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*Keyphrases*

Automated analysis—isoxsuprine HCl tablets, single
Diagram—automatic analyzer system
Dialysis—separation
UV spectrophotometry—analysis

# Evaluation of Factors Affecting the Encapsulation of Powders in Hard Gelatin Capsules I

## Semi-Automatic Capsule Machines

By G. REIER, R. COHN, S. ROCK, and F. WAGENBLAST

**A useful model has been developed which relates particulate properties, capsule size, and the operating rate of semi-automatic filling equipment to filled capsule characteristics. The mean capsule fill weight is dependent on machine speed, capsule size, and specific volume. The weight variation as expressed by the standard deviation is a function of machine speed, capsule size, specific volume, flowability, and the presence of a glidant. Particle size considerations of moderately coarse powders (USP designation) are not directly a part of the model because they are reflected in the other evaluated particulate properties. The model is applicable to powder systems other than those from which it was derived. Mean gross capsule weights of such systems may be calculated with an accuracy often exceeding 95 percent. The utility of the model lies in its ability to provide information concerning the relationship of machine speed, capsule size, powder specific volume, and flow to mean capsule fill weight from simple evaluations of small samples of the formulation to be encapsulated.**

HARD GELATIN capsules have been known since 1848. They were first prepared in London (1), and quickly attained popularity in the United States where capsule manufacturing and filling operations were carried out manually (2). Hard gelatin capsules are today an important part of solid dosage form drug presentation. A variety of useful, elegant capsule products are available to the physician.

Curiously, the literature is devoid of any reports dealing with the encapsulation of dry powders on an industrial scale. The absence of reported works on this subject is even more marked when one considers the detailed investigations published, for example, by Higuchi *et al.* (3, 4), on the physical factors affecting the tableting process.

Current formulation of powders for encapsulation is carried out on an empirical basis and, while this method has apparently met the needs of the pharmaceutical industry, it would be extremely valuable to have a mathematical model which quantitatively defines the variables encountered in capsule filling. Once these variables are known and quantitated, their application to formulations can be assessed before laboratory work is begun.

The present work was conducted to develop a mathematical model which describes the effect of selected physical powder properties as well as mechanical operating conditions on the capsule filling operation, and to ascertain the relationships of these variables on the encapsulation process.

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The industrial pharmacist encounters drugs of widely differing physical natures, some of which require previous densification before encapsulation can be accomplished. Powders of this sort were not included in this study. Further, there are presently available both semi-automatic and automatic capsule filling machines. This report deals only with the semi-automatic type. The areas of encapsulating densified powders and the effect of variables associated with automatic filling equipment will be the basis of future reports.

## EXPERIMENTAL

In order to describe adequately any process, one must have parameters which define that process. Often these parameters are evaluations of the resultant end product. A case in point occurs with capsule production. Mean capsule weight and weight variation are properties which define the completed encapsulation process.

Of the variables affecting encapsulation, those imposed by the filling equipment itself are the speed of operation and the capsule size being filled. Formulation variables include powder particle size and particle size distribution, specific volume, and flowability. The presence or absence of a glidant in the formulation may be expected to have an effect on powder flow. Classically, glidants have been thought to improve flow but recently this concept has been challenged (5).

In order to prepare powder blends varying in mean particle size, particle size distribution, specific volume, and flowability, the following materials were chosen as blend components: microcrystalline cellulose NF,[1] dicalcium phosphate dihydrate unmilled,[2] lactose USP, magnesium stearate USP, and talc USP. Microcrystalline cellulose and dicalcium phosphate dihydrate, unmilled have widely different physical properties, particularly with regard to specific volume and flowability. They were used to vary these properties of the powder blends as desired. Lactose was included as a component because of the need for a filler and its common use as such. A lubricant is necessary for mechanical capsule filling, and magnesium stearate served that purpose. Talc was the glidant.

Three operating speeds, the slowest and the most rapid of which the machine was capable, as well as an intermediate speed, were chosen for study. Three capsule sizes were included in the study.

An experimental design defining the formulation of 42 powder blends from the infinite number that could be formulated was prepared. The lubricant level was maintained throughout at 1%. One-half of the formulations contained no talc, the others 3%. The formulas are given in Tables I and II.

When the two machine operating variables (speed and capsule size) and the three conditions for each are included with the 42 formulations, 378 experimental capsule filling runs are possible. By taking one-third replicates of the operating conditions, the experimental effort was considerably reduced. Each formulation was filled into capsules at one of the nine possible combinations of speed and capsule size, with half of them being studied at two combinations

Table I—Composition of Blends Not Containing Talc

| Blend No. | Component %[a] MCC[b] | DPDU[c] | LA[d] |
|---|---|---|---|
| N1 | ... | ... | 99.00 |
| N2 | ... | 24.75 | 74.25 |
| N3 | 8.25 | 16.50 | 74.25 |
| N4 | 12.37 | 12.37 | 74.26 |
| N5 | 16.50 | 8.25 | 74.25 |
| N6 | 24.75 | ... | 74.25 |
| N7 | ... | 49.50 | 49.50 |
| N8 | 16.50 | 33.00 | 49.50 |
| N9 | 24.75 | 24.75 | 49.50 |
| N10 | 33.00 | 16.50 | 49.50 |
| N11 | 49.50 | ... | 49.50 |
| N12 | ... | 74.25 | 24.75 |
| N13 | 24.75 | 49.50 | 24.75 |
| N14 | 37.12 | 37.12 | 24.76 |
| N15 | 49.50 | 24.75 | 24.75 |
| N16 | 74.25 | ... | 24.75 |
| N17 | ... | 99.00 | ... |
| N18 | 33.00 | 66.00 | ... |
| N19 | 49.50 | 49.50 | ... |
| N20 | 66.00 | 33.00 | ... |
| N21 | 99.00 | ... | ... |

[a] In addition, 1% magnesium stearate was present in each blend. [b] Microcrystalline cellulose. [c] Dicalcium phosphate dihydrate, unmilled. [d] Lactose.

Table II—Composition of Blends Containing Talc

| Blend No. | Component %[a] MCC[b] | DPDU[c] | LA[d] |
|---|---|---|---|
| T1 | ... | ... | 96.00 |
| T2 | ... | 24.00 | 72.00 |
| T3 | 8.00 | 16.00 | 72.00 |
| T4 | 12.00 | 12.00 | 72.00 |
| T5 | 16.00 | 8.00 | 72.00 |
| T6 | 24.00 | ... | 72.00 |
| T7 | ... | 48.00 | 48.00 |
| T8 | 16.00 | 32.00 | 48.00 |
| T9 | 24.00 | 24.00 | 48.00 |
| T10 | 32.00 | 16.00 | 48.00 |
| T11 | 48.00 | ... | 48.00 |
| T12 | ... | 72.00 | 24.00 |
| T13 | 24.00 | 48.00 | 24.00 |
| T14 | 36.00 | 36.00 | 24.00 |
| T15 | 48.00 | 24.00 | 24.00 |
| T16 | 72.00 | ... | 24.00 |
| T17 | ... | 96.00 | ... |
| T18 | 32.00 | 64.00 | ... |
| T19 | 48.00 | 48.00 | ... |
| T20 | 64.00 | 32.00 | ... |
| T21 | 96.00 | ... | ... |

[a] In addition, 1% magnesium stearate and 3% talc were present in each blend. [b] Microcrystalline cellulose. [c] Dicalcium phosphate dihydrate, unmilled. [d] Lactose.

Table III—Operating Conditions for the Encapsulation of Powder Blends

| Machine Speed | Capsule Size[a,b] 0 | 1 | 2 |
|---|---|---|---|
| Fast | N3, 9, 15, 21, T6, 12, 18 | N1, 4, 10, 16, T1, 7, 13, 19 | N5, 11, 17, T2, 8, 14, 20 |
| Medium | N1, 7, 13, 19, T1, 4, 10, 16 | N2, 8, 14, 20, T5, 11, 17 | N6, 12, 18, T3, 9, 15, 21 |
| Slow | N2, 8, 14, 20, T5, 11, 17 | N6, 12, 18, T3, 9, 15, 21 | N1, 4, 10, 16, T1, 7, 13, 19 |

[a] N, talc absent. [b] T, talc present.

[1] Marketed as Avicel by the FMC Corporation, American Viscose Division, Newark, Delaware.
[2] Marketed by Industrial Division, Stauffer Chemical Company, New York, New York.

TABLE IV—PHYSICAL PROPERTIES OF POWDER BLENDS NOT CONTAINING TALC

| Blend No. | Specific Vol., ml./Gm. | Flowability, in.² | Particle Size (Geometric Mean), μ | Particle Size Coefficient of Variation, % |
|---|---|---|---|---|
| N1 | 1.27 | 1.86 | 69 | 11.9 |
| N2 | 1.15 | 2.57 | 70 | 12.7 |
| N3 | 1.20 | 3.33 | 70 | 11.9 |
| N4 | 1.41 | 2.04 | 72 | 9.7 |
| N5 | 1.47 | 2.87 | 63 | 10.2 |
| N6 | 1.60 | 2.22 | 51 | 15.0 |
| N7 | 1.07 | 4.19 | 110 | 13.6 |
| N8 | 1.27 | 3.66 | 95 | 15.2 |
| N9 | 1.36 | 3.17 | 77 | 16.0 |
| N10 | 1.59 | 2.54 | 49 | 18.3 |
| N11 | 1.83 | 2.49 | 80 | 12.2 |
| N12 | 1.07 | 3.50 | 83 | 13.8 |
| N13 | 1.30 | 3.66 | 82 | 20.4 |
| N14 | 1.48 | 2.78 | 58 | 18.3 |
| N15 | 1.90 | 2.63 | 59 | 18.4 |
| N16 | 2.06 | 2.93 | 42 | 16.9 |
| N17 | 1.00 | 4.15 | 112 | 14.8 |
| N18 | 1.56 | 3.27 | 75 | 14.9 |
| N19 | 1.76 | 3.02 | 58 | 21.0 |
| N20 | 2.18 | 2.63 | 47 | 19.4 |
| N21 | 2.93 | 2.24 | 41 | 12.4 |

to maintain a balanced design. Table III shows the operating conditions at which each blend was filled.

## EXPERIMENTAL

**Particulate Properties**—*Specific Volume*—Approximately 50 ml. of powder was placed into a tared 100-ml. graduate. The graduate was tapped 15 times mechanically by means of a Numinco Tap-Pak Volumeter.[3] The volume of the powder after tapping was divided by the weight of the powder to give the specific volume in ml./Gm.

*Flowability*—Powder was allowed to flow gently through a glass funnel by means of a mechanical feeding device[4] onto a calibrated vibrationless flat surface where it formed a cone. The funnel had an orifice of 2.58 mm. and was placed 2.40 cm. above the flat surface. When the apex of the cone reached the funnel orifice powder flow was stopped, and the diameter of the base of the cone determined. The area of the base was calculated (in square inches) rather than the angle of repose. The result was termed "flowability" although the authors realize that such experimental procedures may be measuring interparticle friction rather than flow.

*Mean Particle Size and Particle Size Distribution*—Particle size determinations were made by sieve analysis using 70, 80, 120, 170, and 325 screens. The Ro-Tap testing sieve shaker[5] was used, and powder samples of 100 Gm. were shaken for 10 min. The best linear plot of percent retained *versus* screen size (in microns) was made on log-probability paper. From the plot the geometric mean diameter and the coefficient of variation were obtained.

**Capsule Filling Machine Properties**—Throughout the study a Lilly model 8 capsule filling machine[6] was used.

*Capsule Size*—In order to obtain a meaningful computer analysis it is necessary to have absolute numbers available for data input. This was accomplished in the case of capsule size by measuring the volume in ml. of alcohol USP needed to completely fill the bodies of empty No. 0, No. 1, and No. 2 capsules.

*Capsule Machine Speed*—A tachometer placed on the turntable spindle yielded r.p.m. data directly.

**Filled Capsule Properties**—Preliminary work showed that the elimination of ring-to-ring capsule weight differences could be obtained by discarding the first three rings of capsules. There was no statistical difference as measured by a *t* test between the net weights of capsules selected at random from the fourth, fifth, or sixth rings. Also, further study showed that capsule shells do not vary in weight to a statistically significant extent. To simplify analytical weighings, gross capsule weights are reported throughout.

After filling of the powder hopper, the first three rings were filled and discarded, the hopper refilled, and 15 capsules taken at random from the combined fourth, fifth, and sixth rings and individually weighed on an analytical balance. The mean, standard deviation, and coefficient of variation were calculated.

## RESULTS

Tables IV and V list the evaluated physical properties of the powder blends.

The machine speed r.p.m. values and the capsule size volume measurements are given in Tables VI and VII.

Filled capsule characteristics are shown in Tables VIII and IX.

A multiple stepwise regression analysis of the dependent variables was made with the aid of an IBM 1620-II computer. A full second-order (quadratic) model with all possible two-factor interactions was employed. The stepwise regression method offers the advantage of including only those variables, quadratic terms, and interactions which demonstrate statistically significant effects on capsule weight and weight variation responses.

During the initial data processing it became evi-

[3] Model JEL-ST, distributed by Numec Instruments and Controls Corporation, Monroeville, Pa.
[4] Eriez Hi-Vi, model V3B style 20A, Eriez Manufacturing Company, Erie, Pa.
[5] Manufactured by W. S. Tyler Company, Cleveland, Ohio.
[6] Eli Lilly and Company, Indianapolis, Ind.

TABLE V—PHYSICAL PROPERTIES OF POWDER BLENDS CONTAINING TALC

| Blend No. | Specific Vol., ml./Gm. | Flowability, in.² | Particle Size, (Geometric Mean), μ | Particle Size Coefficient of Variation |
|---|---|---|---|---|
| T1 | 1.44 | 1.56 | 75 | 8.4 |
| T2 | 1.10 | 3.63 | 114 | 9.9 |
| T3 | 1.27 | 2.30 | 76 | 11.9 |
| T4 | 1.20 | 3.14 | 124 | 16.8 |
| T5 | 1.60 | 1.91 | 66 | 13.3 |
| T6 | 1.64 | 3.11 | 88 | 14.3 |
| T7 | 1.17 | 2.43 | 81 | 11.3 |
| T8 | 1.19 | 3.46 | 100 | 12.9 |
| T9 | 1.38 | 3.14 | 74 | 9.6 |
| T10 | 1.54 | 3.24 | 74 | 16.4 |
| T11 | 1.83 | 2.22 | 47 | 15.7 |
| T12 | 1.08 | 4.01 | 96 | 11.5 |
| T13 | 1.27 | 3.02 | 84 | 14.3 |
| T14 | 1.40 | 3.02 | 72 | 16.5 |
| T15 | 1.83 | 2.57 | 51 | 24.2 |
| T16 | 2.25 | 2.81 | 48 | 21.4 |
| T17 | 1.03 | 2.84 | 86 | 13.5 |
| T18 | 1.43 | 3.11 | 74 | 15.3 |
| T19 | 1.78 | 2.96 | 68 | 13.9 |
| T20 | 2.24 | 2.38 | 43 | 22.7 |
| T21 | 2.50 | 2.22 | 43 | 12.2 |

TABLE VI—QUANTIFICATION OF CAPSULE FILLING MACHINE SPEEDS

| Manufacturer's Designation | Experimental Designation | R.p.m. |
|---|---|---|
| A1 | Fast | 8.7 |
| A2 | ... | 7.3 |
| A3 | ... | 6.0 |
| A4 | Medium | 4.8 |
| B1 | ... | 4.0 |
| B2 | ... | 3.3 |
| B3 | ... | 2.7 |
| B4 | Slow | 2.2 |

TABLE VII—QUANTIFICATION OF CAPSULE SIZES[a]

| Size Designation | Vol., ml. |
|---|---|
| No. 0 | 0.669 |
| No. 1 | 0.495 |
| No. 2 | 0.368 |

[a] Body only.

dent that a degree of internal correlation existed between the particle size responses and specific volume and/or flowability. Correlation coefficients calculated with and without particle size factors present showed little difference. It was, therefore, possible to eliminate these factors from further analysis since they had no practical effect on capsule characteristics.

The equations below are the result of the computer analysis.

$$Y_1 = 630.71 - 34.37(X_1) + 1.92(X_1)^2 + 1185.99(X_2) + 561.99(X_2)^2 - 421.46(X_3) + 110.34(X_3)^2 - 11.20(X_4) - 24.31(X_1X_2) + 8.27(X_1X_3) - 433.57((X_2X_3). \quad \text{(Eq. 1)}$$

$$Y_2 = 25.73 + 0.27(X_1)^2 + 40.15(X_2) - 10.01(X_3) + 1.83(X_3)^2 - 14.84(X_4) + 3.23(X_4)^2 - 0.60(X_5) - 4.22(X_1X_2) - 0.54(X_1X_4). \quad \text{(Eq. 2)}$$

$$Y_3 = 4.28 + 0.04(X_1)^2 + 0.23(X_3)^2 - 1.86(X_4) + 0.45(X_4)^2 - 0.13(X_5) - 0.15(X_1X_3) - 0.11(X_1X_4). \quad \text{(Eq. 3)}$$

TABLE VIII—FILLED CAPSULE CHARACTERISTICS OF BLENDS WITHOUT TALC

| Blend No. | Filling Conditions: r.p.m. | Filling Conditions: Capsule Size | Mean Gross Wt., mg. | S. D., mg. | Coefficient of Variation, % |
|---|---|---|---|---|---|
| N1 | 2.2 | 2 | 460.9 | 8.3 | 1.8 |
| N1 | 4.8 | 0 | 751.2 | 15.2 | 2.0 |
| N1 | 8.7 | 1 | 503.9 | 13.3 | 2.6 |
| N2 | 2.2 | 0 | 869.5 | 19.1 | 2.2 |
| N2 | 4.8 | 1 | 581.0 | 10.1 | 1.7 |
| N3 | 8.7 | 0 | 692.8 | 7.9 | 1.1 |
| N4 | 2.2 | 2 | 462.4 | 6.6 | 1.5 |
| N4 | 8.7 | 1 | 495.4 | 11.3 | 2.3 |
| N5 | 8.7 | 2 | 365.5 | 7.0 | 1.9 |
| N6 | 2.2 | 1 | 513.1 | 11.3 | 2.2 |
| N6 | 4.8 | 2 | 381.1 | 7.8 | 2.1 |
| N7 | 4.8 | 0 | 794.6 | 24.1 | 3.0 |
| N8[a] | 4.8 | 1 | 543.9 | 8.7 | 1.6 |
| N9 | 8.7 | 0 | 631.5 | 8.2 | 1.3 |
| N10 | 2.2 | 2 | 405.3 | 14.6 | 3.6 |
| N10 | 8.7 | 1 | 425.9 | 8.9 | 2.1 |
| N11 | 8.7 | 2 | 315.8 | 3.5 | 1.1 |
| N12 | 2.2 | 1 | 696.6 | 21.8 | 3.1 |
| N12 | 4.8 | 2 | 502.2 | 8.6 | 1.7 |
| N13 | 4.8 | 0 | 692.6 | 12.2 | 1.8 |
| N14 | 2.2 | 0 | 681.0 | 22.2 | 3.3 |
| N14 | 4.8 | 1 | 461.9 | 6.8 | 1.5 |
| N15 | 8.7 | 0 | 509.0 | 8.2 | 1.6 |
| N16 | 2.2 | 2 | 330.6 | 12.0 | 3.6 |
| N16 | 8.7 | 1 | 352.6 | 5.0 | 1.4 |
| N17 | 8.7 | 2 | 466.4 | 12.9 | 2.8 |
| N18 | 2.2 | 1 | 558.2 | 11.7 | 2.1 |
| N18 | 4.8 | 2 | 400.1 | 4.6 | 1.1 |
| N19 | 4.8 | 0 | 573.9 | 11.5 | 2.0 |
| N20 | 2.2 | 0 | 539.4 | 18.3 | 3.4 |
| N20 | 4.8 | 1 | 370.2 | 4.2 | 1.1 |
| N21 | 8.7 | 0 | 403.0 | 7.0 | 1.7 |

[a] Excessive binding at 2.2 r.p.m., No. 0 capsule.

where

$Y_1$ = mean gross capsule weight, mg.,
$Y_2$ = capsule weight standard deviation, mg.,
$Y_3$ = capsule weight coefficient of variation, %,
$X_1$ = machine speed, r.p.m.,
$X_2$ = capsule size, ml.,
$X_3$ = specific vol., ml./Gm.,
$X_4$ = flowability, sq. in.,
$X_5$ = presence of talc (+1) or absence of talc (−1).

It is obvious from the complexity of the equations that the measured responses are dependent on many factors and interactions between factors. Since no simple relationship exists for each of the evaluated properties, particulate or mechanical, with capsule characteristics, the equations as such are difficult to use for data analysis. Response surface contours, however, may be generated from Eqs. 1–3.

The shape, or contour, of the solid geometrical surface generated by changes in a response produced by continuous variations in values of two interacting factors is known as a response surface contour. Response surface contours may be plotted two dimensionally as contour charts (6). While only two interacting factors can be accommodated on a single contour chart, the preparation of a number of such charts allows for the analysis of the effect of many factors on a response.

## DISCUSSION

**Mean Capsule Fill Weight**—The computer supplied contour charts for all combinations of capsule size and machine speed, including, in the latter case, intermediate machine speeds not a part of the

TABLE IX—FILLED CAPSULE CHARACTERISTICS OF BLENDS WITH TALC

| Blend No. | Filling Conditions r.p.m. | Capsule Size | Mean Gross Wt., mg. | S. D., mg. | Coefficient of Variation, % |
|---|---|---|---|---|---|
| T1 | 2.2 | 2 | 457.8 | 6.4 | 1.4 |
| T1 | 4.8 | 0 | 720.3 | 17.8 | 2.5 |
| T1 | 8.7 | 1 | 480.9 | 14.8 | 3.1 |
| T2 | 8.7 | 2 | 444.6 | 12.1 | 2.7 |
| T3 | 2.2 | 1 | 591.8 | 16.7 | 2.8 |
| T3 | 4.8 | 2 | 435.8 | 6.5 | 1.5 |
| T4 | 4.8 | 0 | 772.7 | 10.4 | 1.4 |
| T5 | 2.2 | 0 | 743.1 | 19.9 | 2.7 |
| T5 | 4.8 | 1 | 503.7 | 9.1 | 1.8 |
| T6 | 8.7 | 0 | 641.1 | 7.0 | 1.1 |
| T7 | 2.2 | 2 | 506.2 | 6.4 | 1.3 |
| T7 | 8.7 | 1 | 576.1 | 9.4 | 1.6 |
| T8 | 8.7 | 2 | 404.1 | 9.7 | 2.4 |
| T9 | 2.2 | 1 | 555.9 | 8.5 | 1.5 |
| T9 | 4.8 | 2 | 384.1 | 9.0 | 2.3 |
| T10 | 4.8 | 0 | 625.7 | 7.3 | 1.2 |
| T11 | 2.2 | 0 | 604.3 | 9.9 | 1.6 |
| T11 | 4.8 | 1 | 423.3 | 5.3 | 1.2 |
| T12 | 8.7 | 0 | 765.1 | 13.3 | 1.7 |
| T13 | 2.2 | 2 | 463.7 | 3.8 | 0.8 |
| T13 | 8.7 | 1 | 515.0 | 9.5 | 1.9 |
| T14 | 8.7 | 2 | 368.1 | 6.3 | 1.7 |
| T15 | 2.2 | 1 | 452.1 | 6.3 | 1.4 |
| T15 | 4.8 | 2 | 337.2 | 4.5 | 1.3 |
| T16 | 4.8 | 0 | 493.3 | 8.3 | 1.7 |
| T17 | 2.2 | 0 | 1006.4 | 19.0 | 1.9 |
| T17 | 4.8 | 1 | 647.1 | 11.4 | 1.8 |
| T18 | 8.7 | 0 | 641.9 | 8.1 | 1.3 |
| T19 | 2.2 | 2 | 377.0 | 8.4 | 2.2 |
| T19 | 8.7 | 1 | 406.8 | 8.9 | 2.2 |
| T20 | 8.7 | 2 | 277.1 | 3.2 | 1.2 |
| T21 | 2.2 | 1 | 373.5 | 4.9 | 1.3 |
| T21 | 4.8 | 2 | 271.7 | 6.1 | 2.3 |

original experimental data. Thus, 24 contour charts (8 machine speeds × 3 capsule sizes) were drawn, of which Fig. 1 is representative.

It was seen from these contour charts that, for a given capsule size and machine speed, specific volume almost solely determines the mean capsule weight. A decrease in specific volume (increase in density) increases mean weight. Aside from the obvious fact that dense powders weigh more per unit volume, the weight of the powder head in the hopper above the capsule during filling is increased with dense powders thus increasing the pressure on the material being filled. Of course, the size of the capsule shell and the machine operating speed have a direct effect on capsule weight.

**Standard Deviation**—Equations 2 and 3 indicate that the presence of talc acts to decrease the filled capsule weight variation. Such a decrease cannot be attributed to improved powder flow as it was measured. The average flowability of powders containing talc was 2.81 sq. in. while that of powders in which talc was not present was 2.94 sq. in. A possible explanation for the decrease in weight variation when talc is present may be that powder flow is more uniform in the presence of a glidant.

In a tableting study, Augsberger and Shangraw (7) reported the opposite result, an increase in weight variability with the addition of a glidant. They also reported a decrease in mean tablet weight in the presence of talc. In the present work, however, there was no such glidant effect on mean capsule weight as evidenced by the absence of a term for talc in Eq. 1.

Two types of contour charts were constructed for studying the interactions of factors contributing to the weight variation of filled capsules. The first type is the result of fixing machine speed, capsule size, and the presence of talc while allowing specific volume and flow to vary. Figure 2 is representative of the charts of this type that were generated showing standard deviation as an estimate of the weight variation. A minimum standard deviation is obtained at intermediate flow values and medium to high specific volumes. Fixing flow at a medium value and increasing specific volume decreases the weight variation. Fixing specific volume and increasing flow results first in a lowering and then an increasing of the standard deviation.

The second type of contour chart results from fixing specific volume, the presence of talc, and capsule size and plotting machine speed *versus* powder flow. Figure 3 is typical. It can be seen that the interaction of machine speed and flow results in a three-dimensional figure, sections of which are ellipse-like in shape. The center area at the top of the figure is the point where the standard deviation is at a minimum. Moving from this area along either the machine speed or flow axis results in an increase in standard deviation. For each capsule size and specific volume combination there are optimum values of machine speed and flow that produce a minimum standard deviation.

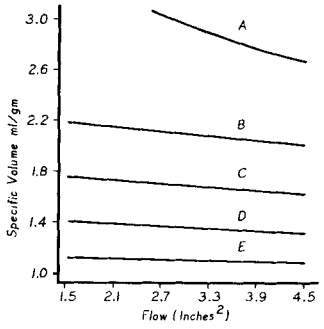


*Fig. 1—Mean gross fill weights of No. 0 capsules as a function of specific volume and flow at a machine speed of 4.8 r.p.m. Key: A, 400 mg.; B, 500 mg.; C, 600 mg.; D, 700 mg.; E, 800 mg.*

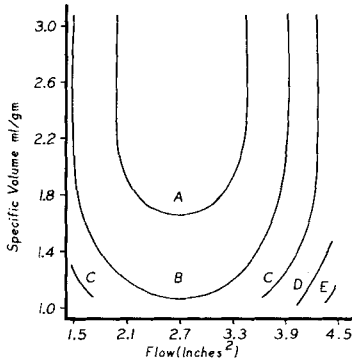


*Fig. 2—The standard deviation of filled No. 2 capsules as a function of specific volume and flow at a machine speed of 4.8 r.p.m. Key: A, 3.0 mg.; B, 6.0 mg.; C, 9.0 mg.; D, 12.0 mg.; E, 15.0 mg. (Talc present.)*

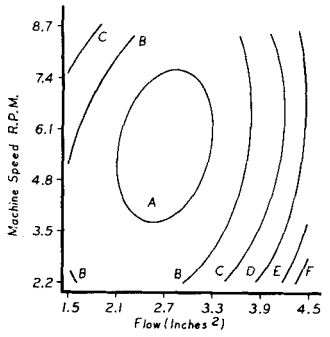


*Fig. 3—The standard deviation of filled No. 2 capsules as a function of machine speed and flow at a specific volume of 2.0 ml./Gm. Key: A, 3.0 mg.; B, 6.0 mg.; C, 9.0 mg.; D, 12.0 mg.; E, 15.0 mg.; F, 18.0 mg. (Talc present.)*

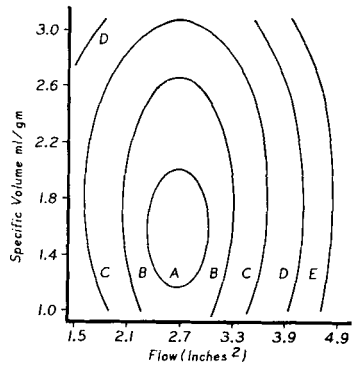


*Fig. 4—The coefficient of variation of filled capsules as a function of specific volume and flow at a machine speed of 4.8 r.p.m. Key: A, 1.4%; B, 1.6%; C, 1.8%; D, 2.2%; E, 2.6%. (Talc present.)*

**Coefficient of Variation**—A similar analysis may be made of the influence of the variables on the weight variation as estimated by the coefficient of variation with one exception. Equation 3 states that the coefficient of variation is independent of the capsule size.

Figure 4 is representative of the contour charts generated in which machine speed and the presence of talc are fixed. There is one area in which the coefficient of variation is at a minimum. Any change in specific volume or flow will move the response from the minimum area.

Of the contour charts illustrating the effect of machine speed and flow on the coefficient of variation when the presence of talc and the specific volume are fixed, Fig. 5 is typical. A minimum area occurs at one particular value of machine speed and flow.

**Fit of the Model to the Data**—The fit of the mathematical model to the data is evidenced by the ability of Eq. 1 to estimate the weights of capsules filled with powders of the same system used in the experimental work but under different filling conditions. The results of this interpolation are shown in Table X where calculated and actual weights of capsules filled with powder blend N7 are compared. Excellent agreement is obtained.

**Applicability of the Model**—To demonstrate the applicability of the model to other powder systems,

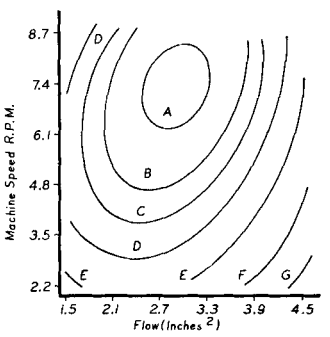


*Fig. 5—The coefficient of variation of filled capsules as a function of machine speed and flow at a specific volume of 2.0 ml./Gm. Key: A, 1.2%; B, 1.4%; C, 1.6%; D, 1.8%; E, 2.0%; F, 2.6%; G, 3.2%. (Talc present.)*

TABLE X—CALCULATED AND ACTUAL WEIGHTS[a]

| Machine Speed | Calculated Weight, mg. | Actual Weight, mg. | Difference, % |
|---|---|---|---|
| A1 | 440 | 431 | 2.0 |
| A2 | 445 | 439 | 1.3 |
| A4 | 473 | 460 | 2.7 |
| B2 | 501 | 473 | 5.6 |
| B4 | 527 | 501 | 4.9 |

[a] Blend N7, No. 2 capsules.

TABLE XI—CALCULATED AND ACTUAL WEIGHTS[a]

| Machine Speed | Calculated Weight, mg. | Actual Weight, mg. | Difference, % |
|---|---|---|---|
| A1 | 722 | 760 | 5.3 |
| A2 | 737 | 760 | 3.1 |
| A4 | 782 | 778 | 0.5 |
| B2 | 821 | 798 | 2.8 |
| B4 | 855 | 870 | 1.8 |

[a] Formula No. 1, No. 0 capsules.

ascorbic acid and thiamine mononitrate blends were prepared. Small samples of these blends were evaluated for specific volume and flow. The compositions and characteristics of these formulations are given below.

Formula No. 1

Ascorbic acid USP[7] ..... 99 parts
Magnesium stearate USP ..... 1 part
Specific volume = 1.13 ml./Gm.
Flowability = 4.91 sq. in.

Formula No. 2

Thiamine mononitrate USP[8] ..... 98 parts
Magnesium stearate USP ..... 1 part
Pyrogenic silica[9] ..... 1 part
Specific volume = 1.62 ml./Gm.
Flowability = 2.99 sq. in.

Using the specific volume and flow values, capsule weights to be expected at various machine speeds were calculated from Eq. 1. A comparison of calculated and actual weights is given in Tables XI and XII. In three cases the percent difference exceeds 5% but in no case does it exceed 6%.

[7] USP fine crystals, Merck and Company, Inc., Rahway, N. J.
[8] USP extra fine crystals, Merck and Company, Inc., Rahway, N. J.
[9] Marketed as Cab-O-Sil by the Cabot Corporation, Boston, Mass.

TABLE XII—CALCULATED AND ACTUAL WEIGHTS[a]

| Machine Speed | Calculated Weight, mg. | Actual Weight, mg. | Difference, % |
|---|---|---|---|
| A1 | 582 | 599 | 2.9 |
| A2 | 591 | 618 | 4.6 |
| A4 | 626 | 658 | 5.1 |
| B2 | 658 | 695 | 5.6 |
| B4 | 688 | [b] | [b] |

[a] Formula No. 2, No. 0 capsules. [b] Excessive machine binding, capsules not filled.

The utility of the model as a capsule formulation aid is to be found in the use of Eq. 1. From an evaluation of specific volume and flow properties of a small sample of the powder to be encapsulated, the equation can be used to predict fill weights at various machine speed and capsule size combinations. In a similar manner, the capsule size necessary for the encapsulation of a powder can be determined from the equation without the necessity of a trial. Further, the equation reveals that the alteration of specific volume is necessary if the desired capsule fill weight cannot be obtained from capsule size and machine speed combinations.

## SUMMARY

A model has been developed which defines and quantitates the factors affecting the encapsulation of powders in hard gelatin capsules using semiautomatic capsule filling equipment. The model reveals that the mean capsule fill weight is dependent on specific volume, flowability, machine speed, and capsule size. The weight variation as estimated by the standard deviation is a function of machine speed, capsule size, specific volume, flowability, and the presence of a glidant. The coefficient of variation as an estimate of the weight variation is a function of machine speed, specific volume, flowability, and the presence of a glidant but independent of capsule size. Particle size considerations of moderately coarse particles (USP designation) are not directly a part of the model because they are reflected in other measured particulate properties.

The model expresses through equations and contour charts useful information for capsule formulation development. For example, from the contour charts it may be seen that the particulate property influencing fill weight to a major extent at a fixed capsule size and machine speed is specific volume. The interaction of specific volume and powder flowability produces an area where weight variation is at a minimum. The mean capsule fill weights that may be expected for any given powder blend may be calculated with an accuracy often exceeding 95% from simple capsule size, machine speed, and particulate property evaluations on small samples of formulation.

Savings in time and material needed to prepare and evaluate trial formulations are a direct result of the use of this model.

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*Keyphrases*

Gelatin capsules, hard—powder encapsulation
Powders for encapsulation—physical properties
Capsule fill weight—factors affecting
Weight variation, capsules—factors affecting
Model, mathematical—variables *vs.* capsule characteristics