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COMMUNICATION

APPLICATION OF SIMPLEX AND STATISTICAL ANALYSIS FOR CORRECTION OF PITTING IN AQUEOUS FILM COATED TABLETS

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ABSTRACT

Pitting or pin hole formation is a tablet defect that is commonly observed in aqueous film coated tablets containing highly moisture-sensitive materials. It is generally believed that pitting is due to dissolution of soluble particles on the tablet surface when the tablet is overwetted during the coating process. An experiment was conducted to study the effects of spray rate and pan speed, the two important factors contributing to this condition. The data thus obtained were analyzed by using the simplex search procedure and the appropriate statistical methods. The levels of the two factors that minimized pitting were achieved as a result of the analysis.

INTRODUCTION

A number of problems encountered in aqueous film coating of tablets such as mottling, picking, peeling, and cracking can be attributed to processing parameters, equipment, ingredients, formulation or a combination of these factors (1-3). Another tablet defect that is commonly observed in aqueous film coated tablets containing

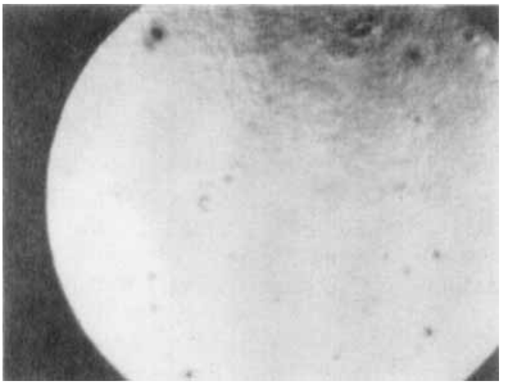

FIGURE 1. Pitting on a tablet surface.

highly moisture-sensitive and water-soluble materials is pitting or formation of pin holes on the tablet surface (Figure 1). It is generally believed that the cause of pitting is due to dissolution of soluble particles on the tablet surface when the tablet is overwetted during the coating process.

Following the process conditions recommended by the manufacturer, the Mini Hi-Coater (Model HCT-Mini, Freund Industrial Co. Ltd.) has been used in successfully coating many different kinds of tablets in the laboratory. However, for coating tablets containing a highly water-soluble and moisture-sensitive material, these recommendations do not always apply. Consequently, adjustment of the processing conditions such as bed temperature, spray rate or pan speed would have to be implemented for reducing the incidence of tablet defects.

This paper illustrates the use of the simplex search procedure (4-9) in combination with the appropriate statistical analysis for determining the levels of the spray rate and pan speed that minimize the pitting or pin hole formation in an aqueous film coated tablet.

MATERIALS

The core formulation consisted of lactose (66.8%w/w), microcrystalline cellulose (20.0%w/w), pregelatinized starch (10.0%w/w), magnesium stearate (0.5% w/w) and the moisture-sensitive model drug, anhydrous citric acid (2.7%w/w). The coating solution consisted of Opadry Y-1-3234 (12%w/w) in distilled water. One lot of cores was used for all the coating experiments.

METHODS

Tablet Preparation and Coating - The core ingredients were screened through a #40 mesh and mixed in a V-blender (P-K LB9959, Patterson Kelley Co.) for seven minutes and the resulting mix was compressed on a rotary machine (Betapress Manesty Machines Ltd.) using concave round tooling (8.73 mm diameter) at a constant speed of 600 rpm. The cores were film coated with 3% coating solids in a Mini Hi-Coater (Model HCT-Mini, Freund Industrial Co., Ltd.).

Coating Conditions - The coating conditions were as follows: charge quantity, 350 g; atomizing air pressure, 2 kg/cm^2; inlet temperature, 83 deg. C and exhaust temperature, 32-33 deg. C.

Simplex Procedure - The factors investigated were pan speed, rpm and spray rate, g per minute (gpm). The responses observed were the number of pits per tablet counted under a stereoscope and the tablet weight variation. The factor constraints as based on equipment limitations and the manufacturer's specifications were 1.0 gpm (low) and 3.0 gpm (high) for the spray rate and 10 rpm (low) and 38 rpm (high) for the pan speed. These limits define the appropriate experimental region for the simplex operation.

The three points or vertices of the initial simplex were chosen and plotted such that each side of the equilateral triangle was equal to 1 gpm scale size (see Figure 2). Tablets were coated according to the factor levels of these three vertices. Responses of the coated tablets were determined. The point with the worst response of the initial simplex was eliminated and reflected to obtain the fourth point which generated the next simplex. Tablets were coated according to the factor levels of the fourth point. Response of this point was evaluated and the process was repeated until an optimum

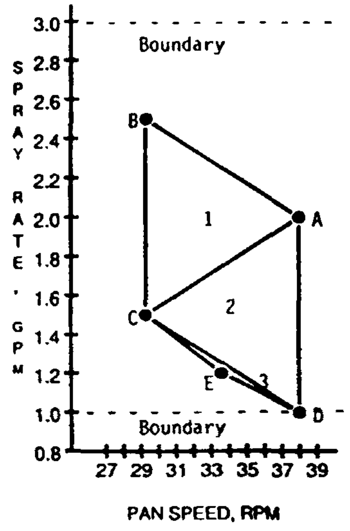

FIGURE 2. Two-factor simplex search for correcting tablet pitting

was reached. Note, in this study, optimum referred to the point where the coated tablets obtained showed essentially no pitting (no more than 1 pit/tablet). Twenty tablets were tested at each vertex of each simplex.

Statistical Analysis - Since the response measured was the number of pits or pin holes per tablet, a Freeman-Tukey (10) double square root transformation ($\sqrt{x}+\sqrt{1+x}$) was applied to the data to achieve normality and to stabilize the variance of this discrete (Poisson) type of response. The analysis of variance procedure was used for comparing the averages of the simplex vertices with respect to the number of pits per tablet. One of the implicit assumptions associated with the analysis of variance procedure is that the variabilities of the groups to be compared are equal. Levene's test (11-15) was performed for comparing the variabilities associated with the vertices. Duncan's Multiple Range test (13-16) was applied for the pair-wise comparisons among the vertices.

Table 1. Results of Simplex Experiments

Vertex	A	B	C	D	E
Factor Levels					
Spray Rate, gpm	2.0	2.5	1.5	1.0	1.2
Pan Speed, rpm	38.0	29.3	29.3	38.0	33.6
Responses					
Average No. of pits/tab	19.8	25.4	7.45	1.15	0.70
Standard deviation	4.82	5.73	3.00	1.04	1.03
Average Weight, mg/tab	239.5	240.3	239.1	238.9	239.4
Standard deviation	2.0	2.2	1.8	1.7	2.1

RESULTS AND DISCUSSION

The simplex series generated in the study based on two factors (spray rate and pan speed) is shown in Figure 2. The simplices were numbered consecutively to show their stepwise formation and movement toward the optimum. The results of the simplex experiments are shown in Table 1 and the results of the pairwise comparisons of the variabilities and of the averages of the vertices are presented in Table 2.

At each experiment, the same amount of coating had been applied to the tablets as indicated by the average weights per tablet showing no significant ($P>0.05$) differences (Table 1). In Figure 2, point B (spray rate = 2.5 gpm, pan speed = 29.3 rpm) in simplex 1 (ABC) yielded tablets with the worst response (25.4 pits/tab, Table 1, $P<0.05$) so that it was reflected to point D. At point D (spray rate = 1.0 gpm, pan speed = 38.0 rpm) of simplex 2 (BCD), pitting was essentially eliminated (1 pit/tab, Table 1, $P<0.05$) and the search was completed at this point. To reduce the processing time, the simplex was made to proceed to form a fourth simplex (CDE) by contraction (to retain the new simplex within the factor boundaries) to point E. Because the tablets produced showed the lowest number of pitting per tablet (<1 pit/tablet, Table 1, $P<0.05$) and the processing time was the shortest at this point (spray rate = 1.2 gpm, pan speed = 33.6

Table 2. Comparison[1] of Variabilities and Averages associated with the Simplex Vertices

Vertex[2]	A	B	C	D	E
AAMD[3]	0.79[a]	0.83[a]	0.89[a]	0.87[a]	0.91[a]
Averages[4]	8.95[a]	10.12[b]	5.55[c]	2.28[d]	1.79[d]
N	20	20	20	20	20

1 Two averages are not significantly different (P>0.05) if they share the same (alphabetical) superscript. Two averages are significantly (P<0.05) different if they have different superscripts.
2 The spray rate and pan speed for A, B, C, D and E are provided in Table 1.
3 AAMD denotes Average Absolute Mean Deviation used in the Levene test for the comparison of variabilities.
4 The entries are expressed in double square-root units (See Table 1 for averages and standard deviation in original units).

rpm), the process condition at point E was deemed to be the optimum. Note, however, that the tablet defect was essentially corrected in four experiments.

The statistical results clearly indicated that points D and E are the two combinations which were statistically significantly lower (P< 0.05) than the vertices A, B, and C with respect to the incidence of pitting or pin hole formation. However, point E was regarded to be the most efficient condition since it required the shorter process time.

In conclusion, simplex technique in conjunction with statistical tests was successfully applied in determining the appropriate conditions for coating tablets in the Mini Hi-Coater with few experiments. Statistical analysis of the responses of the simplex vertices was carried out to provide assurance that the correct decision was made. Therefore, this technique could be gainfully applied for process validation as well as for equipment performance qualification. In addition, because the manufacturer's specifications for equipment may not necessarily be operative in all situations, it is essential to conduct a study in the region of interest to verify the manufacturer's recommendations.

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