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ANALYSIS OF CONTENT UNIFORMITY DATA OF TABLETS WITH TWO ACTIVE INGREDIENTS

Jin W. Lai
Product Development, Knoll Pharmaceutical Company, Whippany, New Jersey, 07981

ABSTRACT

A method based on scatter plots of content uniformity data of tablets containing two active ingredients was utilized to gauge the degree of segregation in the finished product. The difference of semi-axes of the tolerance ellipse imposed on the content uniformity data and the covariance of data were found to be useful in estimating degree of segregation. Direct compression formula of a specific case was found to have slightly more segregation than a wet granulated product.

INTRODUCTION

There is a constant debate over the best manufacturing process to achieve the best content uniformity in companies engaged in the production of low dose solid dosage forms. Many prefer the concise manufacturing process of a direct compression formula while others dread the content uniformity difficulties that may crop up anytime. Mostly the direct compression process receives its notoriety due to perceived problems of segregation. Methods have been reported regarding segregation. Staniforth and Rees (1, 2) used vibration to test the segregation tendencies of adhered actives of an ordered system of powder mixes. Thiel and Nguyen (3) reported the use of demixing potential to gauge the potential for a powder system to segregate. Samyn and Murthy (4) constructed a two-dimensional segregation cell to study the segregation tendencies of powder blends. All three methods mentioned above are, however, indirect measure of segregation with extrapolation to the finished products. Staniforth (5) also reviewed eleven segregation test methods reported in pharmaceutical literature. The only one applicable to tablets was content uniformity test itself. A scatter plot procedure for investigation of segregation is reported here which is applicable both to powder mixtures and finished drug products.

MATERIALS AND METHODS

Experimental tablet formulations of drug A and drug B were prepared by both direct compression and fluidized bed wet granulation methods. The direct compression formula utilized a granular form of drug B blended with a powder of drug A in a high shear mixer. The powder blend was then lubricated with magnesium stearate and compressed into tablets. The wet granulation process involved a typical wet granulation process in a fluidized bed. Samples of tablets were collected from the beginning, middle, and end portions of the tabletting process. Content uniformity test were conducted by using HPLC procedures similar to the compendial HPLC method where both active ingredients of the same tablet were quantified in the same chromatogram. Duplicate assays of the same tablets were conducted.

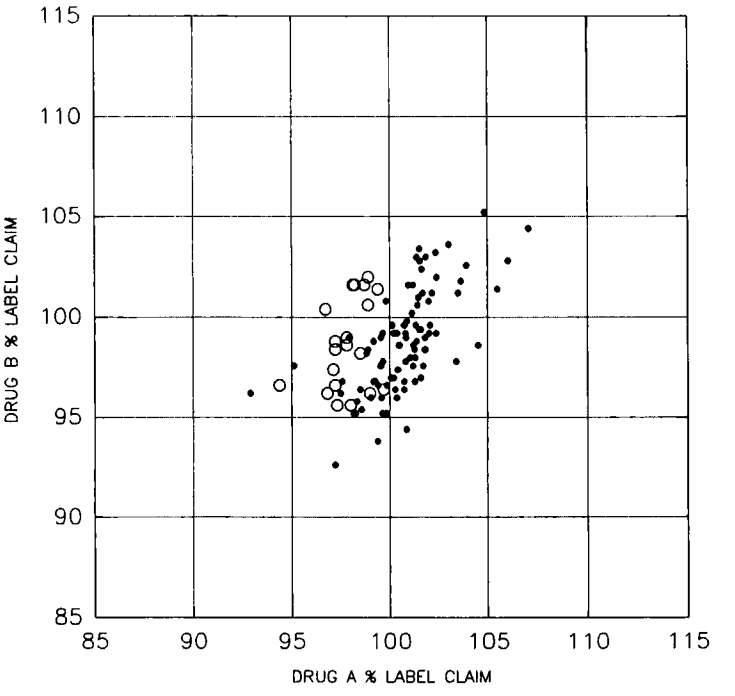

FIGURE 1
Scatter plot of content uniformity data. Unfilled circle, fluidized bed; filled circle, direct compression.

RESULTS AND DISCUSSION

A plot of % drug B label claim versus % drug A label claim was constructed for each formula. These scatter plots are shown in Figure 1. The pattern of data distribution is of interest here. Theoretically, two random variables which are independent of each other will demonstrate a circular or elliptical pattern. A circular pattern is apparent when standard deviations of both ingredients are equal. When one ingredient displays a wider spread of data than the other does, the distribution pattern is elliptical with axes parallel to the x, y axes. When the two variables are related to each other, the above distributions are no longer applicable. When the correlation coefficient equals one, the distribution is along the line $x = y$ if the two variables have the same degree of variation.

Qualitatively, the goodness of mix, which may be affected by particle size, mechanical energy input, mixing time, etc., can be visually checked by the pattern of the spread of data points. The presence of outliers may indicate either dead spots within the mixer, analytical error, or some other anomalies. Thus the method can have some diagnostic merit. The distribution pattern demonstrated by the data from the wet granulation process indicates that very little correlation could be detected and that there is very slight evidence of segregation. On the other hand, the direct compression formula generated a pattern that is more consistent with systems with segregation. Such segregation, however, is not severe enough to jeopardize the compliance with the compendial requirement of uniformity of dosage units in the present case.

TABLE 1. Estimates of Parameters

Process	Direct Comp	Fluidized Bed	Direct Comp@
n	90	30	30
$\bar{x}$	100.755	97.7133	101.209
s_x	2.0803	1.25937	2.1739
s^2_x	4.32764	1.58602	4.72583
$\bar{y}$	98.78	98.5467	99.53
s_y	2.5463	2.16488	2.6670
s^2_y	6.48364	4.68671	7.11264
S_x	385.15996	45.99458	137.04907
S_y	577.04396	135.91459	206.26656
r^2	0.4374	0.0948	0.5914
k	0.035618686	0.123261904	0.12327666
S^2_{xy}	97213.99957	592.62651	16718.07383
l_1	7.58	5.92	8.68
l_2	3.32	3.13	3.06
$l_1 - l_2$	4.26	2.79	5.62
s_{xy}	3.50	0.83	4.46

@ derived from the same data set as the second column.

Assuming that the intrinsic homogeneity of one ingredient is independent of the content of the other in the small ranges of label claim of interest, i.e. 85-115% LC, variations in excess of this constant variation can be viewed as segregation. The degree of segregation can be quantified by imposing a tolerance ellipse over the data points. The method of determining the tolerance ellipse can be found in a standard statistical handbook (6). The necessary equations for calculation are listed below. The measure of segregation can be estimated from covariance s_{xy} or from the difference in the length between the two semi-axes, l_1 and l_2,. Both parameters accentuate contribution from data points located outside of a circular region around the mean.

$$S_x = (n-1)s^2_x$$
$$S_y = (n-1)s^2_y$$
$$r^2 = S^2_{xy}/S_xS_y$$
$$S_{xy} = \sum(x-\bar{x})(y-\bar{y}) = (n-1)s_{xy}$$
$$k = F(n+1)/n(n-2)$$
$$l_1, l_2 = k^{1/4}\{S_x + S_y \pm [(S_x + S_y)^2 - 4(S_xS_y - S^2_{xy})]^{1/4}\}^{1/2}$$

where n = number of samples,
s^2_x = variance of x,
s^2_y = variance of y,
s_{xy} = covariance of x and y,
and F = significance limit.

Using tolerance ellipses with $\alpha = .05$, the differences between the length of the semi-axes are 4.26 and 2.79 for the direct compression and the wet granulation formula, respectively. The

covariances are 3.50 and 0.83 for the direct compression and the wet granulation formula, respectively. Related estimates are shown in Table 1. These values support the notion that the direct compression formula does exhibit more segregation characteristics albeit slightly in the present case. The conclusion remains the same when the data set from the direct compression formula was randomly reduced from a sample size of 90 to the same sample size of 30 as the fluidized bed data.

The method of scatter plot and tolerance ellipse described is useful in characterizing the mixing quality of formulation and process. Applied to finished products, the proposed method is both direct and non-invasive to the system under investigation.

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