bed of glass beads was added to both cells, occupying about half of the chamber volume. The beads acted as dampers, and the 4-mm. size improved the flow characteristics considerably (Fig. 7 *versus* Fig. 4). However, it was necessary to use 1-mm. beads before proper laminar flow was attained (Fig. 8). Laminar characteristics were observed up to 80 ml./min., the highest flow rate used.

Because the photographs and drawings are two dimensional and static, they do not accurately represent the total, dynamic, three-dimensional situation. The video tapes from the television work provide a better record of solvent flow patterns because the actual motion is recorded. As mentioned earlier, visual observation is best.

In a previous investigation (4), constant-surface pellets of salicylic acid were used with the column apparatus. To gain more insight into the results of those experiments, flow patterns were observed in the 25-mm. chamber with the pellet in the center of the lower screen (Fig. 9) and at the side (Fig. 10). The results confirmed that, for a given flow rate, the lowering of the dissolution rate when the pellet was moved to the side of the chamber was due to the lower rate of solvent flow in that region.

SUMMARY

These results indicate that using a bed of 1-mm. glass beads with the column apparatus helps ensure laminar flow over a wide range of liquid velocities. This type of solvent flow is much preferred over the poorly defined, random-type flow characteristic of all beaker methods. Because surface tension slows solvent movement near the sides of the chambers, it is preferable to place the tablet well away from the sides of the cell.

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Dustiness of Pharmaceutical Formulations I: Instrumentation

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Abstract □ Instrumentation for evaluating the dustiness of tableting materials is reported. The sample is dropped into a dust chamber where a controlled flow of air carries the resulting dust particles through a beam of light. The scattered light is received by a photodetector which converts light pulses into electrical pulses. The instrumentation was precalibrated in particle-size ranges of 0.5–10, 11–50, and >50 μ, and the number of particles in each size range is displayed on a digital counter. The particle size refers to the equivalent diameter of the dust particle that generates the same electrical response in the photodetector as the reference particle used to calibrate the instrumentation. Eleven commonly used tableting aids were classified into three categories based on their relative dustiness. Data obtained with the dust counter were shown to correlate with the dustiness resulting from the bulk handling of larger quantities of materials.

Keyphrases □ Dustiness of tableting materials—determination using light-scattering method and equipment □ Pharmaceutical technology—method and equipment for determining dustiness of tableting materials □ Tableting materials—measurement of dustiness □ Light-scattering method and equipment—determination of dustiness of tableting materials

Dust of any kind in a pharmaceutical plant is a serious matter. Areas of particular concern are: (*a*) cross-contamination of other products, and (*b*) potential hazards to the health of workers. There is always a risk of cross-contamination occurring with potentially serious consequences in pharmaceutical plants that utilize the same manufacturing facility to produce a variety of pharmaceutical products. Cross-contamination of a product with penicillin, for example, is capable of causing a serious reaction or even death to a person sensitive to penicillin (1). It is essential, therefore, that dust always be kept under control.

In regard to the workers' health, dust may be classified as a lung-depositing dust, toxic dust, primary irritant dust, sensitizing dust, or nuisance dust. A lung-depositing dust is deposited and retained in the lungs, where it may be benign or cause lung pathology. Toxic dust is a systemic poison which enters the circulation by absorption from the respiratory tract or after being swallowed. A primary irritant is limited largely to the mucous membranes of the eyes, nose, and throat. Prolonged exposure to low-grade irritants is capable of producing disturbances in respiratory function and secondary infection (2). A sensitizing dust elicits the antigen–antibody response in susceptible individuals as a result of either inhalation, skin contact, or ingestion. A nuisance dust is primarily discomforting to the worker and is often associated with increased colds and bronchitis. In general, the inhalation of any kind of dust in sufficient amounts for long periods of time can lead to disturbances in pulmonary function (3).

Particle size, frequency of exposure, quantity of concentration, and chemical action on the body tissue and fluids are important factors that influence whether a

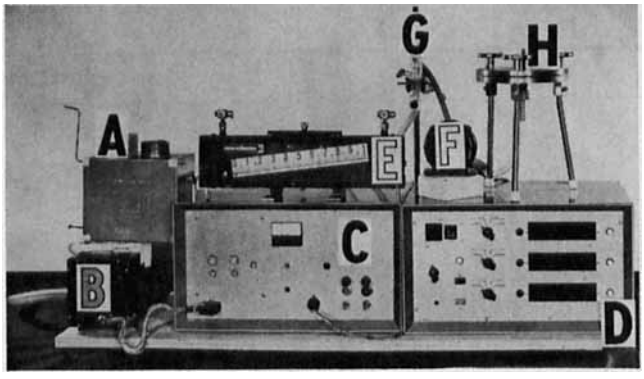

Figure 1—*Photograph of instrumentation showing sample chamber (A), detection chamber (B), pulse height discriminator (C), three-channel counter (D), inclined draft gauge (E), spiral exhauster (F), rotometer (G), and filter assembly (H).*

dust is an industrial health hazard (4). Particles between 1 and 2 μ have the greatest probability of being deposited in the pulmonary air spaces, and particles >10 μ are essentially removed in the nasal chamber and have little probability of penetrating to the lungs (5). Silica dust particles reaching and remaining in the alveoli are believed to be largely limited to the size ranging between 0.1 and 3 μ (6). The published threshold limit values (7) for several hundred materials refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect. The threshold limit values for nuisance dusts are 5 mg./m.^{3} for the respirable fraction and 15 mg./m.^{3} for total dust.

With the enactment of the Williams–Steiger Occupational Safety and Health Act of 1970, there will be more stringent governmental control of the concentration of dust in manufacturing plants; the formulator now has the added responsibility of preparing products that generate minimal dust. Unfortunately, little information is available for selecting low dust-yielding ingredients. Often the formulator is not aware of a dust problem until a production scale-up run is made, at which time it is extremely costly and time consuming to reformulate the product or to design a manufacturing system to control the dust. Furthermore, the present method for evaluating dustiness by simply observing the workroom environment is empirical and may lead to erroneous conclusions. Since the harmful respirable particle size is below the normal limit of visibility, work atmospheres that appear to be only slightly dusty often contain extremely hazardous concentrations of dust (8), and several cases were reported (9) where visible dust was practically absent from the air but the workers still contracted pulmonary disease.

The purpose of the first phase of this study was to develop a practical, objective method for measuring the relative dustiness of pharmaceutical powders. To meet this objective, instrumentation was developed based on light-scattering principles for sizing and counting airborne particles in the harmful respirable range. This report describes the instrumentation and indicates how it may be used to evaluate the relative dustiness of raw materials.

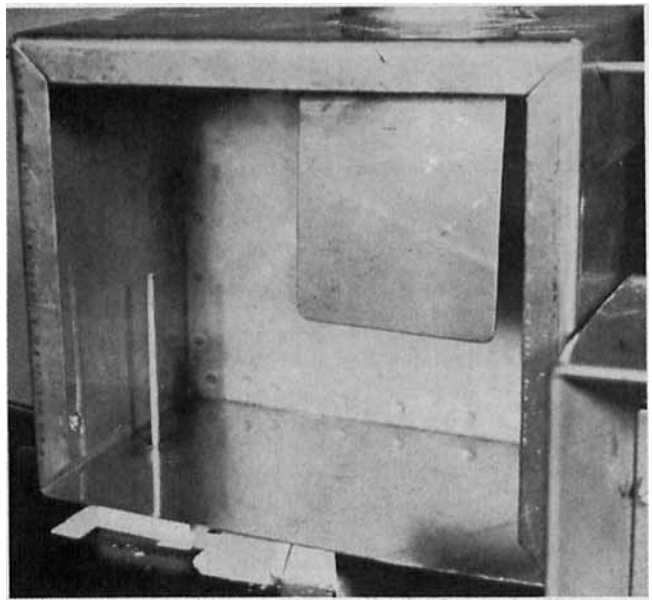

Figure 2—*Photograph of sample chamber (front removed) showing the inlet tube and platform (tripped position).*

EXPERIMENTAL

Instrumentation—The instrumentation (Fig. 1) consists of a sample chamber (A), a detection chamber (B), a pulse height discriminator (C), a three-channel counter (D), an air-flow system which includes a draft gauge[1] (E), a spiral exhauster[2] (F), a rotometer[3] (G), and a filter assembly[4] (H).

The sample is placed on the platform of the sample chamber (Fig. 2) and dropped by tripping the platform lever. The resulting dust particles enter the inlet tube of the sample chamber where they are carried by a controlled flow of air to the detection chamber. In the detection chamber, the dust particles are surrounded by filtered air entering from the filter and passed through a beam of light emanating from a light source[5] within the chamber. Scattered light is picked up by a photomultiplier[6] located within the chamber at a 40° angle from the light beam and converted to an electrical pulse. A preamplifier intensifies the electrical pulse from the photomultiplier, and a pulse height discriminator using stearing logic and pulse height detectors transfers the pulse to one of three channels of the counter. The counter is constructed with digital integrator circuits using wire-wrapped panels. Three separate scalers are used with a common time base generator and three 4.5-digit displays and overrange indicators. Three decades of prescaling are provided for each channel with a range selector switch. The timer can be adjusted in minute intervals up to 10 min. with an expired time indicator light.

Calibration—The instrument was calibrated using reference latex spheres[7] having particle diameters of 0.091, 0.481, 6–14, and 50–100 μ. The reference spheres were packaged as aerosols in which the particles were kept separated from the propellent and sprayed into one opening of a 1-l., three-necked distilling flask. Heat was blown into the second opening, and the third opening was connected to the inlet tube of the detection chamber. For each reference sphere size, the average pulse height was measured at the input of the pulse height discriminator. A linear relationship was found to exist between the size of the reference sphere and the pulse height. The three discriminator circuits were then adjusted so that one channel of the counter measured particle-diameter ranges of 0.5–10 μ, the second channel 11–50 μ, and the third channel >50 μ. The particle size refers to the

[1] Ellison Draft Gage Co., Chicago, Ill.
[2] Model SE2A-1, Rotron Inc., Woodstock, N. Y.
[3] F. W. Dwyer Manufacturing Co., Michigan City, Ind.
[4] GSWP 14200, 0.22-μ filter, Millipore Corp., Bedford, Mass.
[5] Tungsten lamp back-plate assembly from Beckman DU spectrophotometer, model 2400, Beckman Instruments, Inc., Fullerton, Calif.
[6] Type IP 28, RCA, New York, N. Y.
[7] Dow Chemical Co., Midland, Mich.

Table I—Dust Counts in the 0.5–10-μ Range for Several Commonly Used Tableting Aids

Material	Minutes	Mean[a]	*SD*	Mean Limits[b]
Direct compression dextrose	1	25.8	15.1	14.2–37.4
	5	26.9	15.8	
Direct compression sucrose formulation	1	109.8	44.5	76–144
	5	112.1	45.5	
Spray-dried lactose	1	253.9	91.0	184–324
	5	254.7	90.9	
Terra alba	1	429.9	163.3	304–555
	5	443.3	176.1	
Direct compression sucrose	1	1301.7	293.3	1076–1527
	5	1374.8	342.2	
Unmilled dicalcium phosphate dihydrate	1	2269.6	530.7	1862–2676
	5	2409.0	619.7	
Starch	1	4475.9	1562.0	3275–5677
	5	4743.1	1689.5	
Direct compression starch	1	6592.9	1804.1	5206–7980
	5	6837.9	1899.2	
Microcrystalline cellulose	1	8028.8	816.1	7401–8656
	5	8335.8	972.2	
Magnesium stearate	1	8743.9	2299.3	6976–10,511
	5	11,682.3	3130.5	
Talc	1	10,362.1	2478.5	8457–12,267
	5	12,991.2	3903.3	

[a] Mean of nine cumulative counts. [b] The 95% confidence limits about the mean.

Table II—Dust Counts in the 11–50-μ Range for Several Commonly Used Tableting Aids

Material	Minutes	Mean[a]	*SD*
Direct compression dextrose	1	1.3	1.4
	5	1.4	1.5
Direct compression sucrose formulation	1	3.0	2.1
	5	3.0	2.1
Spray-dried lactose	1	8.8	4.1
	5	8.8	4.1
Terra alba	1	11.0	8.6
	5	11.0	8.6
Direct compression sucrose	1	25.9	5.5
	5	25.9	5.5
Unmilled dicalcium phosphate dihydrate	1	71.4	26.3
	5	71.6	26.2
Starch	1	283.0	206.9
	5	283.4	207.2
Microcrystalline cellulose	1	605.2	102.1
	5	605.2	102.0
Direct compression starch	1	666.3	264.9
	5	667.8	265.2
Talc	1	1145.6	445.5
	5	1152.8	449.7
Magnesium stearate	1	2287.4	592.4
	5	2312.2	588.7

[a] Mean of nine cumulative counts.

Table III—Classification[a] of Relative Dustiness of Several Commonly Used Tableting Aids

Group I (0–1000 Counts)	Group II (1001–6000 Counts)	Group III (>6000 Counts)
Direct compression dextrose	Direct compression sucrose	Microcrystalline cellulose
Direct compression sucrose formulation	Dicalcium phosphate	Magnesium stearate
	Starch	Talc
Spray-dried lactose	Direct compression starch[b]	
Terra alba		

[a] Based on mean of nine measurements after 1 min. in the 0.5–10-μ range. The 95% confidence limits about the mean for each tableting aid are within the assigned group's range. [b] Classified between Groups II and III.

equivalent diameter of the particle that generates the same electrical response in the photodetector as the reference particle used to calibrate the instrument (10). Using the soap film method of calibration, the air flow through the inlet tube of the sample chamber was 870 ml./min. at a reading of 0.13[8]. For checking the counting and light circuitry, a secondary calibration system was incorporated in the instrumentation which consists of a d.c. μ ammeter to measure the dark current of the photomultiplier and a 60-Hz. line frequency check for the prescaling, scalers, time base, and display circuitry.

Measurements—A 15-g. sample was placed on a platform located 15 cm. above the floor of the sample chamber. The platform lever was then tripped and the timer was started. Particle counts for each size range were recorded in 1-min. intervals up to 5 min. Three measurements were made for each sample and were repeated on 2 different days for a total of nine measurements. Measurements were made in a temperature- and humidity-controlled room using conventional engineering equipment in which the temperature varied from 23 to 27° and the relative humidity did not exceed 20%.

Materials—The following commercially available USP, NF, or pharmaceutical grade tableting ingredients were evaluated for dustiness: direct compression dextrose[9], unmilled dicalcium phosphate dihydrate[10], spray-dried lactose[11], magnesium stearate, microcrystalline cellulose[12], starch, direct compression starch[13], direct compression sucrose[14], direct compression sucrose formulation[15], talc, and terra alba[16].

RESULTS AND DISCUSSION

One- and 5-min. dust counts in the 0.5–10-μ range (for several commonly used tableting aids) are tabulated in Table I. One-minute dust counts varied from a low mean of 25.8 for direct compression dextrose to a high of 10,362 for talc. Five-minute dust counts varied from 26.9 for direct compression dextrose to a high of 12,991 for

[8] On the Ellison inclined draft gauge.

[9] Celutab, Penick and Ford, Ltd., Cedar Rapids, Iowa.
[10] Stauffer Chemical Co., Chicago, Ill.
[11] Foremost Dairies, Inc., San Francisco, Calif.
[12] Avicel PH 105, FMC Corp., Marcus Hook, Pa.
[13] STA-Rx 1500, Colorcon Co., West Point, Pa.
[14] Di-Pac, American Sugar Co., New York, N. Y.
[15] Nu-Tab, SuCrest Corp., New York, N. Y.
[16] U. S. Gypsum Co., Chicago, Ill.

Table IV—Dust Measurements with the Laboratory Dust Counter and Commercial Air Sampler on Three Selected Tablet Formulations

	Dust Counter[a] Number of Particles		Air Sampler[b] Weight Gain, g.	
	Mean[c]	*SD*	Mean[d]	*SD*
Direct compression dextrose formulation[e]	222.0	38.6	0.0075	0.0020
Dicalcium phosphate formulation[e]	4137.1	775.6	0.729	0.293
Microcrystalline cellulose formulation[e]	12,950.0	1458.9	1.958	0.425

[a] A 15-g. sample, 0.5–10 μ, 1 min. [b] Unico sampler, Gelman type A filter, 30-kg. sample dropped from a 3-ft.^{3} twin-shell dry blender. [c] Mean of nine counts. [d] Mean of four counts. [e] Contains 0.1% FD&C Red No. 2 and 0.5% magnesium stearate.

talc. A paired comparison between the 1- and 5-min. data using the *t* statistic indicated that the 5-min. data were significantly higher than the 1-min. data. Dust particles in the 0.5–10-μ range have the highest probability of being deposited in the pulmonary air spaces and represent the greatest hazard to health.

Although particles in the 11–50-μ range have little probability of penetrating to the lungs, they may be swallowed to produce systemic activity. Dust counts in the 11–50-μ range are listed in Table II. The 1-min. dust counts varied from a low mean of 1.3 for direct compression dextrose to a high mean of 2287.4 for magnesium stearate. Five-minute dust counts varied from a low of 1.4 for direct compression dextrose to a high of 2312.2 for magnesium stearate. The lower dust counts in the 11–50-μ range and the absence of a significant difference between the 1- and 5-min. data are indicative of the faster settling-out rates of the larger size particles.

A classification of relative dustiness was devised based on placing the 1-min. mean counts of the 0.5–10-μ range particles into one of three groups. Group I was assigned a mean count range of 0–1000; Group II, 1001–6000; and Group III, >6000. The 95% confidence limits about the mean (Table I) were used in classifying the tableting aids into the various groups. The tableting aid was classified in the group whose range included the limits about the mean. As indicated in Table III, Group I consists of direct compression dextrose, direct compression sucrose formulation, spray-dried lactose, and terra alba. Group II contains direct compression sucrose, unmilled dicalcium phosphate, and starch. Direct compression starch is classified between Groups II and III. Group III contains microcrystalline cellulose, magnesium stearate, and talc.

An experiment was designed to determine if the data obtained with the dust counter correlated with dust generated during the bulk handling of larger quantities of the same materials. Direct compression dextrose, dicalcium phosphate, and microcrystalline cellulose were selected from the classification as representing various levels of dustiness. To each material, 0.1% FD&C Red No. 2 and 0.5% magnesium stearate were added. Dust counts for each of these three formulations were made using the dust counter as already described. Dustiness of the same three formulations was also measured using an air sampler[17] by dropping 30 kg. of each formulation from a 3-ft.^{3} twin-shell dry blender. The results (Table IV) indicate a high correlation coefficient (r = 0.998) between the dust counts obtained with the laboratory dust counter and the dustiness resulting from the bulk handling of larger quantities of the same material.

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[17] Unico 600, Unico Industrial Equipment Corp., Fall River, Mass.