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Identifying fluid-bed parameters affecting product variability

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Abstract

Recent statistical/graphical methodology identifies the importance of bringing the mean to target while maintaining a low variance. Fluid-bed literature abounds in optimization strategies while overlooking product variability. In the present study, active factors (location effects) related to fluid-bed granulation of lactose with povidone (PVP) were identified using normal probability plotting and basing the slope on the calculated critical pseudo standard error value. An unreplicated fractional factorial design was employed. Residual-Fit spread plots indicated adequate empirical models through least squares. Dispersion analysis using computed residuals and resulting variances indicated spray rate binder state, and certain interactions effecting particle size variability. Additional runs confirmed the feasibility of the approach in maximizing crushing strength and minimizing particle size variability. Various factor effects could be attributed to the solubility of lactose during granulation. Variability due to spray rate was ascribed to the high inlet temperature and the surface area of the fluid-bed charge exposed to the binder solution. Rapid binder film formation promoted intragranular bonds and enhanced compactibility. Using simple empirical modeling and data visualization approaches, factors influencing product characteristics and variability were identified. The applicability of this approach in robust process development is discussed.

Keywords: Fluid-bed granulation; Fractional factorial; Lactose; Normal plots; Povidone; Pseudo standard error; Dispersion

1. Introduction

Granulation, described as size enlargement, occupies an important place in the manufacture of tablets. Current good manufacturing practices, as well as validation requirements, solicit the development of predictable and controllable wet-granulation operations having as few processing steps as possible. Fluid-bed granulation, first introduced by (Wurster, 1959), offers the advantage of combining various wet granulation steps in single equipment. However, since the process of size enlargement in a fluid-bed is a complex interac-

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Table 1
Fractional factorial design

No.	P	B	A	S	I	Particle size (μ)	Crushing strength (kP)
1	−1	−1	−1	−1	1	189.00	11.28
2	1	−1	−1	−1	−1	56.00	3.00
3	−1	1	−1	−1	−1	93.75	5.70
4	1	1	−1	−1	1	80.00	5.93
5	−1	−1	1	−1	−1	212.50	10.02
6	1	−1	1	−1	1	212.50	11.34
7	−1	1	1	−1	1	76.00	6.50
8	1	1	1	−1	−1	125.00	5.20
9	−1	−1	−1	1	−1	351.25	7.73
10	1	−1	−1	1	1	534.00	11.89
11	−1	1	−1	1	1	275.00	11.60
12	1	1	−1	1	−1	219.00	5.90
13	−1	−1	1	1	1	153.50	9.52
14	1	−1	1	1	−1	752.00	10.3
15	−1	1	1	1	−1	374.00	4.87
16	1	1	1	1	1	478.00	8.61

tion involving several variables, a knowledge of these variables is essential in achieving a controllable process (Schaefer and Worts, 1977).

Several studies address the effect of either process, formulation, or apparatus variables in the top-spray fluid-bed. In their investigation of process variables Davies and Gloor (1971), concluded that increasing binder concentrations or decreasing atomization pressure results in granules with increased particle size and higher bulk densities. Schaefer and Worts (1977) concluded that increasing nozzle size resulted in a narrower granule size distribution, and varying spray angles did not significantly effect the size distribution. Granule growth (Schaefer and Worts, 1978) was found to be directly proportional to liquid flow rate and droplet size and inversely proportional to inlet temperature. These studies, though involving the variation of a maximum of one or two factors to study a given response, provide useful information.

Experimental design is an established tool in the pharmaceutical investigation of complex processes for studying a number of variables and their interactions (Schwartz et al., 1973; Schwartz, 1990). Fluid-bed studies using factorial approaches to explore either process or formulation variables have been utilized in product development and improvement. On studying the mode and type of disintegrant incorporation using a full factorial design, Khattab et al. (1993) concluded that distribution of the disintegrant, intra- and extra-granular, resulted in the shortest disintegration time and increased dissolution rates. In a very detailed characterization and optimization of the top-spray fluid-bed process for acetaminophen granulations (Lipps and Sakr, 1994), geometric mean granule size was linearly related to liquid-binder flow rate and inlet air temperature. The process parameters studied during granulation influenced the tableting properties to a greater extent than the compression forces. Tablet properties, such as drug dissolution, were found to be a function of main effects as well as two-way interaction terms for disintegration time (Lipps and Sakr, 1994).

The above studies address the issue of product optimization. In contrast, there is a paucity of literature discussing the effect of process/formulation variables on product variability in the fluid-bed. In addition to developing and optimizing a product it is necessary to develop a robust process to improve production and reproducibility of the fluid-bed process (Valazza, 1994), i.e. operate in conditions that minimize variance and appropriately control the mean level. The objectives of

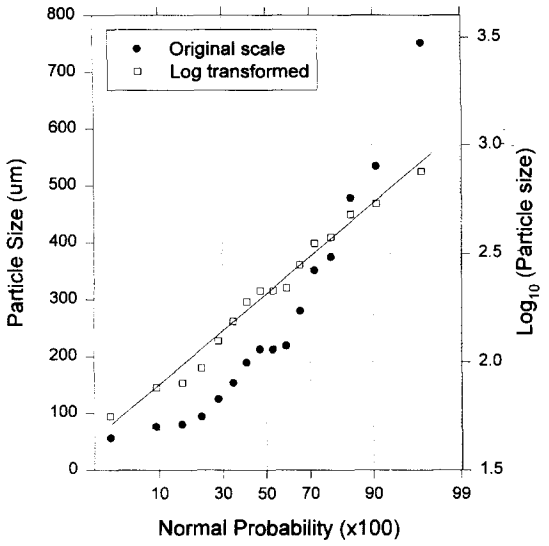

Fig. 1. Log transformation for particle size.

robust process design include making a process insensitive to variation transmitted from components and reducing process variability around the target value (Montgomery, 1990). Fractional factorial designs can serve as screening designs for studying the various factors in complex processes such as the fluid-bed to discover cause and effect through the factor sparsity principle ('Pareto effect', Box and Meyer, 1986b). This article at-

Table 2
Estimated effects for the responses

No.	Term	Effects	
		Particle size[a]	Crushing strength
	Mean	2.307	8.140
1	P	0.031	−0.308
2	B	−0.070	−1.304
3	A	0.062	0.152
4	S	0.240	0.708
5	I	−0.003	1.490
6	P·B	−0.012	−0.119
7	P·A	0.095	0.877
8	P·S	0.078	0.631
9	P·I	0.075	0.117
10	B·A	0.009	−0.695
11	B·S	0.033	0.296
12	B·I	−0.006	−0.070
13	A·S	−0.029	−0.680
14	A·I	−0.097	−0.794
15	S·I	−0.033	0.163

[a]Log 10 transformation used.

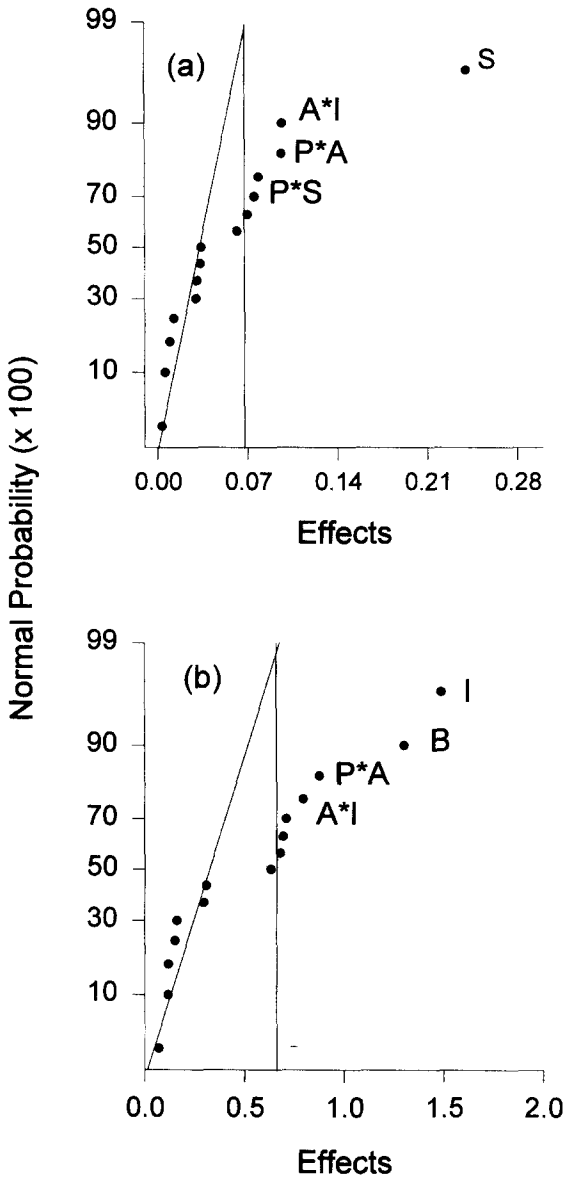

Fig. 2. Normal plot of factor effects for the responses (a) particle size and (b) crushing strength. The slope of the line based on the PSE critical value (vertical line).

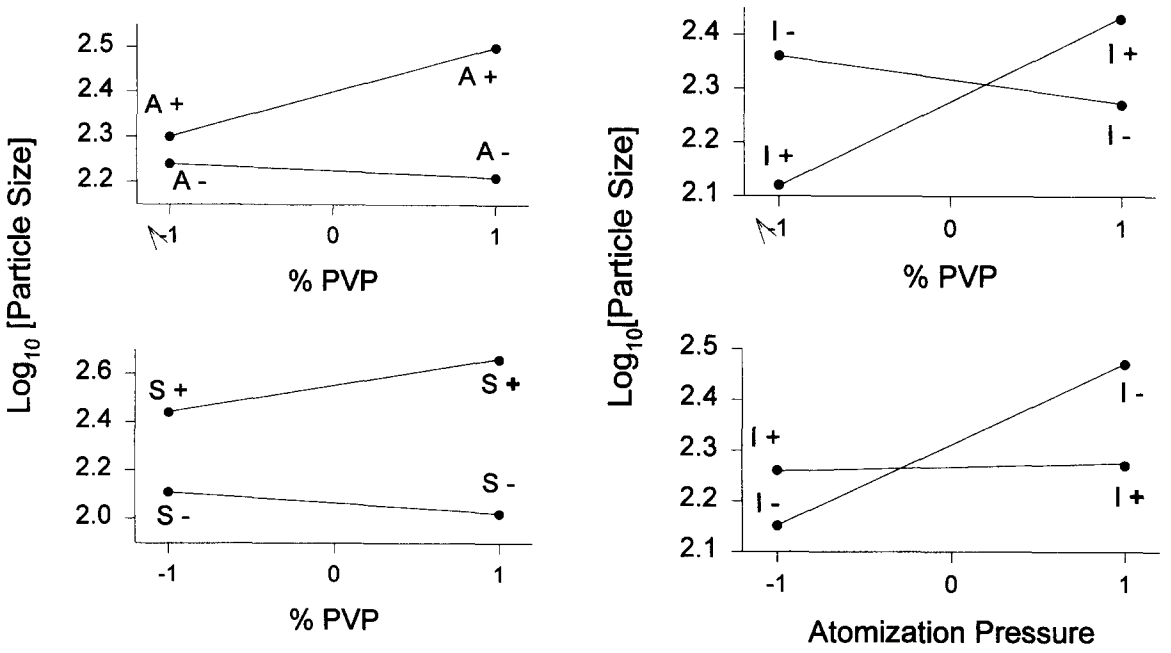

Fig. 3. (a) and (b) Two factor interactions for particle size.

tempts to use simple graphical and statistical modeling procedures to identify the effect of fluid-bed variables influencing location and dispersion in an unreplicated fractional factorial design.

2. Experimental

2.1. Materials

Lactose Hydrous (Lot no. ORI324 Sheffield Products, Norwich, NY, USA); Magnesium Stearate (lot no. 2255-SHD017, Mallinckrodt, St. Louis, MO, USA); Povidone (Plasdone K60, Lot no. HR-CC01A; International Specialty Products, Wayne, NJ, USA);

2.2. Methods

Lactose granulations were prepared using a Uniglatt top-spray granulator (Glatt Air Techniques, Ramsey, NJ, USA). The experimental runs were completed with the conditions as required by the fractional factorial design (2_V^{5-1}) outlined in Table 1. With resolution V, no main effect or two-factor interaction is confounded with any other main effect or two factor interaction. Two factor interactions are confounded with three factor interactions and main effects are confounded with four factor interactions. In Table 1 the letters represent: percent Povidone (P), liquid/dry ($-1/+1$) dry binder addition for povidone (B), atomization pressure (A), spray rate (S), inlet air temperature (I). Liquid binder solutions were prepared by dissolving the appropriate amount of povidone in distilled water using a laboratory propeller-type mixer. In the case where a liquid binder was applied, a povidone solution was sprayed onto the fluidized lactose in the bowl. When no liquid binder was added, the required amount of povidone was added to the bowl, mixed with the lactose and distilled water sprayed onto the fluidized product. Upon completion of binder addition, the granules were dried in the fluid-bed to a moisture content of 0.5–1.5% w/w (Computrac MAX 50, Arizona Instruments, Tempe, AZ, USA). As noted by (Wan and Kim, 1989) the actual amount of povidone deposited

could be less than that introduced due to the loss of povidone adhering to the product container as well as in the fluidized air. The granules were stored in plastic bags under constant conditions of temperature and humidity (25°C at approximately 40% RH) for further evaluation. Particle sizing, tabletting and reponse evaluation were completed within 24–48 h. Responses studied include particle size and tablet crushing strength.

Particle size analysis ($n = 2$) was accomplished by using a ATM L3P sonic sifter, sift and pulse for 10 min (ATM Corp. Milwaukee, WIS., USA) using appropriate US standard series (ATM Corp.). Sampling (5 g) was performed at different sites of the product to ensure homogeneity. The geometric mean (50%) particle size values were determined by log-probability plots.

The granules were mixed with 0.5% of magnesium stearate in a Turbula T2C mixer (Glenmills Inc., NJ, USA) for 3 min. prior to compression at 24.5 KN on an instrumented RB2 Stokes rotary machine (Key Industries, Englishtown, NJ, USA) to a target weight of 200 mg (Mettler AE200, Highstown, NJ, USA) using 9/32 inch flat faced punches. The tablets were collected in high density polyethylene bottles and evaluated for crushing strength (24–48 h post compression, $n = 10$) using a VK2000 (Van Kel, Edison, NJ, USA).

The software used included Microsoft® Excel and Sigma® Plot for all calculations and graphs.

3. Results and Discussion

3.1. Particle size

Table 1 summarizes the particle size data. Fig. 1 displays the normal plots of the particle size data. The data are clearly skewed towards the larger values. The skewing gradually increases resulting in a convex pattern. Log transformation of the data (Fig. 1) overcomes the monotone spread and contributes to removal of the existence of transformable nonadditivity (Box, 1988). In addition since $y_{max}/y_{min} > 3$, one should allow for the possiblity of transformations (Box, 1988). Run # 2 with A-, S-, and I-stalled due to conditions conducive to overwetting. The point appears in the lower tail of Fig. 1.

Table 2 presents the calculated effects for particle size. In the presence of replicated runs, analysis of variance techniques are used to judge the significance of the estimated effects. However in effect-saturated designs with no independent estimate of experimental error, identification of important effects is achieved by either normal probability plotting (Daniel, 1959), a bayesian approach (Box and Meyer, 1986a), or the pseudo standard error, PSE, (Lenth, 1989). The estimated effects from an unreplicated fractional factorial can be thought of as a sample from a normal distribution (null effects) contaminated by non-null effects. Lenth, 1989, in a computationally simple yet powerful method used a robust scale estimate after using a trimming threshold for large effects. Recently Haaland and O'Connell (1995) unified the approaches taken by others (Daniel, 1959; Lenth, 1989). The authors (Haaland and O'Connell, 1995) proposed a more resistant version of the PSE based test, obtained by using different tuning constants for situations with many non-null effects. In the method an initial estimate (s_o) is calculated from the estimated effects ($\beta_1,\ldots\beta_i$) using a quantile q to determine which effects are to be used. and the PSE (Lenth, 1989; Haaland and O'Connell, 1995) is computed as follows:

$$\hat{\sigma}_{PSE(q,b)} = \sigma_{PSE(q,b)} \cdot \text{median}\{|\beta_i|:((|\beta_i| \leq b \cdot s_o(q))\}$$

b is the multiplier of s_o to trim large effects before calculating the final critical value. Haaland and O'Connell (1995) have given modified consistency constants and critical values for the PSE based test. Computational details are not outlined here and can be found in Haaland and O'Connell (1995). An effect greater than the critical value is deemed to be possibly active. The effects are plotted via normal probability and the PSE based critical value is used to define the slope of the plot. The PSE based critical value for log (Particle size) was 0.0643.

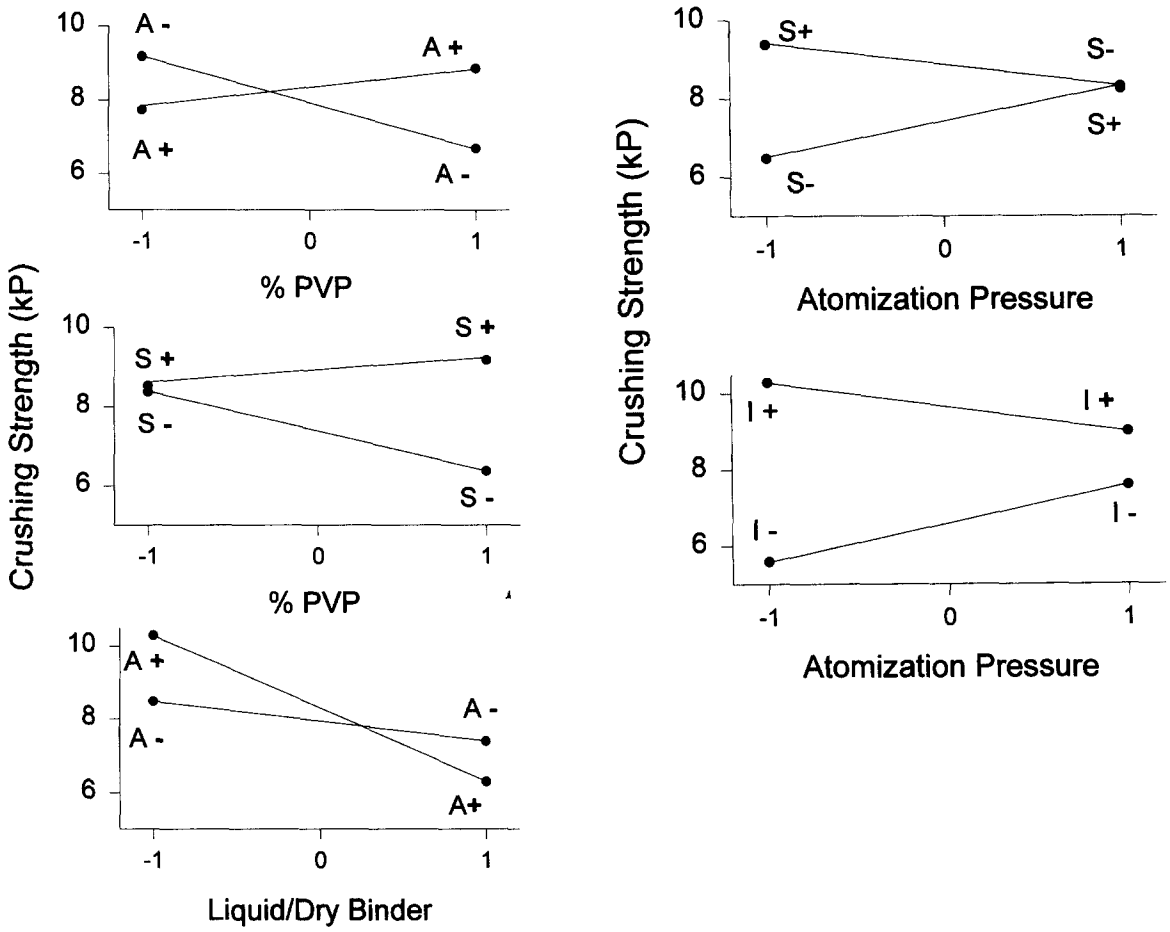

Fig. 4. (a) and (b) Two factor interactions for crushing strength.

Fig. 2a suggests the main effect 'S' as having a major influence followed by six moderate effects including interactions A·I, P·A, P·S, P·I, and main effect 'B'. The mean response interaction plots (Fig. 3a and b) focus attention on potential crossproduct terms. The objective was to achieve an average particle size of 200–300 μ. The interaction plots suggests the following settings: P−, A−, S+, and I+. The effect of spray rate in conjunction with the interactions can be attributed to the aqueous solubility of lactose. With increasing spray rate lactose can solubilize and form larger agglomerates. However, interactions should also be considered.

Table 3 represents least square regression analysis for the log transformed particle size by inclusion of the active effects ascertained from Fig. 2. A residual-fit (r–f) spread plot (Fig. 5a) (Cleveland, 1993) indicates that the response has been adequately fitted. The distributions of the fitted values minus the means and the residuals are viewed through normal plots to visualize the portion of the variation explained by the fit and the unexplained variation, respectively. This can be viewed as a graphical 'R^2'. Additional diagnostic plots include residual vs observed plots, observed vs predicted plots of transformed responses into the original metric. In attempting to identify dis-

persion effects, the location effects have to be eliminated due to aliasing (Box, 1988). This can be accomplished by least square regression analysis of the location effects and computing the residuals obtained. The resulting residuals then contain information about variability (Montgomery, 1990). Residuals are estimated for log (particle size) through the regression model. The plots of residuals against each factor was graphed (Fig. 6). The plot indicates there is less variability on addition of the liquid binder and maintaining the spray rate at a high level. Liquid binder addition facilitates film formation and rapid agglomeration. In the event of dry binder addition the povidone has to solubilize prior to film formation, leading to inhomogeneous or even absence of binder spreading. The possible implications/mechanisms will be elaborated in the next response.

In order to further clarify dispersion interactions, a further analysis of residuals as suggested by (Box and Meyer, 1986b) was completed. The standard deviation of the residuals at the high and low level for each main and interaction effect is calculated. The F_i is then computed using the variances $F_i = s^2(i+)/s^2(i-)$ and subsequently $\ln\acute{F}_i$ (absolute values) is plotted (Fig. 8a). The dispersion interactions are associated with P·I and P·B. Table 4 is the computed

Table 3
Summary of regression results for studied responses

Term	Particle Size[a]		Hardness	
	Estimate	Significance	Estimate	Significance
Constant	2.307		8.144	
P	0.031	0.3376	–	–
B	−0.070	0.479	−1.304	0.0003
S	0.240	0.0000	0.709	0.00083
I	–	–	1.490	0.0001
P·A	0.096	0.0128	0.877	0.0028
P·S	0.078	0.0314	0.631	0.0142
P·I	0.075	0.0367	–	–
B·A	–	–	−0.695	0.0091
A·S	–	–	−0.680	0.0101
A·I	−0.097	0.0122	−0.794	0.0047
R^2	0.929	0.0005	0.964	0.0002

[a]Log 10 transformation used

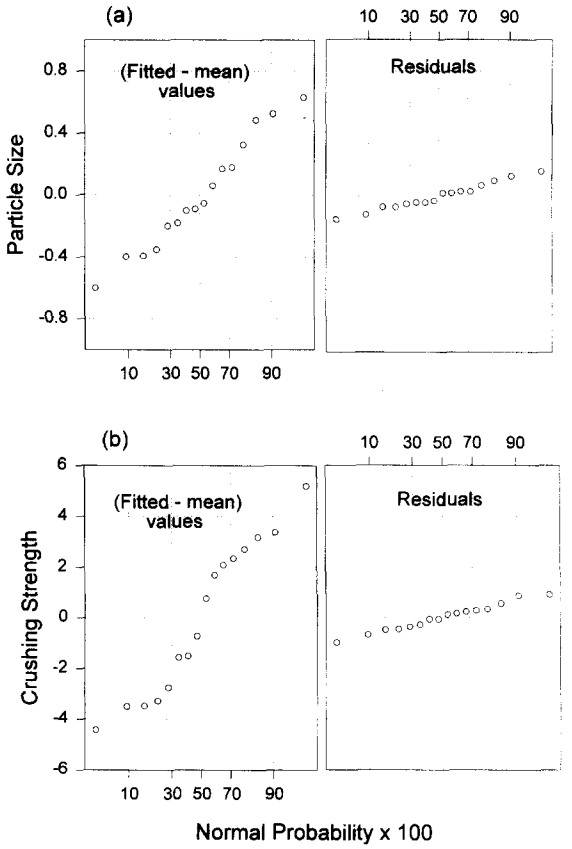

Fig. 5. An r–f spread plot compares the spreads of the residuals and the fitted values minus their mean for the fit to (a) particle size and (b) crushing strength.

variances (of the residuals) for the various factor combinations. On observing the dispersion interaction results for particle size (Table 4 a and Table 4b) the levels of P−, I+, B− would result in least variability. Alternatively the $\ln\acute{F}_i$ values can be plotted through normal probability and the values falling off a straight line are considered as important. The authors (Box and Meyer, 1986b) suggested the use of only large location effects in modeling the data and computing variances.

3.2. Crushing strength

Table 1 summarizes the crushing strength data. The methodology of data analysis for crushing strength is identical to that outlined for

particle size except for no transformation from the original metric. Again $y_{max}/y_{min} > 3$ suggesting the need for data transformation. However analysis in the original metric proved satisfactory. The PSE based critical value (0.662) suggests large main effects I, and B, and moderate effects of S, P·A, A·I, P·S, B·A, and A·S as being of importance. The objective was to maximize the crushing strength. On plotting two factor interactions (Fig. 4a and b) the settings of P−, B−, A−, S+, I+ would achieve maximal crushing strength. Table 3 summarizes the least square regression analysis. Despite a possible lack of fit as indicated in the r–f spread plot (Fig. 5b) the fitted function explains much of the variation. The unexplained variation could be accounted for by the unknown factors in compression and the resulting change in granular morphology not accounted for in the model. On graphing the residuals against the factors (Fig. 7) the conclusions are identical to the log (particle size) data. On observing the dispersion interactions (Fig. 8b, Table 4c and 4d) P−, A−, B−, S+ would result in least variability for the studied response. It is to be noted that no true dispersion interactions exist for P·A.

Table 4
Dispersion interaction tables for particle size (a & b) and crushing strength (c & d)

(a)			
+	0.002		0.015
P			
−	0.015		0.005
	−	I	+
(b)			
+	0.012		0.005
P			
−	0.003		0.017
	−	B	+
(c)			
+	0.154		0.235
P			
−	0.154		0.238
	−	A	+
(d)			
+	0.317		0.350
B			
−	0.157		0.120
	−	S	+

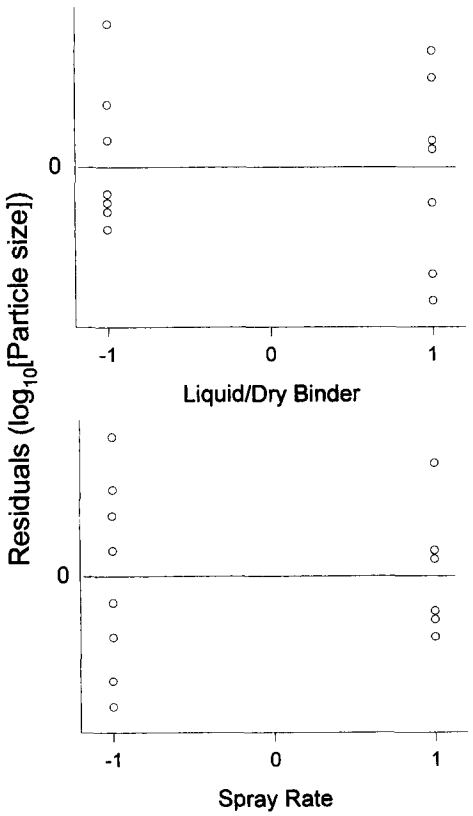

Fig. 6. Plot of residuals (particle size) vs factors.

The final optimal settings are a tradeoff on the required target response, interactions, and dispersion analysis. In order to confirm the settings for optimal response and least variability, experiments with the optimal settings (P−, B−, A−, S+, I+) and with predicted product variable settings (P−, B−, A−, S−, I+) were completed. The results (Table 5) confirm the predictions of maximizing response (crushing strength) and minimizing variability (spread in particle size and standard deveiation for crushing strength). It should be noted that only one predicted dispersion variable ('S') was transposed in the final experiments. The optimal run indicates that rapid spraying, and subsequent rapid povidone film formation due to the high

inlet temperature enhances intragranular binding resulting in higher compactibility. A low spray rate does result in variable spread for the particle size (Table 5). This could be due to the uneven wetting of the substrate due to the high inlet temperature setting as well as the area of the fluidized lactose exposed to the binder solution at low atomization pressure. The standard deviation of crushing strength is lower for the optimal run than the variable run.

In the addition of a liquid binder, the lactose particles are wet by the povidone solution and undergo certain surface dissolution. The binder, as well as the dissolved lactose, contribute to solid bond formation in the drying process. The surface film of a binder and the fused lactose particles contribute to increased compaction potential. The enhanced agglomeration of the lactose particles due to solubility characteristics could contribute to the sphericity of the granules as well (Wan and Kim, 1989). In the dry binder studies the lactose and povidone are wetted simultaneously. The wetted Povidone particles serve as adhesive nucleation cores for lactose particles. At the same time the lactose particles undergo surface dissolution. However lactose agglomerates by themselves are weak and in experiencing the attritional forces of the fluid-bed will break down. The presence of irregular binder film and brittle particulate bonds does suggest low compaction potential. However the granules could be less friable compared to those manufactured by liquid binder addition (Wan and Kim, 1989).

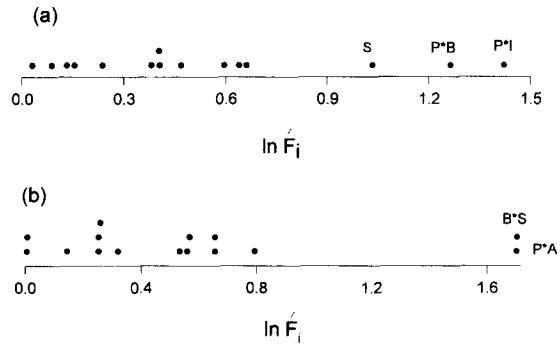

Fig. 8. Dot plot of dispersion for (a) particle size and (b) crushing strength.

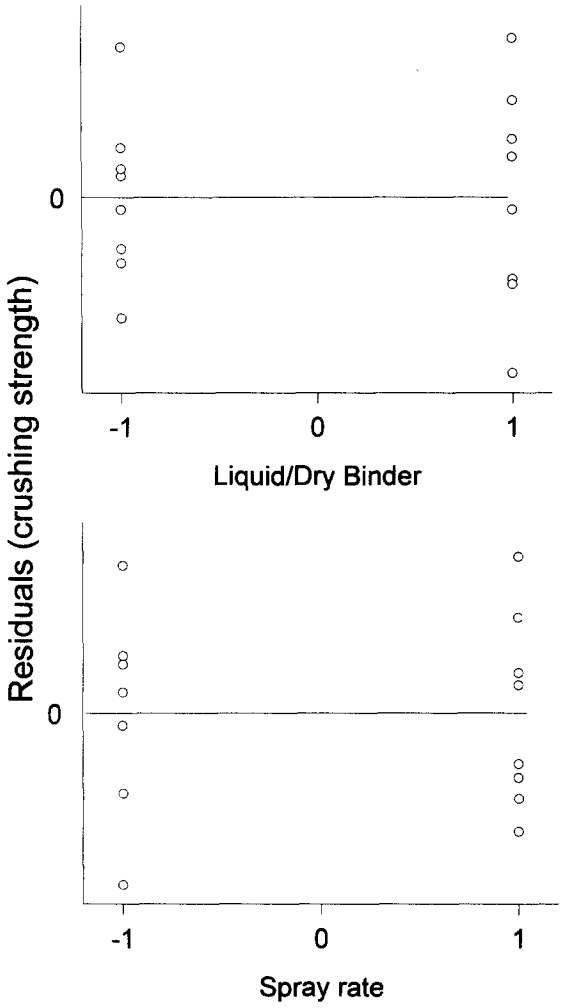

Fig. 7. Plot of residuals (crushing strength) vs factors.

4. Conclusions

There is a trend of employing systematic investigations to identify critical process and formulation variables in pharmaceutical product development through pilot and scale-up activities (Wehrle et al., 1993; Ogawa et al., 1994). In the recent collaborative agreement between

Table 5
Measured characteristics for otptimal and variable runs

Run no.	Optimal run[a]		C.S.[c] (kP)	Variable run[b]		C.S. (kP)
	Particle size			Particle size		
	Avg.[d] (μ)	Spread[e]		Avg. (μ)	Spread[e]	
1	293.75	178–443	13.51	93.75	71–206	8.77
2	231.50	150–395	13.15	76.00	46–160	6.67
3	285.00	202–425	14.02	102.00	53–319	7.08
Mean	270.08		13.56	90.58		7.51
SD[f]	33.69		0.44	13.29		1.11

[a]P−, B−, A−, S+, I+.
[b]P−, B−, A−, S−, I+.
[c]Crushing strength (compression force, 24.5 kN).
[d]Average particle size (calculated as d_{50} from log probability plotting).
[e]Calculated from log probability plotting (16–84%).
[f]Standard deviation

FDA's Office of Generic Drugs and the University of Maryland statistical designs are being employed to investigate scale-up parameters and selection of formulations for in-vivo studies (Rekhi et al., 1994). The need and usefulness in employing data analytical approaches in identifying location and dispersion effects is clear from the above study.

As in every process, variable effects in the fluid-bed are influenced by physico-chemical characteristics of the product. In the agglomeration of water soluble products such as lactose the spray rate primarily influences location and dispersion of particle size characteristics. The state of the binder influences the variability and crushing strength of the product. Careful considerations should be given to interaction and dispersion effects. The above conclusions are empirical and hence may hold only for the ranges of factor level studied. Single shot saturated design are not robust to bad values and are often inadequate to achieve optimization. The suggested approach is to perform sequential experimental designs. The next step would be to augment the design, include replicates, conduct a response surface design to characterize the factor spaces and process/product improvement and/or even include additional variables if required. Further studies concerning robust product development in the presence of environmental conditions (relative humidity and temperature) are ongoing.

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Appendix A: Example pseudso standard error calculation (Refer to Lenth, 1989 and Haaland and O'Connell, 1995)

For $\log_{10}$ (Particle size)

$s_o = 1.48 \cdot \text{median}|\beta_i|$

where β_i equals the coefficients obtained for a particular response

$s_o = 1.48 \cdot 0.0337 = 0.0498$

$1.25 \cdot 0.0498 = 0.0623$

$$\text{PSE based critical value} = 2.15 \cdot \text{median}|\beta_i||\beta_1| \leq 1.25 \cdot s_o = 2.15 \cdot 0.0299 = 0.0643$$

Appendix B: Example dispersion interaction calculation

Log_{10} [Particle Size]

No	P	B	A	S	I	PB	Residuals[a]	s^b_- (for 'P')	s_+ (for 'P')
1	1	1	1	−1	−1	1	0.03	−0.15	0.03
2	−1	1	−1	−1	−1	−1	−0.15	0.13	−0.07
3	−1	1	1	1	−1	−1	0.13	0.07	−0.12
4	−1	−1	1	−1	−1	1	0.07	−0.04	0.03
5	−1	−1	−1	1	−1	1	−0.04	−0.03	0.02
6	−1	−1	−1	−1	1	1	−0.03	−0.04	0.16
7	1	−1	−1	−1	−1	−1	−0.07	0.10	−0.07
8	1	1	−1	−1	1	1	−0.12	−0.05	0.02
9	−1	1	−1	1	1	−1	−0.04	0.093 (Variance)	0.086 (Variance)
10	−1	1	1	−1	1	−1	0.10		
11	1	−1	1	1	−1	−1	0.03		
12	1	1	−1	1	−1	1	0.02		
13	−1	−1	1	1	1	1	−0.05		
14	1	−1	1	−1	1	−1	0.16		
15	1	−1	−1	1	1	−1	−0.07		
16	1	1	1	1	1	1	0.02		
S−	0.093	0.081	0.053	0.109	0.087	0.111			
S+	0.086	0.098	0.067	0.065	0.093	0.059			
In F	−0.156	0.381	0.469	−1.034	0.133	−1.264			

[a]Residuals are obtained from the least square regression analysis (Predicted−Observed).

[b]Residuals corresponding to the levels (low or high) of a particular factor $F_i = s^2_{(i+)}/s^2_{(i-)}$ and subsequently ln $\acute{F}_i$ (absolute values) is plotted.

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