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Keyphrases

Vitamin E analysis—multivitamin products
Dotriacontane—internal standard
GLC—analysis

Technical Articles

Powder Flow Studies IV

Uniformity of Flow: Instrumentation and Applications

By GERALD GOLD, RONALD N. DUVALL, BLAZE T. PALERMO, and JAMES G. SLATER

Use of the recording powder flowmeter for the qualitative evaluation of nonuniform flowing formulations and additional instrumentation for the quantitative measurement of the variation are described. This additional refinement prints out the time, in hundredths of a minute, for preselected weight increments of powder to flow from a hopper. The variation in time is a measure of the uniformity of flow. To illustrate the utility of the instrument, two formulations having similar average flow rates but differing in their uniformity of flow were tableted. The nonuniform flowing formulation tableted on a single-rotary press had a higher coefficient of intertablet weight variation and did not conform to USP standards. Both formulations were tableted on a double-rotary press equipped with induced die feed and low coefficients of variation were obtained in both instances indicating that the die feed mechanism was effective in minimizing intertablet weight variation of an irregularly flowing formulation.

FLUCTUATING FLOW properties of tablet and capsule formulations have been generally overlooked in studying such formulations or at best, evaluated only very subjectively. This has been due, quite largely, to the fact that the two general methods used to evaluate flow of powders, angle of repose measurement, and timed delivery through an orifice, do not distinguish irregularly flowing materials from those which flow smoothly and consistently. For example, Gunsel and Lachman (1) in comparing the flow of formulations prepared with conventionally processed and spray-dried lactose using timed delivery through a funnel found that the formulation having the fastest flow rate exhibited the highest intertablet weight variation.

Another method used to evaluate flow is based on tablet weight variation as actually obtained during tableting trials. Augsburger and Shangraw (2) utilized this method in investigating the effect of various silica-type glidants on the fluidity of direct compression formulations. Increased tablet weight, along with decreased weight variation, indicates improved flowability. This method does give a true picture of the situation under production conditions, but it is time consuming, requiring numerous weighings, and expensive since large quantities of raw material are usually required. Knoechel *et al.* (3) used an instrumented rotary tablet press to evaluate the relative flowability of tableting materials. However, the use of either of these techniques is

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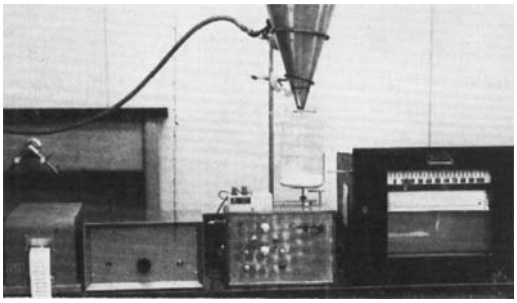

Fig. 1—Photograph of instrumentation showing time interval recorder, attenuator, strain gauge balance, hopper, and strip-chart recorder.

not very practical during the preliminary product development stage.

With the development of more potent drugs, it is becoming increasingly important to prepare dosage forms exhibiting minimum weight variation. Research in this area has been hindered at least in part, by the lack of suitable instrumentation for the direct measurement of variation in flow. This paper describes the use of the recording powder flowmeter (4) for the qualitative evaluation of nonuniform flowing formulations and describes additional instrumentation for the quantitative measurement of the variation in flow. Another objective was to determine the relationship between uniformity of flow and tablet weight variation as it is influenced by certain variables in the tableting process.

EXPERIMENTAL

Instrumentation—The recording powder flowmeter (RPF) consisting of a hopper, strain gauge balance, and recorder described in detail in the first report of this series (4) was redesigned to contain four strain gauges of which two were bonded to the upper surface and two to the under surface of a 0.47 × 0.95 × 25.4-cm. cantilever beam. The instrumentation and electrical diagram are shown in Figs. 1 and 2, respectively. Also included was a transistorized power supply containing a variable span and a zero control potentiometer for balancing the voltage across the two arms of the bridge circuit. It is important in constructing the platform of the cantilever beam that weight applied to the platform be transmitted to a central point on the beam. Otherwise, powder falling on different areas of the platform will cause the millivolt response to fluctuate. The range of the strip-chart recorder was 0–2 mv. for 25.4 cm. full scale and a chart speed of 0.33 cm./sec.

The RPF was further modified by the addition of a microswitch circuit, an attenuator, and a time interval recorder[1] in order to quantitatively measure variation in flow. Span and zero controls on the balance were adjusted so that a selected weight increment such as 50 g. caused full-scale deflection on the strip-chart recorder. At full-scale the pen-drive drum engages the microswitch thereby energizing both the time interval recorder and stepping coil relay of the attenuator. The span potentiometer of the attenuator was then adjusted so that each step in the stepping relay resulted in a voltage of equal magnitude, but opposite polarity to the output of the strain gauge balance, thereby returning the pen carriage to its original position. The time interval recorder prints out the time in hundredths of a minute for each consecutive weight increment and the variation in time is a measure of the uniformity of powder flow.

The instrumentation may be readily used for either qualitative or quantitative measurements by turning the on-off switch of the attenuator and time interval recorder and adjusting the span and zero controls.

Measurement of Powder Flow—Flow measurements were made by allowing 1 kg. of material to flow through a stainless steel conical hopper of 20 cm. top diameter, 30 cm. in length, and interchangeable orifices of 4.76, 6.35, 7.93, 9.52, and 12.70 mm. To study poorly flowing materials, a pressure of 10 p.s.i. was used as described in a previous publication (4).

RESULTS AND DISCUSSION

Application of the RPF for the qualitative evaluation of nonuniform flowing formulations is illustrated in Fig. 3. The flow patterns for aspirin granules[2] and anhydrous dicalcium phosphate (<100 mesh) are indicated by A and E, respectively, and various combinations by B, C, and D. The straight line tracing obtained for aspirin granules indicates uniform flow and the irregular tracing obtained for dicalcium phosphate indicates nonuniform flow. The closer the tracing is to the abscissa, the faster the flow rate. Aspirin had a flow rate of 10.53 g./sec. and dicalcium phosphate 2.38 g./sec. The addition of 25% dicalcium phosphate (Tracing B) increased the flow rate and did not alter uniformity of flow. In contrast, 50% dicalcium phosphate (Tracing C) did not change the flow rate but caused irregular flow. Increasing the concentration of dicalcium phosphate to 75% (Tracing D) resulted in both a slower flow rate and irregular flow. The pulsating characteristic of Formulation D may be measured. From Points a to b in Line D the rate of flow was 9.72 g./sec. and from b to c 3.17 g./sec. representing alternating periods of flooding and starving. The phenomenon of increased flow up to a maximum followed by a decrease on the addition of the finer dicalcium phosphate to the 12/50 mesh aspirin granules is consistent with previous findings in this laboratory (5) relative to the effects of added fines to granules.

To illustrate the utility of the RPF, two formulations having similar flow rates, but differing in uniformity of flow were studied. Figure 4 illustates the flow patterns of both formulations. Formulation A consisted of 32.5% anhydrous dicalcium phosphate, 33% microcrystalline cellulose,[3] 33% aspirin granules,[2] and 1.5% magnesium stearate and had an

[1] Model ET-100, Simplex Time Recorder Co., Gardner, Mass.

[2] Marketed as Aspirin, 10% starch granulation, white, 12–50 mesh, by the Monsanto Co., St. Louis, Mo.

[3] Marketed as Avicel by the FMC Corp., American Viscose Div., Marcus Hook, Pa.

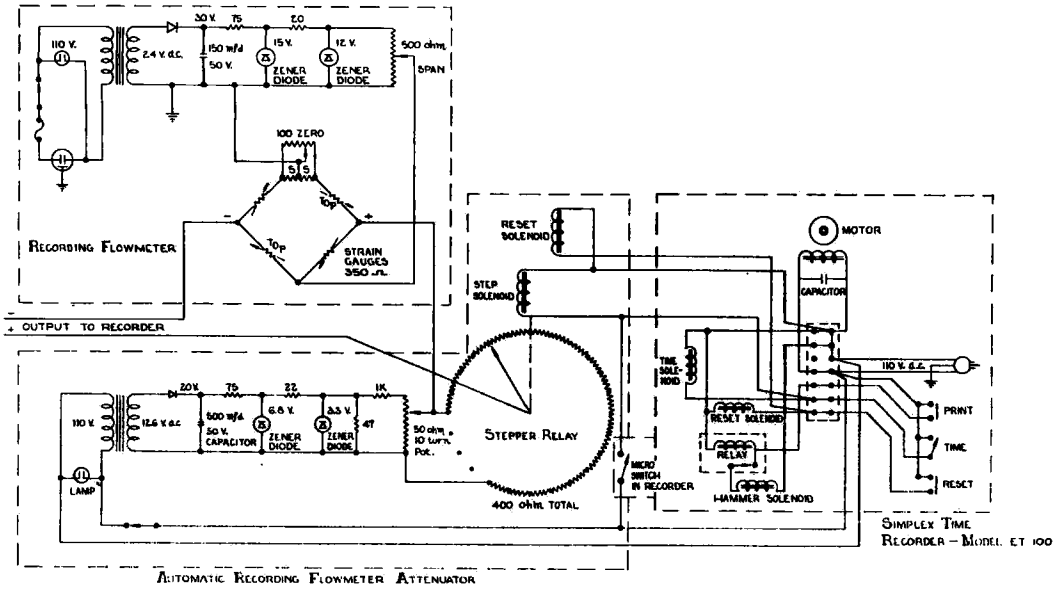

Fig. 2—Electrical diagram for the strain gauge balance, attenuator, and time interval recorder.

irregular flow characterized by flooding and starving. Formulation B consisted of 68.5% sorbitol granules, 30% mannitol powder, and 1.5% magnesium stearate and exhibited uniform flow.

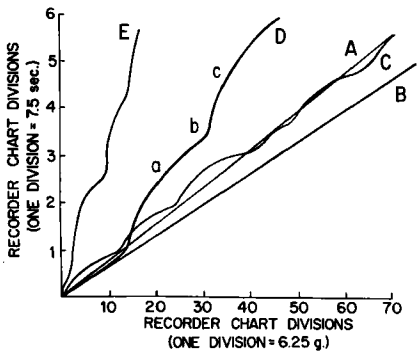

Fig. 3—Flowmeter tracings of formulations containing aspirin granules and anhydrous dicalcium phosphate powder. Key: A, ASA 100/DCP, 0%; B, 75/25; C, 50/50; D, 25/75; and E, 0/100.

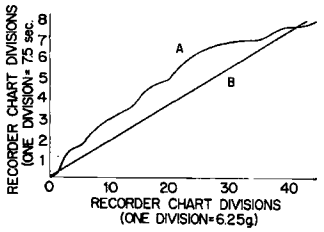

Fig. 4—Flowmeter tracings comparing the flow patterns of two formulations. Key: A, anhydrous dicalcium phosphate, 32.5%; microcrystalline cellulose, 33%; aspirin granules, 33%; and magnesium stearate, 1.5%. B, sorbitol granules, 68.5%; mannitol, 30%; and magnesium stearate, 1.5%.

Formulations A and B were tableted on the single-rotary press (Colton 216) using 10.3-mm. ($^{13}/_{32}$ in.) tooling. Due to the irregular flow of Formulation A the quantity of powder in the feed frame varied. When powder surged through the hopper the feed frame filled and in many instances overflowed; whereas, scanty flow resulted in a feed frame which was nearly empty. Comparative data obtained at three press speeds are given in Table I. The irregularly flowing Formulation A had a higher coefficient of variation at all press speeds and did not conform to the official USP weight variation test. In contrast, the formulation with uniform flow had a lower coefficient of variation and passed the official test.

Both formulations were also tableted on a double-rotary press (Colton 247) using 7.91-mm. ($^{5}/_{16}$ in.) tooling and equipped with an induced die feed. The data obtained are given in Table II. The coefficient of variation for both formulations was low and tablets from each formulation had intertablet weight variation well within the official limits. The induced die feed was, therefore, effective in minimizing intertablet weight variation of this irregularly flowing formulation. These experiments indicate irregular flow is associated with higher intertablet weight variation which may be minimized by appropriate mechanical flowing aides.

The RPF is capable of identifying nonunform flowing materials and is a useful tool in formulating a uniform flowing mixture. However, a definitive study of the factors affecting the uniformity of flow requires an instrument capable of quantitatively measuring the variation in flow. Such an instrument was constructed and the modified RPF measures the time interval in hundredths of a minute for consecutive weight increments of powder to flow, and the variation in time is a measure of the uniformity of flow. Measurements were made on the flow of 25/40 mesh glass beads, aspirin granules, and spray-dried lactose through different size orifices and the data are summarized in Table III. Since the magni-

TABLE I—UNIFORMITY OF TABLET WEIGHTS USING SINGLE-ROTARY TABLET PRESS[a]

Formula	Tab./min.	Av. Wt., mg.	*SD* mg.	*CV*, %	USP XVII
A	548	554	21.5	3.89	Failed
B	548	510	7.6	1.49	Passed
A	687	548	19.7	3.59	Failed
B	687	506	3.5	0.71	Passed
A	863	512	17.4	3.4	Failed
B	863	486	11.8	2.4	Passed

[a] Colton 216, 16 stations, $^{13}/_{32}$-in. diameter stand concave.

TABLE II—UNIFORMITY OF TABLET WEIGHTS USING DOUBLE-ROTARY PRESS[a] WITH INDUCED FEEDING[b]

Formula	Tab./min.	Agitator Setting	Av. Wt., mg.	*SD*, mg.	*CV*, %	USP XVII
A	3,200	50 low	193.3	3.93	2.03	Passed
B	3,200	50 low	160.1	2.68	1.67	Passed
A	3,200	50 high	196.3	3.89	1.99	Passed
B	3,200	50 high	156.9	2.85	1.82	Passed
A	4,000	50 high	190.5	3.45	1.81	Passed
B	4,000	50 high	155.5	3.03	1.95	Passed

[a] Colton 247, 49 stations, $^{5}/_{16}$-in. [b] Model 245.

TABLE III—INTERVAL TIME MEASUREMENTS[a] OF 10 CONSECUTIVE 50-g. INCREMENTS OF 25/40 MESH GLASS BEADS, ASPIRIN GRANULES, AND SPRAY-DRIED LACTOSE

Material	Hopper Orifice mm.	10^{-2} min. Mean	*SD*	*SD* Range	*CV*, %
Glass beads	4.76	28.6	0.64	0.42–0.70	2.24
	6.35	13.2	0.43	0.21–0.67	3.08
	7.93	6.7	0.24	0.21–0.47	4.86
Aspirin granules	7.93	24.7	0.89	0.74–1.22	3.65
	9.52	14.43	0.54	0.39–0.78	3.78
	12.70	6.13	0.23	0.00–0.45	3.75
Spray-dried lactose	4.76	58.8	0.98	0.77–1.25	1.67
	6.35	30.5	0.79	0.53–1.60	2.59
	7.93	17.0	0.61	0.35–0.74	3.59

[a] Based on six determinations.

tude of the standard deviation is related to the magnitude of the interval time measurement, such measurements should be approximtely the same for a valid comparison. For formulations having different flow rates this may be accomplished by varying the size of the orifice and weight increment. For this study, application of the instrument was limited to the comparison of formulations having similar flow rates.

Formulations A and B (Fig. 4) which had previously been evaluated qualitatively were also evaluated quantitatively using the time interval print out. From a plot of increment time measurements in Fig. 5, it is readily evident that Formulation A exhibited greater variation in flow. Formulation A had a *SD* of 8.85×10^{-2} min. and a *CV* of 63.6% as compared to a *SD* of 1.19×10^{-2} min. and *CV* of 7.53% for B. This is in agreement with the qualitative results and illustrates the utility of the instrumentation for quantitative measurements of the variation in flow.

Another application for quantitative measurement is illustrated by a practical example encountered in this laboratory. Qualitative analysis of a poorly flowing formulation indicated that one of the fine powders comprising 12% of the formulation was responsible for the poor flow. This powder was less than 40 mesh and was being offered in a 16/40 mesh granular form. Average flow rates of the formulations containing the powder and the granular form were found to be comparable. However, a plot of increment time measurements (Fig. 6) showed that Formulation A exhibited much greater variation. Formulation A had a *SD* of 1.99×10^{-2} min. and a *CV* of 26.39% as compared to a *SD* of 0.56×10^{-2} min. and a *CV* of 7.47% for Formulation B. Both

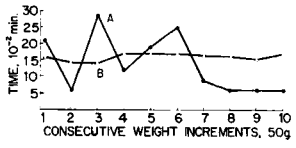

Fig. 5—Increment time measurements comparing the variation in flow of two formulations. Key: A, anhydrous dicalcium phosphate, 32.5%; microcrystalline cellulose, 33%; aspirin granules, 33%; and magnesium stearate, 1.5%. B, sorbitol granules, 68.5%; mannitol, 30%; and magnesium stearate, 1.5%.

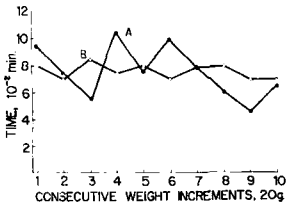

Fig. 6—Increment time measurements showing the effect of particle size of an ingredient comprising 12% of a powder mixture on the uniformity of flow. Key: A, < 40 mesh; B, 16–40 mesh.

formulations were subsequently tableted on the single-rotary press. Tablet weight data using the F test at 95% confidence limits indicated the more uniform flowing formulation had significantly less tablet weight variation.

SUMMARY

Instrumentation has been described for the qualitative and quantitative evaluation of the uniformity of flow of powders through a hopper orifice. For the qualitative evaluation, a recording powder flowometer was utilized in which a recorder tracing identifies fluctuating or inconsistently flowing materials. For quantitative measurement, a print out of the time for preselected weight increments of powder to flow is obtained and the variation in time is a measure of the uniformity of flow. Examples were presented to illustrate the utility of the instrumentation in identifying and evaluating nonuniform flow.

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Keyphrases

Powder flow studies
Instrumentation—powder flow
Flow, powders—uniformity
Tablet weight variation—powder flow effect
Diagram—powder flowmeter

Notes

LSD Analogs II. *N*-[2-(3-Pyridyl)ethyl]-β-alanine Derivatives

By KENNETH J. LISKA and ANJANEYULU S. TADEPALLI

As a continuation of the study of structure-activity relationships in LSD analogs, the ethyl esters and *N,N*-diethylamides of *N*-[2-(3-pyridyl)ethyl]-β-alanine and *N*-methyl-*N*-[2-(3-pyridyl)ethyl]-β-alanine were prepared and evaluated for antiserotonin activity in the isolated rat fundus. All four compounds and one of the intermediates were found to be devoid of activity. SAR implications are discussed.

THE THEORY OF a biochemical etiology of mental illness, especially of schizophrenia, expounded by Woolley (1) and others, has not gained general acceptance. Yet complete rejection of this theory is not justified, for it appears that insufficient data have been accumulated on all aspects of the problem. Among the various kinds of data needed are those on structure-activity relationships in the various chemical types of psychotomimetics. With these data, it might be possible to draw conclusions regarding the mechanism of action of both natural and unnatural neurochemicals and neurohormones.

The aim of this investigation was to continue the preparation of relatives of lysergic acid diethylamide (LSD). In part I (2), serotonin inhibition was utilized as an index of LSD-like activity, and three β-alanine derivatives were found to possess significant pharmacological properties. In the present work, four additional β-alanine derivatives have been prepared and evaluated, again utilizing serotonin inhibitory activity as the criterion.

Woolley believed that serotonin was a key substance in any consideration of a biochemical etiology of schizophrenia, and it is true that all of the psychotomimetic indoles antagonize serotonin (3). Past criticisms of the use of serotonin inhibition as an index of LSD-like activity were based in part on the

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