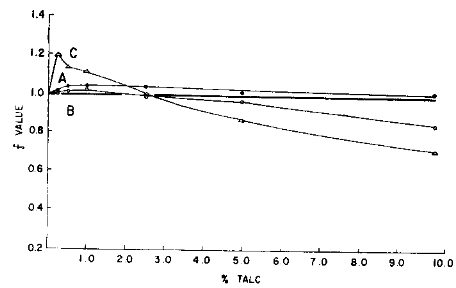

Fig. 6—The effect of talc on the flow rate of lactose granules. Key: A, 10/60 mesh granules; B, 50% 10/60, 50% 60/100; C, 50% 10/60, 25% 60/100, 25% <100.

decreased markedly when added to the other 2 systems which already contained finer particles. Both the fine fraction of the same material and cornstarch appeared to act in a similar manner. In contrast, the optimum concentrations of fumed silicon dioxide, talc, and magnesium stearate were 0.5% or less. All three were more effective in the mixture containing 25% of <100 mesh particles suggesting that these materials act by a different mechanism than fines or cornstarch which were more effective with coarse particles. Both fumed silicon dioxide and magnesium stearate caused sharp decreases in flow rate when used above their optimum concentration.

Jones and Pilpel (14) have classified glidants into two categories: (*a*) those reducing van der Waal's type interparticle cohesive forces and (*b*) those reducing surface rugosity and hence coefficient of interparticle friction. Another possible mechanism is that glidants act by filling void spaces between particles. It appears that fines and cornstarch which were more effective with coarse particles acted either by filling surface irregularities or void spaces; whereas, silicon dioxide, talc, and magnesium stearate possibly acted by reducing interparticle cohesive forces since they were more effective with finer particles and interparticle attraction forces of the van der Waal's type increases as particle size is reduced (19).

SUMMARY

(*a*) In binary mixtures the addition of finer particles increased the flow rate of 10/20 mesh

granules to a maximum, following which a decrease was obtained upon addition of more finer particles. The maximum flow rate was specific for each binary component system and varied with the concentration and size of the added particles.

(*b*) Flow rates of granulations were found to vary considerably, depending upon the degree of wetness and upon the granulating agent used. Granulating agents in order of increasing effectiveness were: 10% starch, 2% methylcellulose, 10% PVP, 10% gelatin, and 10% methylcellulose.

(*c*) Faster flow rates of granulations and blended systems of various particle size distributions were associated with an increase in proportion of 10/60 mesh granules and a decrease in proportion of <100 mesh granules.

(*d*) Effectiveness of glidants was found to be dependent upon particle size of the granules to which they were added. Cornstarch and <100 mesh particles of the same material were found to be more effective for coarse particles; whereas, fumed silicon dioxide, talc, and magnesium stearate were more effective with finer particles.

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Keyphrases

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Lactose granules—wet granulation
Flow rate—granulating process effect
Particle size—flow rate effect
Glidant—flow rate, granules

Rheologic Studies on Dermatologic Lotions

By IVO SETNIKAR, GIUSEPPE GÁL, and SERGIO FANTELLI

The rheologic properties of some dermatologic lotions were studied. The changes in the viscosity, thixotropy, and yield value of the lotions during storage and following various degrees of agitation were recorded. The relevance of these phenomena to production processes and to therapeutic use are discussed. The range of optimum viscosity values of dermatologic lotions is indicated.

Dermatologic lotions are milky, fluid pharmaceutical preparations consisting of a disperse phase of liquid or solid particles in a predominantly aqueous phase.

The rheologic properties of lotions are generally of non-Newtonian type. Indeed, their viscosity often depends upon the shear rate and may be of the dilatant, pseudoplastic, plastic, or Bingham type. They may even exhibit an isothermic reversible decrease in viscosity after an imposed shear rate (thixotropy) or an increase in viscosity (rheopexy).

It is important to know the rheologic properties of a lotion, and the changes they undergo during preparation and during storage in order to adapt the manufacturing operations to these properties and ensure that the lotion possesses the most suitable rheologic properties when it is used therapeutically; few studies on these lines have been published. Woodman and Marsden (1) described the thixotropic properties of a lotion they had prepared. They used "Rheomat" and "Rotovisco" viscosimeters, which involve decanting the lotion into the viscosimeter vessel to measure the viscosity, an operation that alters the rheologic status of a sample with pronounced thixotropic or rheopexic properties.

The ideal instrument for defining the rheologic properties of lotions should (*a*) permit measurement at various shear rates, and (*b*) not require decanting, so that the viscosity of a lotion is not altered before measurement. The latter point is

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