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

Table I—Percent Composition of Powder Blends Used in Flowability Studies

Ingredients	1	2	3	4	5	6	7
Clomacran phosphate, SK&F	—	22.0	22.0	22.0	22.0	22.0	22.0
Lactose USP	—	—	—	—	—	—	72.0
Dicalcium phosphate	—	—	72.0	—	—	—	—
Lactose, spray-dried	96.0	72.0	—	36.0	—	—	—
Free-flowing starch	—	—	—	36.0	73.0	72.0	—
Magnesium stearate USP	3.0	4.0	4.0	4.0	4.0	4.0	4.0
Fumed silica	—	1.0	1.0	1.0	—	1.0	1.0
Sodium lauryl sulfate USP	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Table II—Percent Composition of Powder Blends Used in Effect of Lot-to-Lot Variability Studies

Ingredients	8, 9, 10
Clomacran phosphate, SK&F[a]	42.0
Lactose, spray-dried	55.0
Magnesium stearate USP	3.0

[a] Chemical Lots A, B, and C were used in Formulas 8, 9, and 10, respectively.

Table III—Percent Composition of Powder Blends Used in Effect of Concentration Studies

Ingredients	11	12	13
Clomacran phosphate, SK&F	17.5	35.0	70.0
Lactose, spray-dried	79.5	62.0	27.0
Magnesium stearate USP	3.0	3.0	3.0

phosphate in the powder mixes, and different strength granulations affected the weight variation of the capsules were also evaluated.

EXPERIMENTAL

Materials—Clomacran phosphate, SK&F; lactose USP; magnesium stearate USP; sodium lauryl sulfate USP; free-flowing starch[1]; lactose, spray-dried[2]; terra alba, English[3]; calcium phosphate, dibasic[4]; polyvinylpyrrolidone[5]; fumed silica.[6]

Apparatus—Zanasi automatic capsule-filling machine was used.[7] The recording powder flowometer described by Gold *et al.* (3) was used throughout these studies for the flowability measurements. Since the apparatus was designed to measure flow rates of granulated materials, it was necessary to use a Vibrolator[8] to facilitate the flow of the powder blends from the hopper.

Preparation of Powder Blends—Six powder blends containing a constant concentration of drug, lubricant, and excipient were prepared; different excipients were used in each formula. A formulation without active ingredient was also prepared. The formulas for the various powder blends are listed in Table I.

Each powder blend was prepared in the same manner prior to flow-rate measurements. Several additional powder blends were prepared in order to determine the effect of lot-to-lot variability and concentration of the active ingredient on the weight variation of finished capsules. The formulas for these blends are listed in Tables II and III. Flow-rate measurements were not obtained for powder blends listed in Tables II and III.

[1] Dry-Flo Starch, National Starch and Chemical Corp., New York, N. Y.
[2] Foremost Foods Company, Industrial Div., San Francisco, Calif.
[3] Whittaker, Clark and Daniels, Inc., New York, N. Y.
[4] Kind & Knox Gelatin Co., Camden, N. J.
[5] Plasdone C, GAF Corp., Industrial Products Div., New York, N. Y.
[6] Cab-O-Sil, Cabot Corp., Boston, Mass.
[7] Model LZ 164, United Shoe Machinery Corp., Boston, Mass.
[8] Model UCV-6, Martin Engineering Co., Neponset, Ill.

Clomacran phosphate granulations were prepared with different lots of chemical at several concentrations of active ingredient to determine what effect granulating would have on the weight variation of finished capsules. The formulas for the granulations are listed in Table IV.

Flow-Rate Measurements—Flow rates expressed in g./sec. were determined with the flowometer for the seven powder blends. Each value represents an average of four determinations. Samples were run on 2 different days to minimize variations due to ambient conditions.

Preparation of Capsules—The powder blends evaluated for their flow properties were filled into No. 4 capsules. Any necessary adjustments were made for the first formulation and kept constant throughout the study.

Twenty groups of 10 capsules each were collected from each of the seven formulations encapsulated. These capsules were in turn divided into groups of five according to the dosator from which they had been obtained. All capsules were weighed on a torsion balance to establish the control weight during the filling operation, and one of the five capsules from each group was randomly selected and weighed on an analytical balance. Accurate weights were obtained for 20 capsules from each dosator for the seven powder blends.

Similar procedures were employed during the encapsulation of the formulations prepared to evaluate the effect of lot-to-lot variability and concentration of active ingredient. The granulation was treated in a similar manner. Nos. 1, 3, and 4 capsules were used to encapsulate the 100-, 50-, and 25-mg. strengths, respectively.

RESULTS AND DISCUSSION

Rate of Flow Measurements—Stoyle (1) has outlined the essential characteristics for powder blends which are to be encapsulated with the Zanasi capsule-filling machine. During the authors' preliminary investigation it was observed that whenever capsules prepared from a particular powder blend had a high coefficient of weight variation, a cavity was left in the powder bed in the hopper which was not completely refilled after the dosator removed the charge. This observation prompted these flow-rate measurement studies. The flow-rate measurements served as a screen to select a combination of

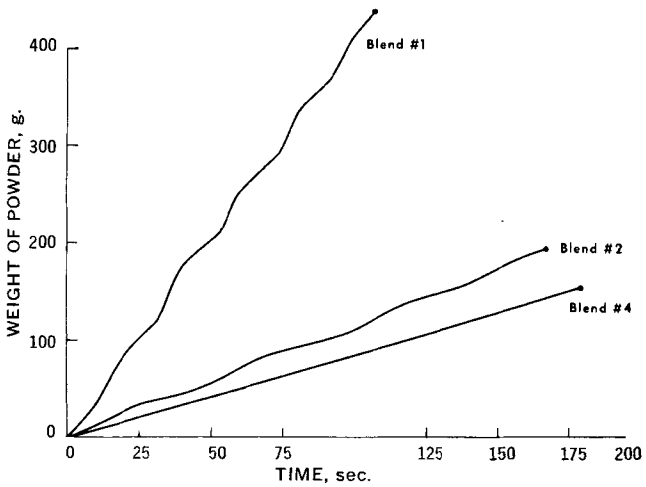

Figure 1—*Flowometer recording for several powder blends.*

Table IV—Percent Composition of Clomacran Phosphate Granulations

Ingredients	14	15	16	17	18	19
Clomacran phosphate, SK&F (Lot C)	22.0	37.0	36.0	—	—	—
Clomacran phosphate, SK&F (Lot D)	—	—	—	19.0	32.0	36.0
Terra alba, English	54.0	39.0	40.0	53.0	45.0	40.0
Sucrose USP	11.0	11.0	11.0	16.0	12.0	11.0
Starch USP	8.0	8.0	8.0	7.0	7.0	8.0
Polyvinylpyrrolidone	4.0	4.0	4.0	4.0	3.0	3.0
Magnesium stearate USP	1.0	1.0	1.0	1.0	1.0	2.0

Table V—Rate of Flow Measurements for Various Powder Blends

Blend	Rate of Flow, g./sec.
1	4.08
2	1.01
3	0.95
4	0.75
5	0.58
6	0.52
7	Did not flow

Table VI—Capsule Weight Variation Data for Seven Clomacran Phosphate Blends

Blends	$\bar{X}$, mg.	σ, mg.	CV
1	175	1.8	1.0
2	168	2.8	1.7
3	164	3.9	2.4
4	136	5.0	3.7
5	114	4.5	3.9
6	120	5.4	4.3
7	169	8.3	4.9

ingredients having the best flow properties. Flow-rate data obtained for seven capsule blends are shown in Table V.

It is evident from these data that the flow-rate varies with the different blends. Figure 1 illustrates the relative order of flow rate for three of the powder blends evaluated. The actual rates were determined by dividing the total weight flowing through the hopper by the total elapsed time.

Capsule Weight Variation—The weight variation for the seven capsule blends was calculated as a percent of capsule fill, since the density of the mixes differed, depending upon the excipients used in each case. For the lot of empty capsules used to encapsulate the powder blends, the mean and standard deviation were determined to be 37.1 and 1.3 mg., respectively. Utilizing these values and the standard deviation for the finished capsules, it was possible to calculate the standard deviation for the capsule fill alone. The values for the mean and standard deviation and the coefficient of variation for the seven powder blends are listed in Table VI.

Figure 2 illustrates a plot of rate of flow *versus* coefficient of variation for five blends.[9] A linear response was obtained and a correlation coefficient of 0.96 was calculated which indicates a good fit of the data. It is evident from this correlation that the flowability of the powder blends is related to the weight variation of the clomacran phosphate capsules filled on the Zanasi capsule-filling machine.

On the basis of flowability and weight variability data, powder blend No. 2 appeared to have the essential characteristics for encapsulation using the Zanasi. Subsequent powder blends containing varying concentrations of ingredients similar to those of powder blend No. 2 were evaluated on the basis of coefficient of weight variation of finished capsules. Since a correlation of 0.96 had been obtained between flowability and coefficient of variation for several capsule blends, it was felt that weight variation of finished capsules could be used to evaluate future powder blends. A coefficient of weight variation of 3% was arbitrarily set as a maximum. Any formulation that exceeded this limit was considered unsatisfactory.

Effect of Different Lots of Clomacran Phosphate Chemical—Table VII illustrates what effect various lots of clomacran phosphate chemical had on the capsule weight variation of finished capsules. A variation was noted when different lots of chemical were used, and further examination of the chemical indicated a difference in particle size. Figure 3 shows photomicrographs of several lots of clomacran phosphate chemical. The data suggest that a difference in particle size is responsible in part for the observed weight variation. The chemical of larger particle size shows less variation. Formula No. 10 prepared with chemical Lot C had a coefficient of weight variation outside the 3% limit.

Effect of Concentration of Clomacran Phosphate—The data in Table VIII indicate that the concentration of clomacran phosphate

[9] Data for powder blends Nos. 1 and 7 were not included in this figure. Blend No. 1 had no active ingredient and Blend No. 7 did not flow.

Table VII—Capsule Weight Variation for Powder Blends Containing Different Lots of Clomacran Phosphate Chemical

Formula	Lot of Chemical	$\bar{X}$, mg.	σ, mg.	CV
8	A	281	1.6	0.6
9	B	229	4.9	2.1
10	C	219	7.3	3.3

Table VIII—Capsule Weight Variation for Powder Blends Containing Different Concentrations of Clomacran Phosphate

Formula	Dosage Strength, mg.	$\bar{X}$, mg.	σ, mg.	CV
11	25	258	3.9	1.5
12	50	235	10.8	4.6
13	100	153	12.4	8.1

in the powder blend has an effect on the weight variation of finished capsules. The greater the concentration of active ingredient in the blend, the greater the weight variation. The differences in fill weight are due to the change in density of the capsule blends as the concentration of active ingredient is increased. The formulas for these blends are listed in Table III. A coefficient of variation greater than 3% was observed for Formulas No. 12 and No. 13; therefore they were considered unsatisfactory for encapsulation.

Effect of Granulating Clomacran Phosphate—When granulations of different strengths of clomacran phosphate were prepared using different lots of chemical as shown in Table IV and the resulting

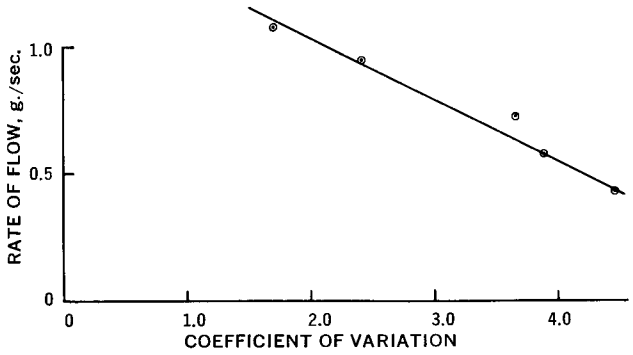

Figure 2—*A plot of rate of flow* versus *coefficient of variation for five powder blends.*

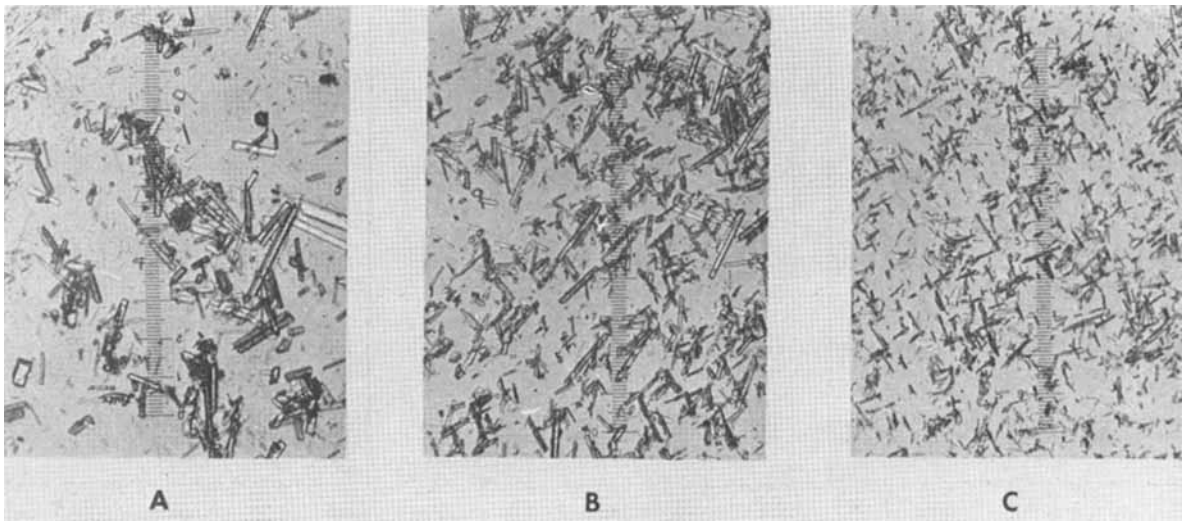

Figure 3—*Photomicrographs for several lots of clomacran phosphate chemical. Each scale division is equivalent to 6 μ.*

Table IX—Capsule Weight Variation for Clomacran Phosphate Granulations

Formula	Dosage Strength, mg.	$\bar{X}$, mg.	σ, mg.	CV
14	25	187	2.4	1.3
15	50	228	2.0	0.9
16	100	443	3.8	0.9
17	25	213	2.0	1.0
18	50	263	2.8	1.1
19	100	452	4.0	0.9

powder was filled into capsules, there was no appreciable difference in the weight variation of the finished capsules. These data are shown in Table IX.

The granulation process essentially eliminated the effect of lot-to-lot variability and concentration of the active ingredient. In every instance the granulated formulas showed a coefficient of variation of less than 1.5%, regardless of the lot of chemical or the concentration of active ingredient in the powder blend.

SUMMARY

1. The flowometer is a useful device for evaluating the flow properties of powder blends intended for encapsulation with an automatic capsule-filling machine.

2. A correlation of 0.96 was obtained between the rate of flow for five powder blends prepared for encapsulation and the coefficient of variation of the finished capsule fill weight.

3. Capsule weight variation was affected when different lots of clomacran phosphate were used. The particle size of the chemical contributed in part to the weight variation of the finished capsule.

4. The concentration of active ingredient in the capsule mix affected the weight variation. When formulating capsule blends of different strengths for encapsulation with an automatic capsule-filling machine, it may be necessary to reformulate to maintain satisfactory weight control.

5. The use of a granulated powder overcomes most of the problems normally encountered and provides finished capsules of uniform weight.

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