Method for Predicting Fill Weight Variation When Packing Powders Using Vacuum/Purge Fillers

R. C. LIJANA [x] **and J. D. TAULBEE**

Received December 18, 1981, from the *Procter & Gamble Co., Miami Valley Laboratories, Cincinnati, OH 45247.* Accepted for publication March 15, 1982.

Abstract □ The present report demonstrates that for at least four pharmaceutical powders, the variation in fill weight associated with a vacuum/purge filling port is correlated with the length–diameter ratio of that port. This relationship has been mathematically modeled, and a design curve based on production data is presented, which depicts this relationship over a wide range of length–diameter ratios. For powders with properties similar to those presented, the design curve may be used to determine the dimensions of the port which will yield acceptable process weight control. Fill weight variances also can be predicted given a fixed port diameter. For other powders, the model can be used to create design curves with a few data points.

Keyphrases □ Vacuum/purge fillers—method for predicting fill weight variation when packing powders □ Pharmaceutical powders—method for predicting fill weight variation when packing powders using vacuum/purge fillers □ Models, mathematical—method for predicting fill weight variation when packing powders using vacuum/purge fillers

Industry employs a variety of methods to fill containers with measured amounts of solids (1–6). The pharmaceutical industry most frequently uses vacuum/purge filling: the powder to be filled is drawn under vacuum from a hopper into a cylindrical port of preset dimensions. The powder is held against a piston under vacuum until a container is available for loading, then light air pressure replaces the vacuum and discharges the powder.

The weight of the powder slug is determined by the bulk density of the powder and the geometry of the filling port. The diameter of the port (d) is determined by the choice of a filling wheel and can be varied only by changing wheels. The depth of the port, or the length (l), can be adjusted at any time but is generally set before a filling run begins. The choices of filling wheels and port length settings to achieve the proper powder weight delivery are normally determined by trial and error, requiring a large number of determinations. Since variability around the desired weight is an important consideration in pharmaceutical solid dose preparation, selecting the combination of settings yielding the minimum variation is desirable.

Design curves, *i.e.*, mathematical models fitted to empirical data and correlating equipment variables with desired results, frequently have been used in the chemical process industries to reduce dependence on trial and error adjustments. Unfortunately, the literature is lacking convenient mathematical relationships by which the operation and precision of filling equipment for the pharmaceutical industry can be predicted and optimized. Piston compaction/ejection equipment was studied (7), and the compaction forces needed to achieve the required fill weight, given powder bed height, and piston height were tested. Earlier, a mathematical model was developed (8) for filling gelatin capsules. Similar fillers were studied (9) but there was only an interest in the packing properties of various powders as a source of fill-weight variation. Thus, none of these contributions are directly applicable to the stated problem.

The object of the present work, therefore, was to develop a design curve relating the variance of powder fill weights to equipment variables for a specific set of vacuum/purge fillers and a specific set of pharmaceutically useful powders. It was hoped that the technique and the design curve used might also be shown to be more generally useful.

THEORETICAL

The variance in powder fill weights can be transformed into a dimensionless parameter and normalized by a new variable, CV, the coefficient of variation, defined as:

$$CV = \frac{S}{\overline{W}} \times 100\% \qquad \text{(Eq. 1)}$$

where S is the standard deviation of fill-weight data, and $\overline{W}$ is the average fill weight.

The independent variable for the model can incorporate both equipment and component effects as follows. Assuming the walls of an individual cylindrical port to be smooth, then the variation in the weight of a powder plug is proportional to the exposed lateral surface area and to the pressure drop across the cylinder. Assuming further that the pressure drop is constant across the length of the powder plug (distance) and time, then the pressure drop is solely a function of component properties and the integrity of the piston/filler which is used to set port length: $\Delta p = f$ (crystallinity, particle size, particle shape, piston integrity).

The component properties can be related to the bulk density of a material. Piston integrity can decrease during the course of routine filling due to blinding, but measured port pressure changes alert the operator to the need for piston replacement. Thus, $\Delta p = f$ may be reduced to:

$$\Delta p \propto \rho \qquad \text{(Eq. 2)}$$

where ρ is the material bulk density.

Viewed from another perspective, the bulk density of a material determines the length of a contained powder plug and, therefore, the length of exposed cylinder for a specified fill weight and port diameter. This diameter, in turn, is an equipment parameter which determines the exposed lateral surface areas. Therefore, the independent dimensionless variable for the design curve may be:

$$\frac{l}{d} \qquad \text{(Eq. 3)}$$

where l is the length of the powder plug and d is the diameter of the port.

Consideration of certain boundary conditions, which will be more fully discussed, suggests that the model should have both vertical and horizontal asymptotes. Such a model can be constructed as follows:

$$y = A + B_1/(x - v) + B_2/(x - v)^2 + \ldots + B_n/(x - v)^n \qquad \text{(Eq. 4)}$$

where y is CV, x is the l/d ratio, A is the horizontal asymptote, and v is the vertical asymptote.

The vertical asymptote should be fixed at zero, otherwise the model has the unrealistic characteristic that once the l/d ratio is less than v, the CV begins to decrease with decreasing l/d ratio.

The model of choice to attempt to fit the design curve, then, is:

$$y = A + B_1/x + B_2/x^2 + \ldots + B_n/x^n \qquad \text{(Eq. 5)}$$

where terms are added until the parameter for the last term is not statistically different from zero.

The interpretation of Eq. 5 is that A is the smallest value of CV, which can be attained by varying the l/d ratio. Implied also is that CV will increase as the l/d ratio becomes small. This is reasonable, because with

0022-3549/83/0200-0119$01.00/0

Table I—Filler Dimensions and Calculated Packed Densities for Zinc Acetate Powder Filling

	Plug Diameter	Plug Length	Density g/cm³	*l/d*
d	0.95 cm	1.3 cm	0.650	1.3
constant	0.95 cm	2.5 cm	0.664	2.7
	0.95 cm	3.8 cm	0.656	4.0
	0.95 cm	5.0 cm	0.659	5.3
l	0.48 cm	2.5 cm	0.666	5.3
constant	0.79 cm	2.5 cm	0.640	3.2
	0.79 cm	2.5 cm	0.638	3.2
	0.95 cm	2.5 cm	0.664[a]	2.7
	0.95 cm	2.5 cm	0.664	2.7
	0.95 cm	2.5 cm	0.643	2.7
	1.3 cm	2.5 cm	0.678	2.0
	1.3 cm	2.5 cm	0.660	2.0

[a] This measurement was repeated from the first section of Table I.

l/d ratio decreasing, the cylinder is becoming shorter and wider, and large surface area effects would contribute to a more variable fill. Conversely, if the cylinder becomes very long in relation to its diameter, pressure drop effects would add to variability and *CV* would be expected to rise. Therefore, the minimum *CV* would be expected to occur at an *l/d* ratio between the extremes.

The model (Eq. 5) does not provide for increasing *CV* with very high *l/d* values, because this phenomenon did not occur in this work. If necessary, the model (Eq. 5) can easily be modified by adding a term Ce^x, where *C* would be a small positive number. The parameter Ce^x would not contribute noticeable amounts to the expression until *x* (the *l/d* ratio) became quite large.

EXPERIMENTAL

Materials—Two vacuum/purge powder fillers were used. When small quantities of containers were packed, a semi-automatic portable powder filler[1] was used at a rate of ~5–10 containers/min. Larger quantities of containers were filled at a rate of 15–65 containers/min using an automatic powder filler[2].

Use of these two units provided port diameters ranging from 0.48 to 1.3 cm and lengths ranging from 0.19 to 9.5 cm.

Four powders currently used in marketed or investigational pharmaceutical finished-dose forms were available for study. The four materials are listed with their bulk densities. All are fine powders (<15-μm average particle size), low and constant in moisture content, and nonfree-flowing.

Material	g/cm³
1. Erythromycin base[3]	0.520
2. Zinc acetate[4]	0.655
3. Tetracycline hydrochlorides[5] and sodium bisulfite[6]	0.745
4. Similar to 3, but with different proportions	0.732

Methods—Since the first purpose of this work was to develop design curves for two fillers in use, actual production conditions and data were used. Values of *l/d* commonly used were selected and fill weights were measured. For each unique combination of product, filler, filling port diameter, and filling port *l/d* ratio, 10–60 weight measurements were taken. In all, four materials, seven port diameters, and 39 *l/d* ratios from 0.20 to 10.0 were tested. Eighty-eight coefficients of variation were calculated.

In addition to measuring fill weights, packed densities were calculated for a number of the combinations. These densities were used to test the implicit assumption of constant density in the model.

RESULTS AND DISCUSSION

Figure 1 shows the design curve relating *CV* to the *l/d* ratio for all collected data. The equation for this curve is:

$$CV = 0.35 + \frac{1.3}{l/d} \qquad \text{(Eq. 6)}$$

[1] Model LM-14, Perry Industries, Inc., Hicksville, N.Y.
[2] Model E-1200, Perry Industries, Inc., Hicksville, N.Y.
[3] Abbott Laboratories, Chicago, Ill.
[4] J. T. Baker, Phillipsburg, N.J.
[5] Ankerfarm, Milan, Italy.
[6] Virginia Chemical, Portsmouth, Va.

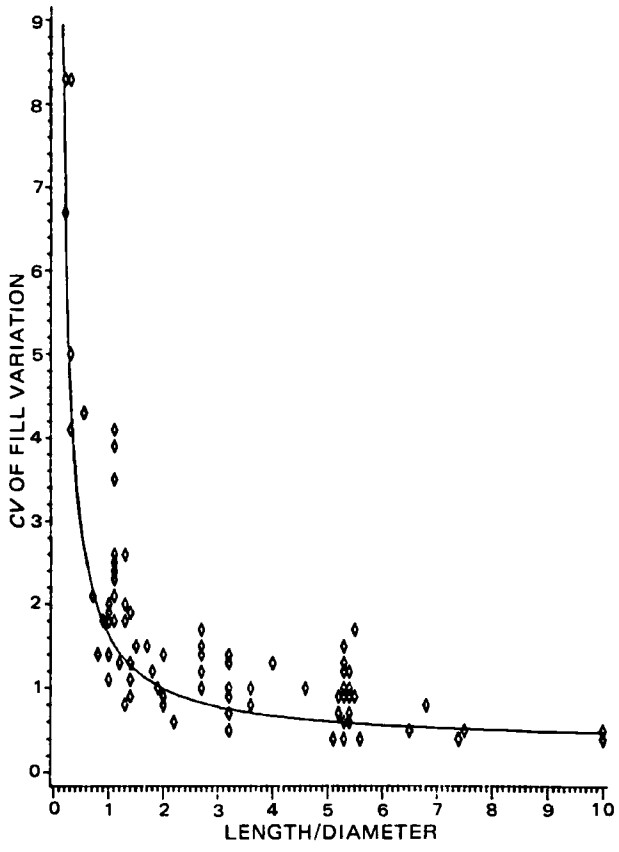

Figure 1—*Powder filling precision* versus *port size (powder plug and port dimensions) for vacuum/purge filling of four pharmaceutical powders.*

Table I shows the packed densities for samples taken during filling of zinc acetate powder.

The model was fit for each separate component using a weighted least-squares procedure with weights $1/y^2$.

Weighting was thought desirable for two reasons: the estimated *CV*s for low *l/d* ratios were expected to have higher variability, and the estimate of *A*, the minimum achievable *CV*, is an important result of curve fitting and weighting the lower *CV* values gives a better picture of the true minimum.

This proved to be reasonable, since the sum of squared deviations of the data about the model was less when the weighting procedure was used.

In all cases, the actual version of the model (Eq. 5) derived was:

$$y = A + B_1/x \qquad \text{(Eq. 7)}$$

because terms in higher powers of $1/x$ did not have coefficients that were statistically significantly different from zero, as seen in Table II. (All tests of statistical significance were done at a two-sided, 5% level.)

To examine whether another form of model might provide a better fit to the data, another fit was examined:

$$y = a \exp(b/x) \qquad \text{(Eq. 8)}$$

where *a* and *b* are the parameters of interest.

This model, like the other model (Eq. 7), has a horizontal asymptote, *a*, and a vertical asymptote, $x = 0$. The model (Eq. 8) was fitted to the zinc acetate powder data. The sum of weighted squared deviations about the model was 8.29, >1.5 times that obtained with the model (Eq. 7) for the same data (Table II). The chosen model (Eq. 7) gives a better fit than the (Eq. 8) model.

The curve in Fig. 1 is the result of combining the data for all materials. To test the validity of combining the data, statistics of the two largest blocks of data were examined. A comparison of the estimates of *A* and B_1 (Table II) of the zinc acetate data with those of erythromycin showed no statistically significant differences between them (*p*-values of 0.50 and 0.95 for *A* and B_1, respectively). There is no statistical evidence to indicate a difference in design curves for the types of powders or equipment used. Thus, it is concluded that one general physical phenomenon underlies these data and dictates the shape of the curve.

Table II—Results of Fitting Model [a] to the *CV versus l/d* Data for Four Powders and Two Fillers

Powder	Estimate of A	Estimate of B_1	p-Value for H_0:$B_1 = 0$	p-Value for H_0:$B_2 = 0$	Sum of Squared Observations	Sum of Weighted Squared Deviations about the Model
Zinc acetate [b]	0.361	1.43	0.0001	0.83	145.50	4.99
Erythromycin [b]	0.277	1.40	0.0016	0.91	19.97	2.91
Pooled data from zinc acetate and erythromycin [b]	0.294	1.47	0.0001	0.76	187.96	8.09
All four [c]	0.408	0.94	0.0001	0.37	2.63	0.55
All four [d]	0.347	1.29	0.0001	0.73	195.84	10.86

[a] Model from Eq. 5. [b] Filled with Model LM-14, Perry Industries, Inc., Hicksville, N.Y. [c] Filled with Model E-1200, Perry Industries, Inc., Hicksville, N.Y. [d] Combinations of powders filled with Model LM-14 or Model E-1200, Perry Industries, Inc., Hicksville, N.Y.

The shape of the curve describes several things about the characteristics of vacuum/purge fillers. It indicates that, in most cases, a powder plug l/d ratio ≥ 1.5 will yield acceptably small fill-weight variances. It indicates, further, that as the l/d ratio decreases to <1.5, powder-filling precision rapidly becomes worse and is extremely sensitive to l/d ratio changes. This is logical since the exposed surface area becomes a much greater percentage of the total surface areas as the l/d ratio decreases. It also indicates that when the l/d ratio rises >1.5, precision approaches a nonzero limiting value. This asymptote predicts that efforts to increase weight control through port (or component) changes in this region will go unrewarded.

It could be speculated that the validity of the entire approach rests on the assumption of a constant packed powder density. A variable packed density could lead to random variation in fill weight which would confound any model. To examine this, data in Table I were used. These density data are shown in two sections: one with a constant d value and one when l is constant. When d is constant and l increases, density does not significantly change. When l is constant and d increases, density does not change either. Thus, the implicit assumption of constant density used in the model development is valid.

This provides a basis for selecting the length for a filling port of preset diameter from a design curve, thereby eliminating the necessity for large-scale experimental testing of different port sizes. Given the bulk density of a powder or a mixture of powders and the required fill weight, one may use the design curve to determine the port length yielding acceptable process weight control for any preset port diameter (l/d ratio of ~ 1.5 is a good general choice). In addition, the curve allows prediction of fill-weight variances given a fixed port length. The model has been established with a large data base, it fits the data well, and it satisfies engineering constraints.

For powders similar to those used in this work, the design curve can be used as is. For powders with significantly different characteristics, a few data points will allow the curve to be established. In any such operation, various l/d ratios producing the desired fill weight should be established, then the model (Eq. 5) fitted to the data with nonsignificant terms deleted. If very high l/d ratios are used, Ce^x should be added to the model, where C is to be estimated. A plot of the data with the fitted curve will then allow a reasonable choice of the l/d ratio.

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ACKNOWLEDGMENTS

The authors thank E. G. Helton for technical writing assistance.

Antacid Effects on the Gastrointestinal Absorption of Riboflavin

STUART FELDMAN[x] and WYATT HEDRICK

Received November 14, 1977, from the *Department of Pharmaceutics, University of Houston, Houston, TX 77030.* Accepted for publication March 17, 1982.

Abstract □ The effect of aluminum hydroxide, magnesium hydroxide, and a combination of aluminum–magnesium hydroxide suspensions on the oral absorption of riboflavin was examined in five subjects. Coadministration of aluminum hydroxide or magnesium hydroxide suspension with riboflavin (30 mg) resulted in an increase in time of peak urinary excretion rate of riboflavin when compared with control studies. There was no increase in the peak excretion rate or total urinary excretion of riboflavin when the antacid-treated subjects were compared to the control studies. *In vitro* experiments indicated that significant binding of riboflavin to the aluminum hydroxide and magnesium hydroxide suspensions occurred. The results of the present investigation are consistent with the reported effect of aluminum ion on GI motility and the known influence of gastric emptying on the absorption of riboflavin from the GI tract.

Keyphrases □ Absorption, GI—antacid effects on riboflavin □ Riboflavin—antacid effects on GI absorption □ Antacids—effects on the GI absorption of riboflavin

Antacids are a therapeutic class of drugs which have great potential for drug absorption interactions. Since they may be purchased over-the-counter, they are widely used by the public and may be taken concurrently with many other drugs. Antacids have been reported to alter the GI absorption of a number of drugs through the formation of