cedure described in this paper is being applied to a series of complex pharmaceutical mixtures which will be the subjects of future articles.

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TECHNICAL ARTICLES

Utilization of the Solids Processor for Preparation of Tablet Granulations

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Abstract □ Various factors relating to the use of vacuum tumble dryers for the preparation of tablet granulations were studied. A dryer was employed (the 1-cu. ft. solids processor) which has a working capacity of 15–18 kg. for most pharmaceutical granulations. A typical process involves the wetting of the substrate with a drug solution and then drying at a predetermined temperature and vacuum. It was found that uniform drug distribution for low-dose tablet formulations could be obtained. Drying rates were determined for spray-dried lactose and dicalcium phosphate dihydrate at two temperatures and three tumbling speeds. Drying times varied from 35 to 60 min. A series of modified direct compression formulations was studied in which microcrystalline cellulose was used at two levels; two lubricants, calcium stearate and stearic acid, were employed; and lubricant addition was carried out by two methods, internal and external. The effects of these factors on tableting characteristics were monitored by an instrumented tablet machine (Stokes BB-2), and the final physical properties of the tablets were determined. A series of antacid granulations was prepared in which the influence of mixing time and the amount of granulating fluid was varied. The resulting granulations and tablets were characterized as described above.

Keyphrases □ Solids processor—preparation, tablet granulations □ Tablet granulations, preparation—solids processor □ Vacuum tumble dryers—data, mixing, drying, formulation, processing factors

New technology for the formulation of solid dosage forms has been developed over the past 5–10 years. The availability of new materials *per se*, new forms of old materials, and the invention and utilization of new machinery have allowed the formulation and manufacture of many products by simplified methods. Thus, the use of direct compression of medicinals, especially those in the low- and medium-dose range, has overtaken older traditional methods of wet granulation and slugging. Emphasis on faster dissolution rate and providing the drug in a readily available form are other reasons for updating tablet formulation and technology.

Some methods for simplified processing of tablet granulations have been described. A spray-drying process was reported by Raff *et al.* (1). A placebo granulation was prepared by spray drying and the drug, colorant, and tablet lubricant were added to the granulation and blended. A one-step spray-drying process could conceivably be feasible if the high inlet temperature would not physically or chemically affect the drug. Later, Kornblum described a spray-drying process for the preparation of a granulation for the formulation of sustained-action tablets (2).

The Littleford-Lodge mixer has been shown to be of value in mixing small quantities of active ingredients with inert diluents (3). In experiments using 250 mcg. of micronized salicylamide per 100 mg. of terra alba, coefficients of variation for drug content were from about 1 to 4% over a 0.5–10-min. interval of mixing. Mixing unmicronized salicylamide gave a significantly higher coefficient of variation.

An air-suspension technique for the preparation of tablet granulations was described by Wurster (4). These granulations were 16–20% active by weight, and deviation of content from theory was about −1 to +6%. The amount of solids lost was 1–8%.

Some of these methods might be satisfactory for active products in the low-dose range, arbitrarily in the

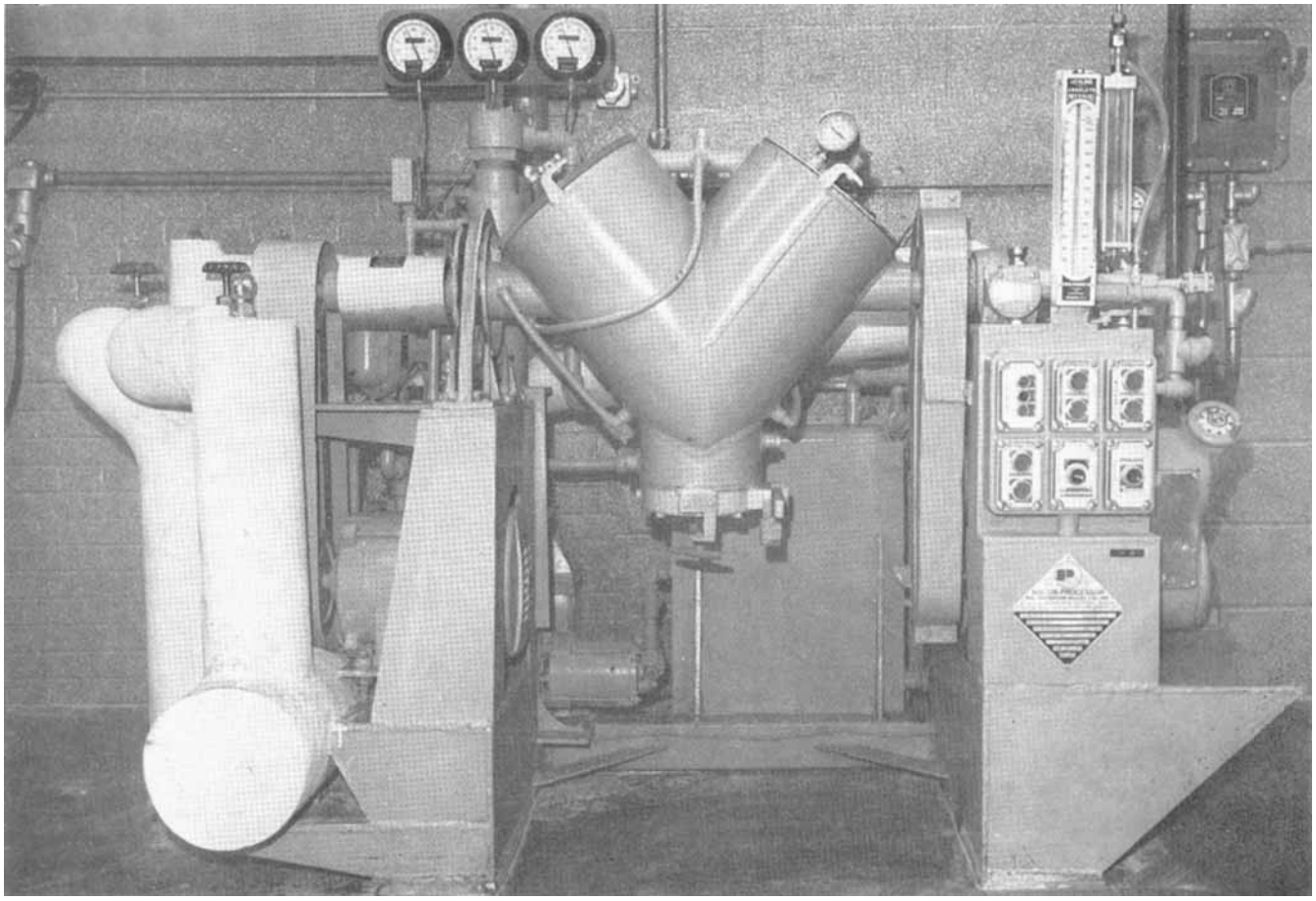

Figure 1—*Photograph of the 1-cu. ft. vacuum tumble dryer used throughout the study.*

area of 0.5–5 mg. per tablet. Ordinarily, tablet weights for these drug potencies would be 100–200 mg. When low microgram (10–100) quantities of drug are to be incorporated into a tablet, it is the generally accepted procedure to dissolve the drug in an appropriate solvent and apply the solution to the tablet substrate. The reasoning for this procedure is that drug particles often vary substantially in physical characteristics from the tablet substrate. Adequate dry blending of low-dose drugs would be dependent on a number of factors. Among these are the relative size distribution of the substrate compared to the drug, the ratio of drug to the substrate, the degree of affinity of the substrate for the drug, and the degree of static charge. The type of mixer used and mixing time are additional practical considerations. In one report, the mixing technology for 0.1-mg. reserpine tablets weighing 100 mg. (5) was studied. It was found that 100 mg. of the ultimate dry mix obtained had a coefficient of variation of 3.5%. However, on wetting this mix and granulating with water, the resulting granules had a coefficient of variation of 4.3%. The explanation for the slight segregation in the mix was the fact that the various components had different affinities for the water.

From these considerations, it was believed that vacuum tumble dryers (VTD) would provide advantages to the total processing of pharmaceutical granulations. Formerly, two reports on the use of twin-cone vacuum dryers for pharmaceutical material had appeared (6, 7), but no data on the total processing of tablet granulations were reported. VTD provides a method for addition of drug from solution, thus eliminating the various problems encountered in dry mixing procedures; among these are colorant blending and static charge. Since the material is agitated during drying, the tendency for the drugs to migrate, a factor which might produce nonuniformity within the powder bed, is minimized. Other advantages which are readily apparent are: (*a*) drying in vacuum can be carried out at lower temperatures, thus heat-labile drugs may be processed more favorably; (*b*) installations are compact; (*c*) solvent can be recovered; (*d*) complete enclosure of the mixing chamber virtually eliminates the possibility of contaminating adjacent areas with potent drug; (*e*) tumble dryers are easy to clean; (*f*) discharging of material from the VTD is easy and this results in high yields of finished product. One-step processing of some formulations might be feasible and this alone greatly simplifies manufacturing procedures. It was also believed that overall processing time might be shorter than could be achieved with other equipment. In opposition to these advantages are the relatively high cost of vacuum dryers and the fact that this equipment is not available in many pharmaceutical processing plants.

A general study of the technology for using VTD was undertaken in order to better understand its overall applicability to the processing of pharmaceutical

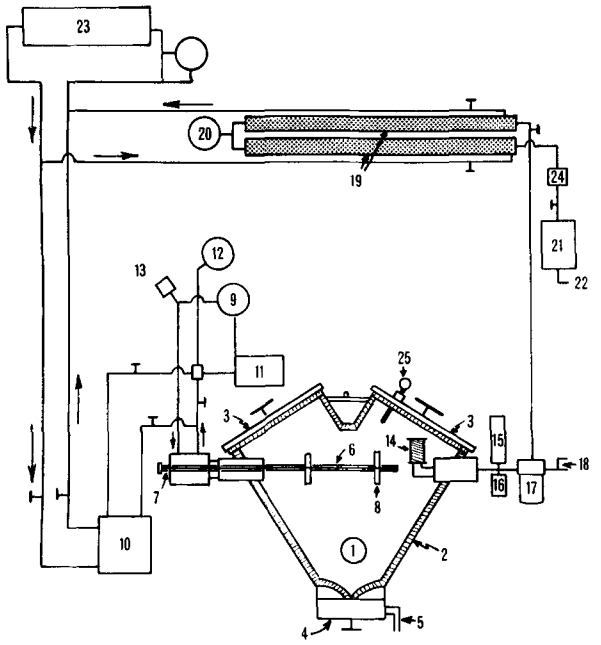

Figure 2—*Diagrammatic view of the 1-cu. ft. vacuum tumble dryer. Key: 1, shell; 2, jacket; 3, access covers; 4, discharge cover; 5, butterfly valve; 6, intensifier bar; 7, liquid feed tube; 8, dispersing disks; 9, chromalox immersion heater; 10, heat exchanger; 11, pump; 12, expansion tank; 13, thermometer; 14, felt ring filter; 15, mercury manometer; 16, vapor temperature thermometer; 17, solids separator; 18, ball valve; 19, condensers; 20, receiver; 21, vacuum pump; 22, vent; 23, chilling unit; 24, expansion tank; 25, solenoid valve; and 26, vessel thermometer.*

granulations. Experiments on mixing, drying, formulation factors, and processing factors were carried out and are reported here.

EXPERIMENTAL

General Description of Equipment—The equipment employed was a 1-cu. ft. vacuum tumble dryer[1] which is shown in Fig. 1. A schematic representation is illustrated in Fig. 2. The shell, 1, is fabricated of 304 stainless steel, and all pipes and fittings are 304 stainless steel. It has a working capacity of about 15–18 kg. for most pharmaceutical materials and is driven by a $^3/_4$-hp. Reeves Vari-Speed Motodrive which can turn the shell at speeds to 47 r.p.m. The shell is jacketed, thus providing a method of heating or cooling the material being processed. Access covers are provided on both sides and a butterfly valve and additional cover are used for discharging the material. The intensifier bar is operated by a separate 3-hp. motor. The bar functions as a disperser for added liquid material. A liquid feed tube is used in conjunction with the intensifier bar for the addition of liquids. Liquids are dispersed between two sets of disks on the intensifier bar. Spacings between the disks may be varied from 0.013 to 0.051 cm. (0.005 to 0.020 in.). The prongs on the dispersing disks are used for more vigorous mixing or for the reduction of agglomerates.

The jacket is heated by means of chromalox immersion heater and a liquid circulating pump. Heated liquid may be chilled by shunting the circulation through a heat exchanger which is connected to the same chiller that is used for the condensing system.

The vacuum and condensing system consists of a felt ring-type filter in the vessel, a vapor temperature thermometer, an absolute mercury manometer, a solids separator, two slanted condensers leading to a receiver, a Kinney KC-8 vacuum pump, and a Carrier model 30EA005 liquid chilling package. An ethylene glycol–water mixture was used in the chilling unit and the temperature of the circulating liquid was generally −2 to −5°. A solenoid valve between the vacuum pump and the condensers closed when the vacuum pump was turned off, thus preventing the condensers from being fouled with oil. The vacuum pump was vented to the atmosphere for removal of vapors which collect in the oil.

[1] Solids Processor, Patterson-Kelley Co., Inc., East Stroudsburg, Pa.

Table I—Composition of Tablet Granulation for the Determination of Uniformity of Mixing

	One Tablet	110,000 Tablets
Methylparaben USP	0.20 mg.	0.0220 kg.
Isopropyl alcohol NF		1.500 l.
Microcrystalline cellulose NF	52.50 mg.	5.775 kg.
Starch USP	15.00 mg.	1.650 kg.
Spray-dried lactose USP	80.80 mg.	8.888 kg.
Calcium stearate NF	1.50 mg.	0.165 kg.
	150.00 mg.	16.500 kg.

General Operation—Material is placed in the shell and the access covers are fitted and sealed against the recessed O-rings. Care must be taken to obtain a good seal because small amounts of material between the lid and O-ring may cause a leak which interferes with the operation of the processor. The material may be mixed by tumbling, and if lumps are present the intensifier bar may be turned on. Dispersion blades on the intensifier bar effectively break up agglomerates and give additional agitation for better mixing. Liquids are then added *via* the liquid feed tube. For the preparation of low-dose tablets, typically 1000–1500 ml. of drug solution is added to 15–18 kg. of substrate. Usually the time period of addition is 5 min., but shorter intervals are also satisfactory. Part of the solvent containing no drug is retained for flushing the liquid feed tube and dispersing disks. Heat and vacuum are then applied to the shell. The degree of vacuum that may be used is determined by the inspection of the vapor pressure–temperature curve for the solvent being used and the temperature of the condensate. For isopropanol the condensed liquid had a temperature of about 23°; thus, a vacuum of 40 mm. of Hg could be applied without causing the isopropanol to boil. Upon reaching a vacuum of 40 mm. of Hg, the vacuum pump is shut off. Evaporation and condensation of the solvent continue at about this level of vacuum until most of the solvent is collected. The receiver is emptied at this point and full vacuum is applied to the system to remove the last traces of solvent. Generally, this process using isopropanol takes about 30–50 min. and solvent recoveries are 90–95%. Ordinary materials used for producing low-dose tablet formulations are easily emptied from the shell, giving very high yields of finished product. No problems with the sticking of materials to the shell were encountered in this work.

Materials—Spray-dried lactose USP XVII, dibasic calcium phosphate dihydrate USP XVII, isopropyl alcohol NF XII, stearic acid USP XVII, calcium stearate NF XII, starch USP XVII, microcrystalline cellulose NF XII (Avicel PH 101), methyl *p*-hydroxybenzoate, an estrogenic steroid, and an antacid powder containing magnesium trisilicate, aluminum hydroxide, and magnesium hydroxide.

Equipment—Stokes BB-2 27 station tablet machine instrumented to detect and measure compression force (CF), ejection force (EF), and lower punch pulldown force (LPPF); an air-actuated pressure-regulated hardness tester; a friabilator (8); and a USP XVII tablet disintegration tester.

Evaluation of VTD for the Distribution of Low-Dose Ingredients—Preliminary experimentation on the preparation of drug concentrates, which were to be diluted for the production of tablets by the direct compression method, indicated that homogeneous blends could be obtained. The drug concentrates varied in composition from about 0.20 to 0.75% w/w. An experiment was designed for checking typical drug distribution in a 150-mg. tablet containing 200 mcg. of active ingredient. A model drug, methylparaben, was chosen for this work in order to minimize any assay difficulties which might occur. Tablets were prepared according to the formula shown in Table I.

Microcrystalline cellulose, starch, and spray-dried lactose were placed in the VTD and mixed well by tumbling. Methylparaben was dissolved in 1 l. of isopropyl alcohol and added to the powder mix.

Table II—Percentage Composition of Granulations Used in Preparing a Low-Dose Tablet and Method of Lubricant Addition

	Experiment Number							
	1	2	3	4	5	6	7	8
Starch USP	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Microcrystalline cellulose NF	20.00	20.00	20.00	20.00	35.00	35.00	35.00	35.00
Spray-dried lactose USP	68.87	68.87	68.87	68.87	53.87	53.87	53.87	53.87
D & C red No. 30 lake	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
Stearic acid USP	1.00	1.00	—	—	1.00	—	1.00	—
Calcium stearate NF	—	—	1.00	1.00	—	1.00	—	1.00
Isopropyl alcohol NF								
Lubricant addition[a]	I	E	I	E	I	I	E	E

[a] I—internal; E—external.

An additional 500 ml. of isopropyl alcohol was used for rinsing the liquid feed tube and intensifier bar. The general procedure previously given was used to dry the granulation. Jacket temperature was set at 66° and the entire process was completed in 40 min. At the end of the run, three 100-g. samples of granulation were withdrawn from the two sides and bottom of the processor. Samples of granulation weighing approximately 150 mg. each were assayed in duplicate in order to determine uniformity of mixing. A spectrophotometric procedure was utilized for assay of methylparaben. This involved treating the sample with 0.05 *N* sodium hydroxide, filtering, and reading at 295 mμ. A blank was similarly prepared from the active granulation, but the solution was neutralized with 0.05 *N* HCl to quench the absorbance of methylparaben at 295 mμ. The precision of the method was estimated by assaying six samples of the bulk 100-g. sample from the bottom position.

Factors Affecting the Drying Rate of Spray-Dried Lactose and Dicalcium Phosphate Dihydrate—Preliminary work on drying 16.5–18-kg. charges of these materials indicated that two machine factors might affect drying rate. Temperature, of course, was one factor and speed of tumbling the second factor. Two temperatures, 42 and 66°, and three tumbling speeds, 7, 17, and 31 r.p.m., were studied.

Isopropyl alcohol (1500 ml.) was added to 16.5 kg. of spray-dried lactose or 18.0 kg. of dicalcium phosphate dihydrate over a 5-min. period. The choice of the material to be run, the temperature, and tumbling speeds were randomly selected. After liquid addition *via* the liquid feed tube, a vacuum of 60 mm. Hg was applied and the jacket temperature was turned on. At the end of an additional 5 min., the vacuum was reduced to about 40 mm. Hg and the processing continued until 1400–1450 ml. of isopropanol had been collected. Measurements of the condensate collected were made every 5 min. by means of measuring the height of the liquid in the receiver which had been previously calibrated. The condensate was drained from the receiver and full vacuum was applied. Usually an additional 10–40 ml. of isopropanol was collected.

Preparation of Low-Dose Tablet Granulations—The problem of mixing very small quantities of drugs with diluent is usually overcome by adding a solution of the drug to the diluent. VTD seemed ideal for such granulations since the drug could be added through the liquid feed tube and the mixture could then be conveniently dried in a closed system. Furthermore, it also seemed reasonable to add colorants and tablet lubricant by means of solution or suspension, thus allowing a one-step processing method.

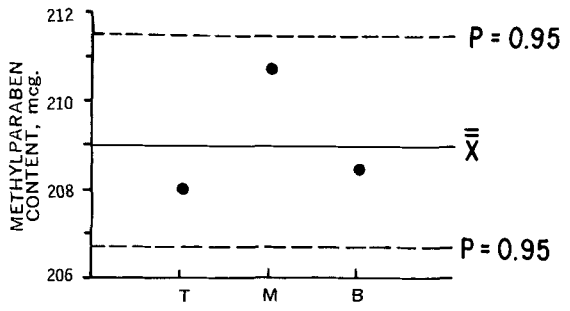

Figure 3—*Evaluation of mixing for methylparaben, 200 mcg./150 mg., prepared in the vacuum tumble dryer. Key: T, top; M, middle; and B, bottom.*

A factorial experiment was designed in order to test a number of formulation variables. These were the level of microcrystalline cellulose, 20 and 35%; kind of lubricant, stearic acid and calcium stearate; and method of lubricant addition, internal or external. Other excipients common to all formulas were spray-dried lactose and starch; the overall formulas are given in Table II with the method of lubricant addition.

A steroid drug was used at 10- and 25-mcg. levels during initial investigation. It was decided to carry out formulation screening without drug since excessive quantities were required and the formulations not containing drug had the same physical and compression characteristics as active granulations.

The general procedure for preparing these granulations was to blend the lactose, starch, and microcrystalline cellulose in the VTD. In the case of internally lubricated formulations, a suspension of the lubricant and the colorant was made in isopropanol and added to the powder blend by means of the liquid feed tube and rotating intensifier bar. In formulations where the lubricant was added externally, only the colorants were added from suspension in isopropanol. The same procedure was used for drying as described previously under drying rate experimentation, but a temperature of 66° and a speed of 7 r.p.m. were used for all runs. Lubricants, when added externally, were passed through a No. 60 screen onto a portion of the dried granulation, preblended, and then added to the bulk of the granulation and drum rolled for 20 min.

Finished granulations were characterized by determining flow rate through a standard Stokes BB-2 hopper, by compression on an instrumented Stokes BB-2 tablet machine, and by measuring finished tablet characteristics. Tablets were prepared using 0.71-cm. ($^{9}/_{32}$-in.) flat-faced beveled-edge punches at a weight of 150 mg. and a speed of 1400 tablets per minute.

Preparation of an Antacid Granulation by the Standard Wet Granulation Technique—The components of this granulation were

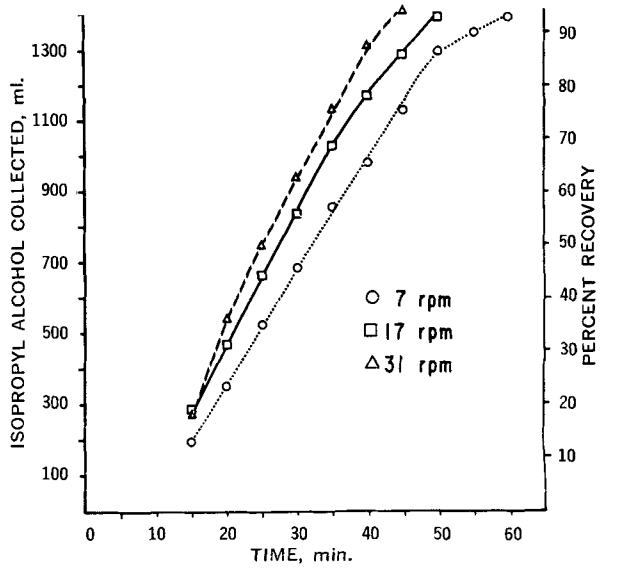

Figure 4—*Isopropyl alcohol recovery in the vacuum tumble dryer for dicalcium phosphate dihydrate at three speeds. Drying temperature, 42°.*

Table III—Typical Process Record for Vacuum Tumble Dryer[a]

Total Time, min.	Temperature: Jacket	Batch	Vapor	Vacuum, mm. Hg	Total Condensate, ml.	Remarks
0	—	—	—	—	—	Set jacket temperature to 66°
5	—	—	—	—	—	Set vacuum to 60 mm.
10	46	27	27	78	—	Set vacuum to 40 mm.
15	57	32	27	42	370	
20	66	37	28	44	860	
25	66	44	29	39	1310	
30	68	51	30	36	1430	
35	66	57	30	39	1470	Empty receiver, apply full vacuum
40	66	58	29	8	1470	

[a] Material: spray-dried lactose, 16.5 kg. Date: June 4, 1968. Liquid: isopropanol, 1500 ml. Tumbling speed: 31 r.p.m. Jacket temperature: 66°.

mixed in the VTD by means of the impeller bar while tumbling. Batch size was 15 kg. Varying amounts of water from 2100 to 2800 ml. were added, and agitation time with the intensifier bar was varied to determine whether these were important factors in the actual processing of the granulation. The water was added over a 5-min. period *via* the liquid feed tube and rotating intensifier bar. Drying temperature was at a jacket setting of 60° and tumbling speed was 25 r.p.m. Mesh sizes, bulk density, and flow rates were measured on all samples. Tablets were compressed on the Stokes BB-2 instrumented tablet machine using 1.58-cm. (0.63-in.) flat-faced beveled-edge punches at a theoretical weight of 1.33 g.

RESULTS AND DISCUSSION

Evaluation of Mixing—Replicate assays of a well-mixed granulation from the bottom position resulted in a mean content of 202.2 mcg. and a standard deviation of 1.40. Results from duplicate positional assays are plotted in Fig. 3 along with 95% confidence limits derived from the standard deviation obtained from the replicate measurements. There is a lack of any significant difference in the content of the three positional samples. In view of the turbulent condition of the powder bed during liquid addition, uniform mixing was expected. The VTD was fitted with lucite lids rather than the standard steel access covers. This allowed a viewing of the condition of the contents under the various processing conditions. Liquid addition at the rate of 200–300 ml. per minute was observed, and it was noted that the high degree of turbulence produced by the intensifier bar in conjunction with tumbling of the VTD effectively wetted only the powder. It seemed unlikely that localized wetted areas could be produced under these processing conditions. On drying, the mixture was free flowing, and localized sticking was not experienced.

Drying Rates—Little information has been published on drying pharmaceutical materials and particularly complete tablet granulations in VTD. Swartz and Suydam (7) described the drying of calcium sulfate dihydrate, lactose, and mannitol in the Rovac twin-shell processor after addition of 1000 ml. of water to 10 kg. of substrate. Under the conditions of heat and vacuum employed in the Rovac drying, a rising rate, constant rate, and falling rate drying cycle was observed. Heat transfer coefficients for the system were calculated and reported.

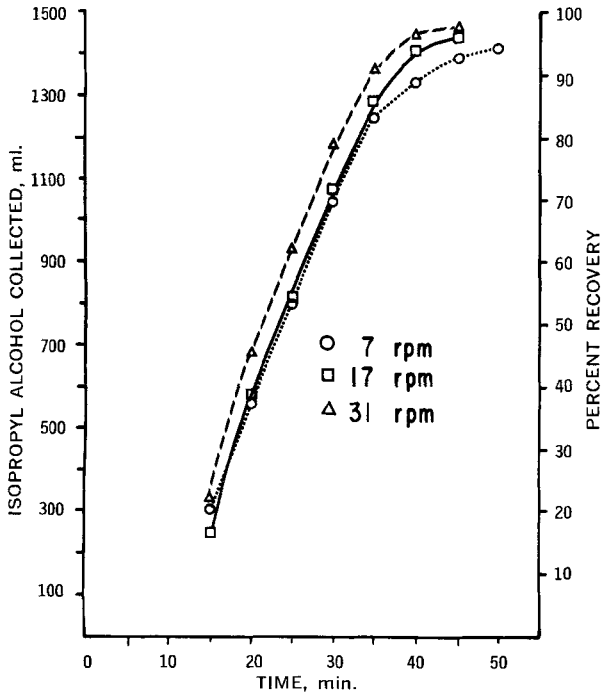

Figure 5—*Isopropyl alcohol recovery in the vacuum tumble dryer for spray-dried lactose at three speeds. Drying temperature, 66°.*

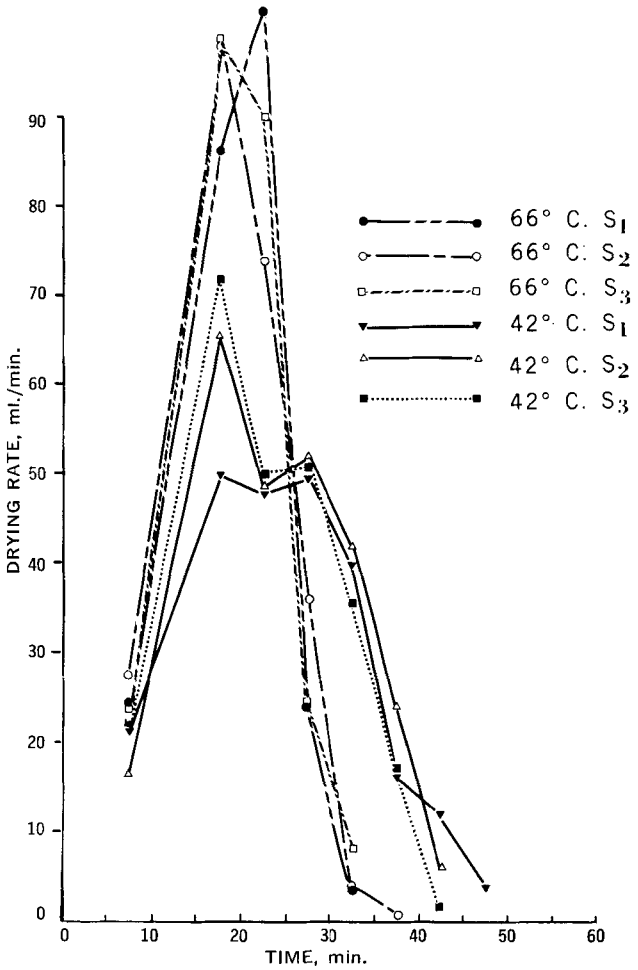

Figure 6—*Drying rates for spray-dried lactose using 1500 ml. of isopropyl alcohol and a 16.5-kg. load. Key: S_1, 7 r.p.m.; S_2, 17 r.p.m.; and S_3, 31 r.p.m.*

Table IV—Drying Time Factors for Vacuum Tumble Dryers

Size, cu. ft.	Drying Time Factor
1	1
10	2.10
20	2.70
30	3.01
40	3.37
50	3.70

Isopropyl alcohol is often the solvent of choice for addition of drugs to a tablet substrate; therefore, this solvent was chosen for experimentation. A typical processing sheet for these experiments is shown in Table III. Liquid was added over the first 5-min. period and the jacket temperature was turned on. After about 15 min. the jacket circulating fluid reached the setting of 66°. Batch temperature was 46° after 10 min. of operation and eventually reached 66° by the end of the run. Condensate begins to flow well after 10 min. and is rapidly collected over the next 25 min. of processing. The increased vapor temperature through the run indicated that isopropyl alcohol vapors were being collected in a somewhat superheated condition. During some processes it is advisable to backflush the felt filter by means of quickly opening the ball valve (item 18 in Fig. 1). Inrushing air forces dry powdered material off the filter, thus allowing better vapor flow from the vessel.

Comparative condensate volumes collected as a function of time are shown in Fig. 4 for dicalcium phosphate dihydrate at 42°. These data clearly point out the advantage of drying at a high tumbling speed over slow tumbling. The process is completed in 45 min. at a tumbling speed of 31 r.p.m., but 60 min. is required for drying at 7 r.p.m. Similar data were obtained for drying spray-dried lactose, Fig. 5. When drying was carried out at 66° the effect of tumbling speed was much diminished and the drying time becomes almost entirely temperature dependent.

Drying rates were calculated and are shown in Figs. 6 and 7 for spray-dried lactose and dicalcium phosphate dihydrate. At 66° the drying rate reached a maximum of about 100 ml./min. for lactose and between 67 and 87 ml./min. for dicalcium phosphate. At this higher temperature setting, a sharply rising drying rate occurs followed by a very sharp drop in rate. Drying at 42° gives a somewhat lower drying rate and a subsequent increase in overall processing time of about 10–15 min. A nearly constant drying rate was noted for dicalcium phosphate at the two lower speeds and for lactose only at the lowest speed. The effect of tumbling speed on drying rates is probably due to the greater surface area exposed at the higher speeds. At these higher speeds the effect of centrifugal force on holding the material to the walls might be considered a factor which would retard drying rate. However, the materials employed in this study were in motion even at high speed, and this factor would then contribute to the somewhat increased drying rates.

Larger VTD requires longer drying periods, but drying time does not increase proportionately with size. The manufacturer was asked for information on drying time in larger processors, and the factors for various sizes are listed in Table IV (9).

Predicted drying time for a process in a 30-cu. ft. VTD would be three times the time in a 1-cu. ft. VTD. Thus, a process requiring 35 min. in the 1-cu. ft. VTD would require 105 min. in a 30-cu. ft. VTD or 135 min. for a process requiring 45 min. in the smaller unit. These drying times are quite reasonable in view of drying times and extra handling needed by alternate methods.

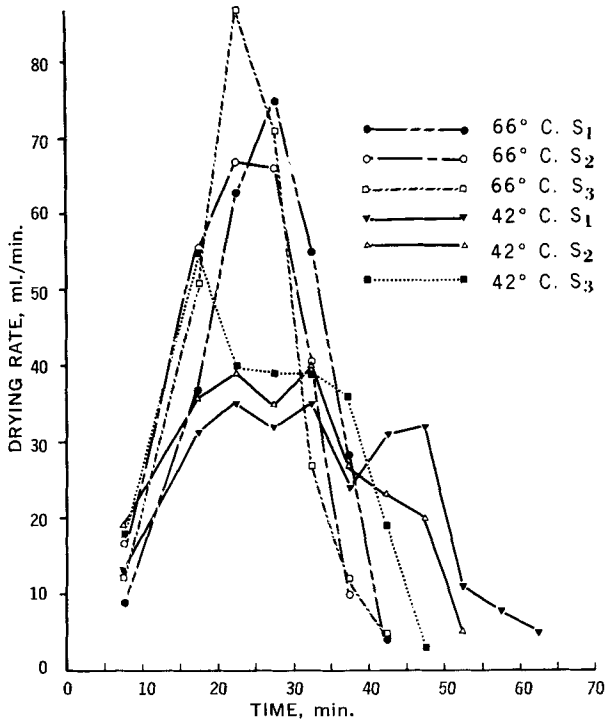

Figure 7—*Drying rates for dicalcium phosphate dihydrate using 1500 ml. of isopropyl alcohol and a 18.0-kg. load. Key: S_1, 7 r.p.m.; S_2, 17 r.p.m.; and S_3, 31 r.p.m.*

Low-Dose Tablet Granulations—Granulations were processed in a routine manner similar to those carried out for spray-dried lactose in the drying rate experiments. Overall processing time was 45 min. and about 93–97% of the added isopropanol was recovered. All materials were free flowing when dried and no sticking to the lids or vessel itself occurred. Yields were very high.

Flow rates were determined by loading 4.0 kg. of granulation into the standard hopper used for the BB-2 machine and noting the weight delivery onto a balance at 15- or 30-sec. intervals. Distance from the bottom of the hopper to the balance platform was 15.24 cm. (6 in.). This type of experiment gives an indication of the glidant activity of the granulation and also whether or not flow is sluggish. Sluggish or nonlinear flow rates have been shown to increase variability of tablet weights under some conditions of tableting (10). All eight of the granulations prepared exhibited linear flow rates as calculated by regression analysis. Flow rates for the various granulations are given in Table V in g./sec.

The highest flow rates are for granulations containing stearic acid added from alcoholic solution. Lubricant added internally generally gives higher flow rates except for calcium stearate at the high level of microcrystalline cellulose. These data might be indicative of a lubricant coating around the substrate particles.

An attempt was made to compress tablets at hardnesses of about 6 and to measure the resulting compression properties and physical

Table V—Compression Data and Physical Data for Granulations Prepared in the Vacuum Tumble Dryer

	Experiment Number							
	1	2	3	4	5	6	7	8
Flow rate of granulation, g./sec.	28	27	16	10	32	19	15	21
Compressive force, lb.	1732	1549	2488	1854	1128	1506	634	952
% Coefficient of variation, compressive force	3.44	7.23	5.54	5.34	5.51	3.28	4.60	5.11
Hardness, kg./sq. in.	6.1	6.8	4.6	3.2	6.4	6.8	5.9	5.6
Friability, %	0.11	0.07	10.98	9.82	0.00	0.00	0.00	0.00
Disintegration time, sec.	45–60	30–45	60–75	60–90	60–120	150–210	15–30	15–30
Average ejection force, μSt.	77	82	83	66	71	74	49	69
Coefficient of wt. variation	1.74	1.01	0.60	0.56	0.90	0.74	0.98	0.92

Table VI—Summary of Physical and Compression Data for Antacid Tablets

Formula	Water, ml.	Mixing Time, min.	Flow Rate, g./sec.	Bulk Density,[a] g./ml.	Average Compressive Force	Coefficient of Compressive Force Variation, %	Hardness, kg./sq. in.	Coefficient of Weight Variation, %
1	2100	5	37.4	0.813	3291	1.65	10.2	0.538
2	2100	7	32.8	0.793	3301	1.52	11.2	0.538
3	2300	5	21.6	0.819	3762	8.91	9.8	0.538
4	2300	7	35.7	0.813	3801	2.95	11.1	0.361
5	2500	5	40.6	0.806	3586	2.89	11.3	0.313
6	2500	7	42.9	0.813	3536	2.75	10.7	0.277
7	2700	5	40.7	0.819	3402	2.47	11.6	0.387
8	2700	7	68.8	0.819	3644	2.65	9.5	0.470

[a] Determined using the Numinco bulk density tester.

properties. These data are summarized in Table V. Tablets were compressed from all eight granulations, but two of these, 3 and 4, demonstrated very high friability of 10–11%. A considerable amount of capping occurred during the friability test. While a relatively high compressive force was used to tablet these formulations, average hardnesses of only 4.6 and 3.2 were attained. Each of these formulations contained calcium stearate and a lower level of microcrystalline cellulose.

Formulation factors were quite significant in the amount of compressive force needed to make a tablet and to a lesser extent on the magnitude of ejection force. In Fig. 8, average compressive force is shown as a function of the formulation factors. All three factors were very significant statistically. The most significant factor was the level of microcrystalline cellulose. Low level (20%) formulations required compression at an average of 1906 lb. but the higher level (35%) formulations were compressed at an average of 1055 lb. Formulations with the higher microcrystalline cellulose levels had hardnesses of 5.6–6.8 and were virtually nonfriable. Granulations containing internally added lubricant (I) required higher compressive force than externally added lubricant (E), Fig. 8. The higher force for the internally lubricated substrate is related to crystal fracture and realignment in order to obtain a particle bonding. The calcium stearate formulations were compressed on the average at higher compressive force levels than stearic acid formulations.

The effect of formulation factors on the resultant ejection force is shown in Fig. 9. The type of lubricant is seen to have no significant effect on ejection force, but both method of lubricant addition and microcrystalline cellulose level were highly significant. The degree of difference between externally and internally lubricated granulations is small from the practical viewpoint. It appears that internally added lubricant may be satisfactory over a long run and that the final mix step, so common for all tablet granulations, could be omitted. Since microcrystalline cellulose itself does not adhere to die walls when directly compressed, it seems reasonable that increasing its level in tablet formulations reduces ejection force. It is conceivable that savings in both tool and machine wear are possible by working at lower compressive forces. Whether or not this factor is worth considering over the use of more expensive raw materials has not been determined.

Disintegration times on all formulations were good. Formulas 5 and 6 indicate a tendency toward longer disintegration times on these internally lubricated granulations. Drug dissolution studies would be required to determine further the extent of drug availability as a function of lubricant addition method.

The coefficient of weight variation for all formulas seemed to be reasonable but Formulation 1 was somewhat higher than the others. During the flow rate studies, it was noted that this formula tended to plug the hopper on several occasions. On other runs, uniform flow was observed. The somewhat sluggish nature of this granulation probably accounts for the higher weight variability.

Preparation of Antacid Tablets—Granulations were produced using various levels of water and two mixing times as noted in Table VI. Increments of water were increased by 200 ml. in successive experiments. Preliminary experiments indicated that at least 2000 ml. of water was required to produce a granulation that could be tableted and that 2800 ml. produced an overwetted granulation which balled up in the processor. Tablets were compressed at hardnesses of about 10 kg./sq. in. and the resultant compressive force was measured.

Statistical comparison of flow rates of the granulations showed a significant difference in slopes between experiments. A trend towards higher flow was noted as the amount of water used to granulate increased. The mesh sizes of all granulations were about the same with the exception of Formula 8 which was coarser. In Formula 8 the highest level of water and the longest mixing time were used. This coarser mesh pattern could account for higher flow rate. Formula 3 exhibited the lowest flow rate and also the highest

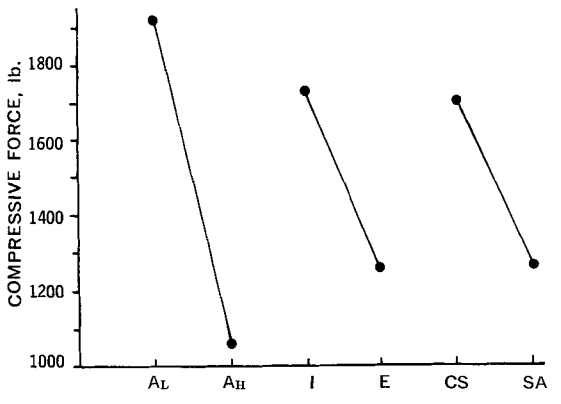

Figure 8—*Average compressive force as a function of formulation factors for direct compression granulations. Key: A_L, microcrystalline cellulose 20%; A_H, microcrystalline cellulose 35%; I, internal lubrication; E, external lubrication; CS, calcium stearate; and SA, stearic acid.*

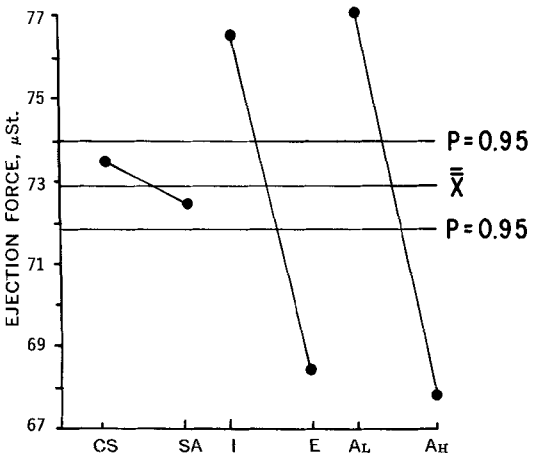

Figure 9—*Effect of formulation factors on ejection force. Key: CS, calcium stearate; SA, stearic acid; I, internal lubrication; E, external lubrication; A_L, microcrystalline cellulose 20%; and A_H, microcrystalline cellulose 35%.*

coefficient of variation of compressive force. However, weight variation of Formula 3 was comparable to other experiments.

Comparing experiments, hardness was not directly proportional to compressive force, indicating that these formulations require a somewhat different compression force for preparing tablets of an average hardness of 10. It is believed the variability in required compression force between different granulations of the same formula might be large enough to preclude using compressive force as a possible specification in this type of product. The reasons for shifts in required compression force have not been reported at this time nor their importance described.

All formulations were satisfactory with respect to chew and mouthfeel characteristics, and no substantial difference could be found between formulations when tasted by a small taste panel.

Moisture recovery on drying was 98–99%, and processing times varied from 105 min. for the lowest amount of added water to 120 min. for the highest amount of added water. Whether these relatively long processing times, compared with an isopropanol process, are acceptable depends to a large degree on the kind of product being made and the required rate of production.

SUMMARY AND CONCLUSIONS

Various data on the operation of a 1-cu. ft. VTD as related to general tableting technology have been reported. The results indicate that vacuum tumble drying is a satisfactory process for some particularly common types of tablet formulations. It was found that adequate mixing could be obtained and that the short processing time coupled with good yields were other advantages. Obviously the use of such equipment on a larger scale requires the usual considerations of loading, unloading, cleaning, *etc.* While the authors' experience in working with the VTD on a pilot scale was highly satisfactory, other alternate methods are available. However, the convenience factor as well as other advantages listed earlier seems to indicate the VTD may often be the process of choice.

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Encapsulation of Clomacran Phosphate {2-Chloro-9-[3-(dimethylamino)propyl]acridan Phosphate} I: Effect of Flowability of Powder Blends, Lot-to-Lot Variability, and Concentration of Active Ingredient on Weight Variation of Capsules Filled on an Automatic Capsule-Filling Machine

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Abstract □ A correlation has been shown to exist between the flow properties of clomacran phosphate powder blends and capsule fill weight variation when an automatic capsule-filling machine is used. A correlation of 0.96 was obtained for the capsule mixes tested. Weight variation of the finished capsules is also affected by lot-to-lot variability and concentration of clomacran phosphate. Granulation of the active ingredient overcomes most of the problems normally encountered and provides finished capsules of uniform weight.

Keyphrases □ Clomacran PO_4—encapsulation □ Weight variation—clomacran PO_4 □ Powder blends flowability, lot variability effects—capsule weight variation □ Concentration effect, clomacran PO_4—capsule weight variation

Automatic capsule-filling machines are a recent addition to the equipment available to the industrial pharmacist for the encapsulation of powders. A detailed description of the operation of one of these machines (the Zanasi capsule-filling machine) was reported by Stoyle (1). He pointed out that, with a well-formulated product, capsules can be filled with a high degree of filling accuracy. Recently Reier *et al.* (2) evaluated the factors affecting the encapsulation of powders using a semiautomatic filling machine, but the literature has little information on the development of formulations to be used with an automatic capsule-filling machine. The purpose of this paper is to report data related to some of the problems encountered during the development of a capsule mix containing clomacran phosphate for use with the Zanasi capsule-filling machine.

In these studies, an attempt has been made to correlate the flowability of powder mixes, as measured with the flowometer described by Gold *et al.* (3), with the weight variation of capsules observed during encapsulation with the Zanasi. In addition, the way in which lot-to-lot variability, the concentration of clomacran