

*Original Research Article***OPTIMIZATION OF SPRAY DRYING PROCESS USING CENTRAL COMPOSITE DESIGN (CCD)****Sabyasachi Banerjee*, Sudesh Bhagvan Shetye, Samrat Vaidya, Rajesh Vooturi, P Srinivasa Rao, Sandeep Kachhwaha**

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ABSTRACT:

Spray-drying process was used for the development of drug complex with β -CD (β -cyclodextrin). The purpose of this research was to investigate the effects of formulation and process variables on the resulting powder characteristics in order to optimize them. A face-centered central composite design was applied to optimize the spray drying process on a pilot scale (15 liters). Spray drying process variables investigated were: inlet temperature, spray rate and batch size. Based on the process variables moisture content, impurities and batch yield after the spray drying were determined. Multiple regression modeling was used to optimize the spray drying process parameters and additional experiments confirmed that these models were valid. Other powder properties like Hausner ratio and Carr's index were also evaluated at the optimal operation conditions.

Keywords: Spray drying, Process variables, Powder properties

Correspondence*: Sabyasachi Banerjee Scientist CPS –Formulations Dr. Reddy's Laboratories Limited FTO-II, Bachupally Hyderabad, Andhra Pradesh, India. E.: sabyasachib@drreddys.com; C.: +91 9676773153; F.: 91 40 44642512**INTRODUCTION:**

Spray drying technique (SDT) is used to increase bioavailability of poorly soluble APIs. Through proper formulation and selection of excipients, the SDT is applicable to compounds with a broad range of physiochemical properties [1]. This technique transforms liquid feed into dry powder in a one step, continuous particle processing operation and can be applied to a wide variety of materials. In addition, formulation processes including encapsulation [2], complexes formation [3] and even polymerization [4] can be accomplished in a single step. This technique is widely used in the pharmaceutical field since it allows the preparation of dry powders with specific characteristics such as particle size and shape [5]. The model drug candidate (Meloxicam) selected is a poorly soluble compound with low systemic exposure when administered orally. The therapeutic efficacy of (Meloxicam) is greatly hampered due to its poor bioavailability and low aqueous solubility. One of the approaches to overcome these problems is to use cyclodextrins (CDs) as drug carriers. These oligosaccharides are most interesting because they form drug complexes in both the solution and solid state, wherein either the whole guest, or part of it (commonly the less polar part), is sequestered inside the hydrophobic cavity [6]. In the present study to overcome poor dissolution and oral bioavailability, a drug complex with β -CD (β -cyclodextrin) was developed by SDT. This process consists of three step: (a) atomization. (b) Dehydration and (c) powder collection. Practically the liquid feed is atomized by an atomizer

creating a spray of fine droplets into a chamber of heated air from which the solvent quickly evaporates resulting in dried particles [7]. It exhibits advantages like the rapidity of the process, the possibility of modulate the physicochemical characteristics of the resulting powders, which could be beneficial for the scale up potential. Compared to freeze-drying spray-drying takes less time and is cheaper process. Nevertheless, spray-drying requires particular attention in the process control because of limitations and the high number of parameters. These limitations include problems with efficient particle collection and the potential instability of materials sensitive to high temperatures. Each process variable is critical and this explains some of the difficulties encountered in spray-drying process optimization involves the evaluation of parameters concerning both spray-dryer and feed formulation [8-9].

Till date, the impact of the process variables on the spray-dryer outcomes and on the prepared products characteristics is still an open question that should be addressed.

Design of experiments (DOE) is a well-established method for identifying important parameters in a process and optimizing the parameters with respect to certain specifications [10]. Several studies have utilized DOE on the spray drying process [11, 12, 13], where the effect of process parameters on various particle characteristics have been studied. However, these studies have all focused on single prediction equations obtained from the statistical analysis and have not utilized multivariate data analysis. The present study focuses on a deeper understanding of the SDT of (Meloxicam) by using Central Composite Design (CCD).

In this paper, we presented a more extensive investigation of this application using experimental designs. The major goal was the study of the relationship between the formulation and process variables and their influence on the resulting powder characteristics. Process variables like (inlet temperature, spray rate, nozzle size) which could influence the spray dried powder properties were studied through an experimental design i.e CCD. The most widely studied spray dried powder properties in the literature are moisture content, Bulk and tap density (Hausner ratio and Carr's index).

SDT process was optimized on pilot scale by developing an empirical model. In view of the small scale results, the following variables were investigated in the design: Inlet temperature, spray rate, and batch size. The nozzle size and nozzle pressure were kept constant during the experiments and the droplet size of the spray solution depended mainly on the spray rate. The process was optimized with the target of increasing the product performance and batch yield.

Other spray dried powder properties [Moisture content, Hausner ratio and Carr's index] were also considered here in order to evaluate the quality of powder.

MATERIALS AND METHODS

Materials

The model drug (Meloxicam USP) was procured from Dr. Reddy's Laboratories Ltd. Hydroxy propyl beta cyclodextrin was purchased from Signet Laboratories (Dedham, MA), Pearlitol SD 200 was purchased from Signet chemical corporation, Mumbai. L- Arginine was purchased from Aji Nomoto co., INC (Kanagawa, Japan) and SLS from Signet chemical corporation, (Vanguard). All other chemicals were of analytical grade.

Preparation of Spray Drying Solution

Spray Drying Process

The spray dried powder was produced in the Pilot Spray Dryer (PSD-01, Lab-India). The spray solution consists of model drug (Meloxicam), 8.6% w/w, cyclodextrin (64.68% w/w), Mannitol (8.6% w/w), SLS (0.86% w/w) and L-Arginine (17.24% w/w). The ingredients were added to specified amount of water and stirred using a magnetic stirrer until visually clear solution is produced. The solution is then filtered using 0.45 μ membrane filter and filtered solution is placed in the spray drier feed tank. The spraying process was carried out according to the settings of the process variables of the specific run. Spraying was continued until all the solution was used and after wards 0.5 liters of water was sprayed in order to rinse the pipes. After completion of spray drying cycle, samples were collected from top, middle and bottom of the powder collected and stored in a airtight plastic bag for the determination of the powder properties.

Physical and chemical characteristics of the spray dried powder:

Moisture content:

The residual moisture content of the spray-dried powders was measured by Karl Fisher titration in dry methanol using a DL38 titrator (Mettler-Toledo, Greifensee, Switzerland). Sample masses were approximately 30 mg and Hydranal composite 5 (Riedel-de-Haen) was used as the titration reagent. Measurements were performed in triplicate.

Particle size:

The particle size distribution was measured according to the method described by Rambali et al. [14]. A set of sieves (60, 80, 100, 140, 200 and 230) in combination with the Retsch VE 1000 sieve shaker (Retsch, Haan, Germany) were used for this analysis. A 100-g spray dried powder sample was transferred to the pre-weighed sieves and shaken an amplitude of 1.5mm for 5 min. The sieves were then re-weighed to determine the weight fraction of granules retained on each sieve. These weights were converted in mass percentage. The geometric mean of particle size was calculated from these mass fractions.

Hausner index:

The Hausner ratio is an indication of the compressibility of a powder. It is calculated by the formula $H = \rho_T / \rho_B$, where ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped density of the powder. The Hausner ratio is frequently used as an indication of the flowability of a powder. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Carr's index

The Carr's index is an indication of the compressibility of a powder. It is calculated by the formula $C = 100 * (V_B - V_T) / V_B$, where V_B is the freely settled volume of a given mass of powder, and V_T is the tapped density of the same mass of powder. It can also be expressed as $C = 100 * (\rho_B - \rho_T) / \rho_B$, where ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped density of the powder.

The Carr index is frequently used as an indication of the flowability of a powder. A Carr index greater than 25% is considered to be an indication of poor flowability, and below 15%, of good flowability [15].

Batch Yield:

The Percentage batch yield is calculated by subtracting the total weight of output material after spray drying process from the total weight of the input material taken for the batch manufacturing.

Assay:

Drug content is estimated by HP 1100 (Agilent USA) liquid chromatography system, controlled by HP chem station software. It was equipped with an isocratic pump, an auto sampler, a column thermostat and UV detector. The mobile phase consists of a 70% 0.025M phosphate buffer with pH adjusted to 6.8 with potassium hydroxide and 30% acetonitrile. The mobile phase was prepared daily and degassed by sonication under reduced pressure and filtered through a 0.45 μ m membrane filter. The column was thermostated at 37° C. The mobile phase was delivered isocratically with a flow rate of 1.0 mL per minute, the injection volume was 10 μ L and the wave length for UV detection was 257nm. For chromatographic separation, Water symmetry C18, 250X4.6 mm, 5 μ column was used. The total analysis time was 15 minutes. The column temperature was maintained at 25° C.

Impurities by HPLC:

Drug related impurities are analyzed by HP 1100 (Agilent USA) liquid chromatography system, controlled by HP chem. station software. It was equipped with an isocratic pump, an auto sampler, a column thermostat and UV detector. The mobile phase consists of a 82.5 % 0.025M phosphate buffer with pH adjusted to 6.8 with potassium hydroxide and 17.5 % acetonitrile. The mobile phase was prepared daily and degassed by sonication under reduced pressure and filtered through a 0.45 μ m membrane filter. The column was thermostated at 37° C. The mobile phase was delivered isocratically with a flow rate of 1.2 mL per minute, the injection volume was 10 μ L and the wave length for UV detection was 257nm. For chromatographic separation, Water symmetry C18, 250X4.6 mm, 5 μ column was used. The total analysis time was 120 minutes. The column temperature was maintained at 25° C.

RESULTS AND DISCUSSION**Design Development:**

For the optimization of the spray drying process a face-centered central composite design (FcCCD) was applied. The practical reasons it was preferred the more usual spherical central composite design, because the axial points yield variable combinations, that would lie out side the equipment performance. CCD offers an advantage over other Response Surface Methods (RSM) as it is a complete block design. Block design is advantageous when all of the experiments cannot be carried out in one day or with one batch of material. One of the commendable attributes of the Central Composite Design is that its structure lends itself to sequential designs with reasonable amount of information for testing lack of fit. The factorial part of the design can be run first to determine if an optimum is within the design space. This part allows the estimation of linear and interaction terms. Center runs provide information about existence of curvature in the system and the axial points allow the efficient estimation of pure quadratic terms.

The Face centered Central Composite Design consisted of 20 runs. The runs were randomized in order to exclude block effects. The settings of the process variables are listed in Table. 1.

Table 1: Process variable and setting in the face centered central composite design.

Process variable	Level		
	Low	Central	High
Inlet temperature	150	200	250
Spray rate	15	30	45
Batch size	5	10	15

In table 2 the design matrix is displayed. Response Surface Modeling was used in order to find those variable combinations that give optimum results.

Design Matrix:

The design matrix is prepared based on the 3 variable factors and 8 responses using the statistical software program **Design Expert (version No. 7.3.1) Face Centered Central Composite Design** which consisted of 20 experiments (14 non center and 6 centre points; axial points (α value) are considered as +1 and -1). Face centered CCD is preferred as the region of interest and region of operability is same and is a cuboidal region. Face centered CCD is particularly useful when one can not experiment outside the cube though experimentation at the extremes in the region of interest is permissible. The details of experiments are mentioned in Table 2.

Factors and Responses

Responses were measured for each experiment and the results are summarized in Table 2

Table 2: Summary of Factors and Responses

Run	Variable Factors			Responses							
	Inlet Air Temperature	Spray Rate	Batch Size	Assay	Impurity -I	Impurity-II	Indi. max	Total impurities	Moisture Content	Hausner ration	Carr's index
Units	°C	mL/Min	Liters	% Area	% Area	% Area	% Area	% Area	%w/w		%
1	250±5	45±1	5	93.05	0.68	0.12	0.29	0.84	4.96	0.63	15.41
2	150±5	45±1	5	90.38	3.41	1.18	2.54	7.04	4.17	0.61	20.36
3	200±5	30±1	10	91.18	1.52	0.18	0.34	1.31	4.27	0.63	15.41
4	200±5	30±1	10	91.6	0.61	0.4	0.34	1.48	3.54	0.61	15.35
5	200±5	30±1	5	90.07	1.67	0.3	0.34	1.40	3.86	0.67	16.50
6	150±5	45±1	15	92.26	1.89	1.02	0.31	2.18	3.65	0.58	23.28
7	150±5	30±1	10	91.11	1.05	0.07	0.27	0.91	5.36	0.63	23.40
8	150±5	15±1	5	93.32	1.51	0.41	0.27	1.43	5.16	0.76	30.69
9	250±5	30±1	10	97.47	1.9	0.16	0.49	1.42	5.42	0.68	15.53
10	200±5	15±1	10	96.35	1.92	0.85	0.49	2.29	5.11	0.49	14.94
11	250±5	45±1	15	95.18	1.52	0.8	0.46	2.30	4.72	0.79	24.73
12	200±5	30±1	10	91.56	1.03	0.53	0.3	1.92	4.83	0.67	16.50
13	200±5	30±1	10	96.41	1.45	0.67	0.44	2.26	4.16	0.68	15.53
14	250±5	15±1	5	97.26	1.45	0.68	0.44	2.26	4.03	0.74	33.66
15	200±5	45±1	10	95.2	1.44	0.67	0.44	2.25	3.74	0.65	15.47
16	250±5	15±1	15	93.24	0.55	0.59	0.40	1.97	3.86	0.63	13.40
17	200±5	30±1	10	95.04	1.04	0.58	0.39	1.95	3.8	0.62	14.38
18	150±5	15±1	15	93.63	1.03	0.58	0.39	1.95	3.83	0.52	15.06
19	200±5	30±1	10	96.23	1.04	0.53	0.35	1.76	3.7	0.65	15.47
20	200±5	30±1	15	95.93	1.07	0.54	0.36	1.79	3.58	0.63	15.41

Statistical Data Analysis

Experimental data on process variables and observed responses were analyzed statistically using Design Expert[®] software to build statistical models for each response. ANOVA was carried out to the data in order to identify / study the significant terms in the model.

A. Assay

Regression analysis of the data was carried out and a full quadratic model was fitted. ANOVA was carried out to study the significance of the terms of the model. The polynomial equation obtained is as follows:

$$Y = 90.82 + 0.03 X_1 + 0.79X_2 - 0.67 X_3 + 5.18(E-004) X_1X_2 + 3.32(E-003) X_1X_3 + 4.58(E-003) X_2X_3 - 2.18X_1^2 - 0.01X_2^2 - 5.18X_3^2 \quad (\text{Adjusted } R^2 = 0.4619)$$

Since the full model contains many insignificant terms, a partial quadratic model (reduced model) was fitted using regression analysis by eliminating some of the insignificant terms as explained earlier. The final partial quadratic equation obtained is as follows;

$$Y = 87.24 - 0.03 X_1 + 0.97 X_2 - 0.63 X_3 + 3.32(E-003) X_1X_3 - 0.016X_2^2 \quad (\text{Adjusted } R^2 = 0.5875)$$

The results from full and partial quadratic model are summarized in Table 3.

Table 3: Comparison of Full and Partial Quadratic Model

Source	Full Model		Partial Model	
	F Value	P Value	F Value	P Value
Model	2.81	0.0614	6.41	0.0027
X ₁	0.035	0.8558	0.045	0.8344
X ₂	0.15	0.7026	0.20	0.6604
X ₃	0.064	0.8050	0.084	0.7764
X ₁ *X ₂	0.40	0.5430	Eliminated	Eliminated
X ₁ *X ₃	1.81	0.2079	2.36	0.1464
X ₂ *X ₃	0.31	0.5899	Eliminated	Eliminated
X ₁ ²	2.683(E-003)	0.9597	Eliminated	Eliminated
X ₂ ²	11.65	0.0066	29.36	< 0.0001
X ₃ ²	0.015	0.9045	Eliminated	Eliminated
Predicted R ²	-0.4513		0.5875	
Adjusted R ²	0.4619		0.4033	
Std. Dev.	1.75		1.53	

Where X₁ is Inlet Temperature, X₂ is Spray rate and X₃ is Batch size.

Interpretations Based on Partial Quadratic Model:

- Partial quadratic model for efficiency explains better than full model.

- The model F value of 6.41 and P value of 0.0027 implies model is statistically significant relative to noise and hence can be used for further exploration and prediction.
- Interaction term of X_1 and X_3 is not significant ($P=0.1464$), this implies that interaction of inlet temperature and Batch size is not significantly affecting the Assay.
- Square term of spray rate (X_2^2) is the significant ($P<0.0001$) term indicating there is non-linear relationship between assay and spray rate.
- Adjusted R square value 0.4033 implies reasonable predictability strength of the model, thus model is improved after reduction.

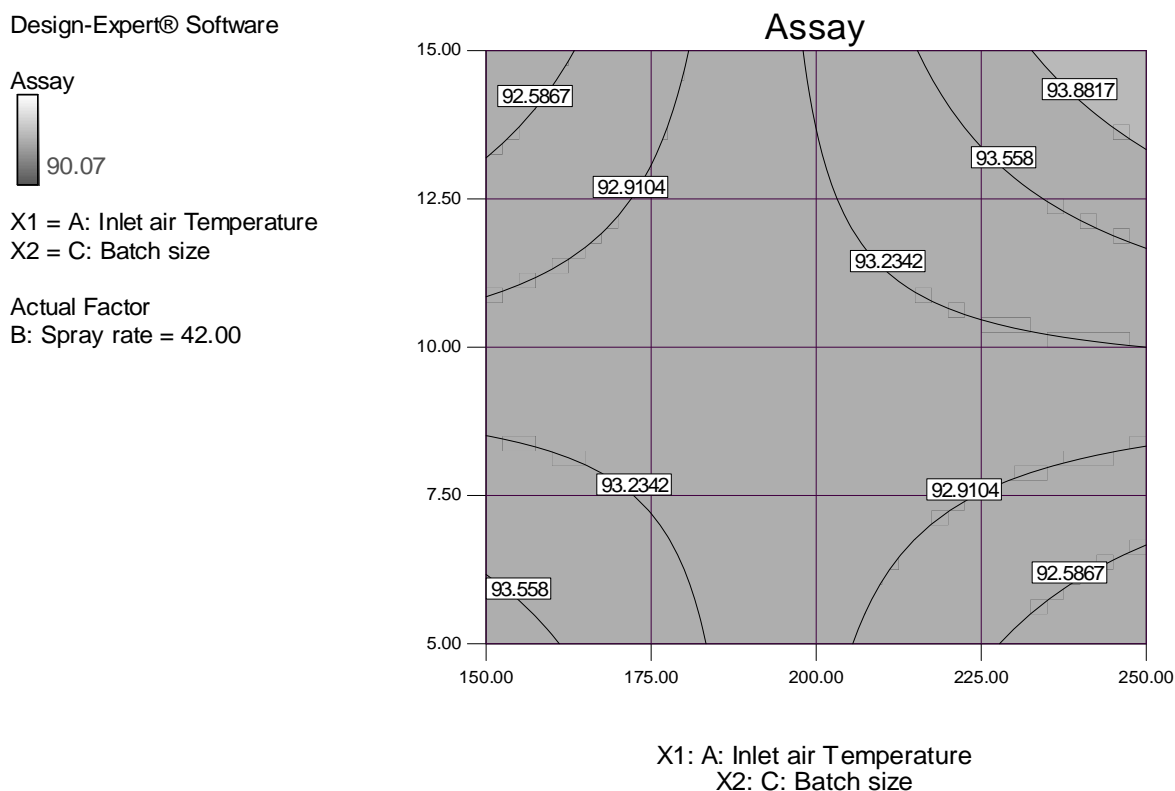


Figure 1: Typical contour plot showing effect of inlet temperature and spray rate on Assay

B. Moisture content

Regression analysis of the data was carried out and a full quadratic model was fitted.

ANOVA was carried out to study the significance of the terms of the model.

The polynomial equation obtained is as follows:

$$Y = 17.72 - 0.12 X_1 - 0.11 X_2 + 0.07 X_3 + 1.66 (E-005) X_1 X_2 + 5.55 (E-004) X_1 X_3 + 7.21 (E-003) X_2 X_3 + 2.76 (E-004) X_1^2 + 8.94 (E-004) X_2^2 - 0.01 X_3^2$$

(Adjusted $R^2 = 0.4176$)

Since the full model contains many insignificant terms, a partial quadratic model (reduced model) was fitted using regression analysis by eliminating some of the insignificant terms as explained earlier.

The final partial quadratic equation obtained is as follows;

$$Y = 18.38 - 0.132 X_1 - 0.060 X_2 + 0.014 X_3 + 5.55000E-004 X_1 X_3 + 7.216670E-003 X_2 X_3 + 3.06750E-004 X_1^2 - 0.016 X_3^2 \quad (\text{Adjusted } R^2 = 0.4920)$$

The results from full and partial quadratic model are summarized in Table 4.

Table 4: Comparison of Full and Partial Quadratic Model

Source	Full Model		Partial Model	
	F Value	P Value	F Value	P Value
Model	1.849365	0.2898	3.63	0.0245
X ₁	0.950121	0.3849	2.40	0.1474
X ₂	0.106633	0.7604	1.55	0.2371
X ₃	0.204545	0.6745	0.44	0.5194
X ₁ *X ₂	0.380087	0.5709	0.74	0.4077
X ₁ *X ₃	5.744537	0.0746	Eliminated	Eliminated
X ₂ *X ₃	0.953984	0.3840	11.20	0.0058
X ₁ ²	0.094694	0.7736	9.00	0.0111
X ₂ ²	7.522228	0.0518	Eliminated	Eliminated
X ₃ ²	0.075449	0.7972	2.49	0.1409
Predicted R ²	-0.3141		0.3244	
Adjusted R ²	0.4176		0.4920	
Std. Dev.	0.49		0.46	

Where X₁ is Inlet Temperature, X₂ is Spray rate and X₃ is Batch size.

Interpretations Based on Partial Quadratic Model:

- Partial quadratic model for efficiency explains better than full model.
- The model F value of 3.63 and P value of 0.0245 implies model is statistically significant relative to noise and hence can be used for further exploration and prediction.
- Interaction term of X₂ and X₃ is the significant (P= 0.0058) term, this implies that interaction of spray rate and batch size is significantly affecting moisture content.
- Square term of spray rate (X₁²) is the significant (P =0.0111) term indicating there is non-linear relationship between moisture content and spray rate.
- Adjusted R square value 0.4920 for the model implies reasonable predictability strength of the model, thus model is improved after reduction.

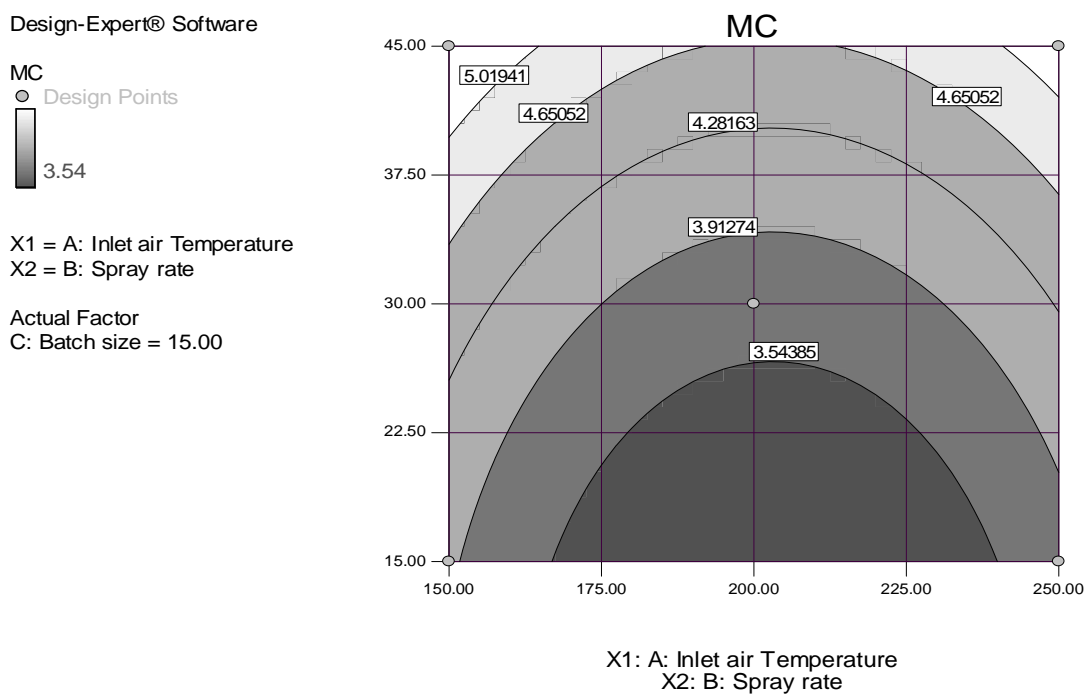


Figure 2: Typical contour plot showing effect of inlet temperature and spray rate on moisture content

C. Impurity-I

Regression analysis of the data was carried out and a full quadratic model was fitted.

ANOVA was carried out to identify the significance of the terms of the model. The polynomial equation obtained is as follows:

$$Y = -2.96 + 0.027 X_1 + 0.074 X_2 + 0.064 X_3 - 5.66(E-004) X_1X_2 - 5.70 (E-004) + 1.60 X_1X_3 (E-003) \quad (\text{Adjusted } R^2 = 0.2257)$$

Since the full model contains many insignificant terms, a partial quadratic model (reduced model) was fitted using regression analysis by eliminating some of the insignificant terms.

The final partial quadratic equation obtained is as follows;

$$Y = 4.72 - 0.0506 X_1 + 0.090 X_2 - 200000E-003X_3 - 5.66667E-004X_1X_2 + 1.81600E-004X^2 \quad (\text{Adjusted } R^2 = 0.4163)$$

The results from full and partial quadratic model are summarized in Table 5.

Table 5: Comparison of Full and Partial Quadratic Model

Source	Full Model		Partial Model	
	F Value	P Value	F Value	P Value
Model	1.76	0.1957	3.71	0.0239
X ₁	2.17	0.1712	2.74	0.1202
X ₂	4.07	0.0712	5.13	0.0399
X ₃	3.422E-003	0.9545	4.313E-003	0.9486
X ₁ *X ₂	4.95	0.0504	6.23	0.0256
X ₁ *X ₃	0.56	0.4731	Eliminated	Eliminated
X ₂ *X ₃	0.39	0.5441	Eliminated	Eliminated
X ₁ ²	2.40	0.1524	4.44	0.0535
X ₂ ²	0.16	0.6984	Eliminated	Eliminated
X ₃ ²	0.019	0.8929	Eliminated	Eliminated
Predicted R ²	-5.3323		-0.5004	
Adjusted R ²	0.2645		0.4163	
Std. Dev.	0.54		0.48	

Where X₁ is Inlet Temperature, X₂ is Spray rate and X₃ is Batch size.

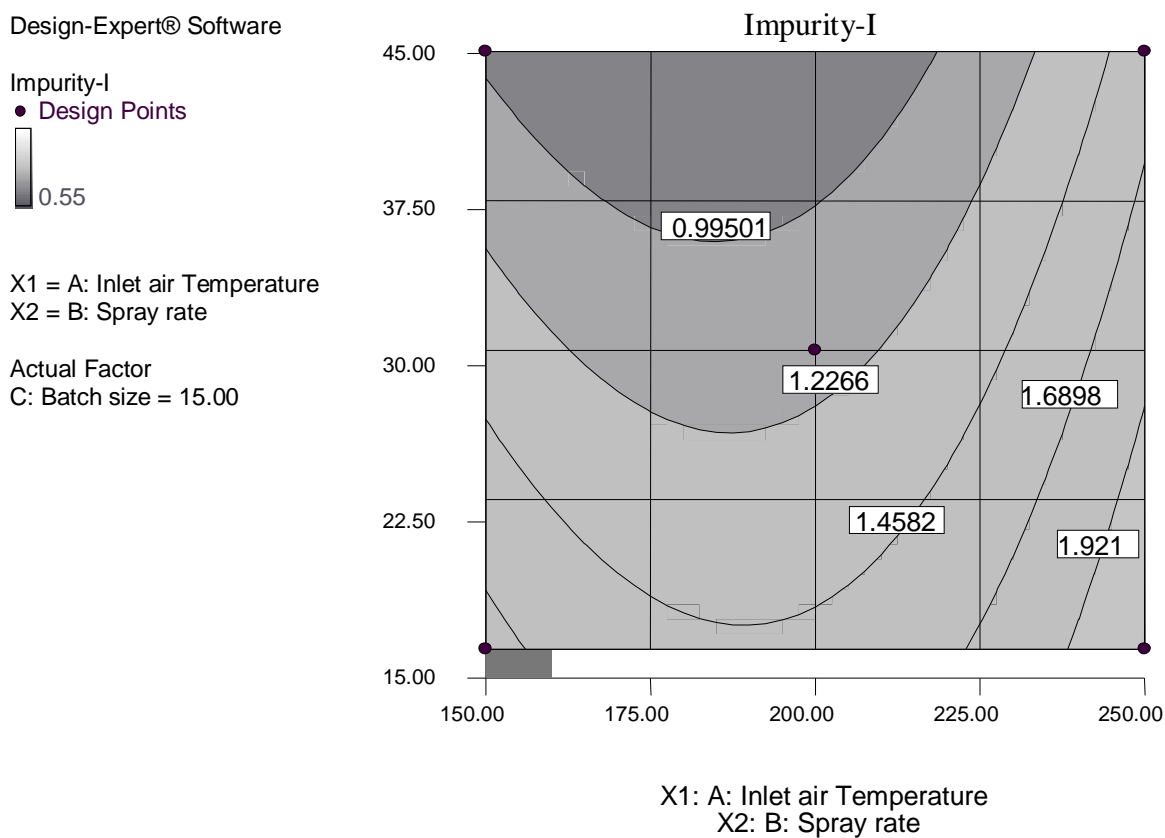


Figure 3: Typical contour plot showing effect of inlet temperature and spray rate on impurity-I

Interpretations Based on Partial Quadratic Model:

- Partial quadratic model for efficiency explains better than full model.
- The model F value of 3.71 and P value of 0.0239 implies model is statistically significant relative to noise and hence can be used for further exploration and prediction.
- Interaction term of X_1 and X_2 is the significant ($P = 0.0256$) term, this implies that interaction of inlet temperature and spray rate is significantly affecting impurity-I.
- Square term of inlet temperature (X_1^2) is the significant ($P = 0.0535$) term indicating there is non-linear relationship between Impurity-I and inlet temperature
- Adeq precision is 6.942. The value gives a measure of signal to noise ratio and a ratio greater than 4 is desirable hence this model can be used to navigate the design space
- Adjusted R square value 0.4163 implies reasonable predictability strength of the model, thus model is improved after reduction.

D. Impurity-II

Regression analysis of the data was carried out and a full quadratic model was fitted.

ANOVA was carried out to identify the significance of the terms of the model. The polynomial equation obtained is as follows:

$$Y = -4.17 + 0.038X_1 + 0.029 X_2 + 0.016 X_3 - 2.033(E-004) X_1X_2 - 1.10(E-004) X_1X_3 - 2.00 X_2X_3 - 6.29(E-005)X_1^2 + 1.21(E-005) X_2^2 + 5.09 (E-004)X_3^2 \quad (\text{Adjusted } R^2 = 0.9175)$$

Since the full model contains insignificant terms, a partial quadratic model (reduced model) was fitted using regression analysis by eliminating some of the insignificant terms. The final partial quadratic equation obtained is as follows;

$$Y = -3.80 + 0.035 X_1 + 0.028 X_2 - 1.40000E-003 X_3 - 2.03333E-004 X_1X_2 - 5.92000E-005 X_1^2 \quad (\text{Adjusted } R^2 = 0.9340)$$

The results from full and partial quadratic model are summarized in Table 6.

Interpretations Based on Partial Quadratic Model:

- Partial quadratic model for efficiency explains better than full model.
- The model F value of 54.78 and P value of <0.0001 implies model is statistically significant relative to noise and hence can be used for further exploration and prediction.
- Interaction term of X_1 and X_2 is significant ($P = 0.0001$) term, this implies that interaction of inlet temperature and spray rate is significantly affecting level of impurity-II.
- Square term of inlet temperature (X_1^2) is the significant ($P < 0.0006$) term indicating there is non-linear relationship between impurity-II and inlet temperature.
- Adjusted R square value 0.9340 implies high predictability strength of the model, thus model is improved after reduction.

E. Total Impurities

Regression analysis of the data was carried out and a full quadratic model was fitted.

ANOVA was carried out to identify the significance of the terms of the model. The polynomial equation obtained is as follows:

$$Y = -10.37 + 0.103 X_1 + 0.082 X_2 + 0.0435 X_3 - 1.04833E-003 X_1 X_2 - 2.53500E003 X_1 X_3 + 6.41667E-003 X_2 X_3 - 7.40000E-005 X_1^2 + 3.11111E-004 X_2^2 + 8.80000E-003 X_3^2$$

(Adjusted $R^2 = 0.7032$)

Since the full model contains many insignificant terms, a partial quadratic model (reduced model) was fitted using regression analysis by eliminating some of the insignificant terms using regression analysis. The final partial quadratic equation obtained is as follows;

$$Y = -10.13 + 0.073 X_1 + 0.14 X_2 + 0.41 X_3 - 1.04833E-003 X_1 X_2 - 2.53500E-003 X_1 X_3 + 4.04444E-004 X^2$$

(Adjusted $R^2 = 0.6155$)

The results from full and partial quadratic model are summarized in Table 7.

Table 6: Comparison of Full and Partial Quadratic Model

Source	Full Model		Partial Model	
	F Value	P Value	F Value	P Value
Model	24.48	<0.0001	54.78	<0.0001
X ₁	129.85	<0.0001	162.33	<0.0001
X ₂	47.36	<0.0001	59.21	<0.0001
X ₃	0.069	0.7977	0.087	0.7728
X ₁ *X ₂	26.31	0.0004	32.90	<0.0001
X ₁ *X ₃	0.86	0.3767	Eliminated	Eliminated
X ₂ *X ₃	0.25	0.6248	Eliminated	Eliminated
X ₁ ²	9.62	0.0112	19.36	0.0006
X ₂ ²	2.89	0.9582	Eliminated	Eliminated
X ₃ ²	0.063	0.8069	Eliminated	Eliminated
Predicted R ²	0.5053		0.8627	
Adjusted R ²	0.9175		0.9340	
Std. Dev.	0.084		0.075	

Where X₁ is Inlet Temperature, X₂ is Spray rate and X₃ is Batch size.

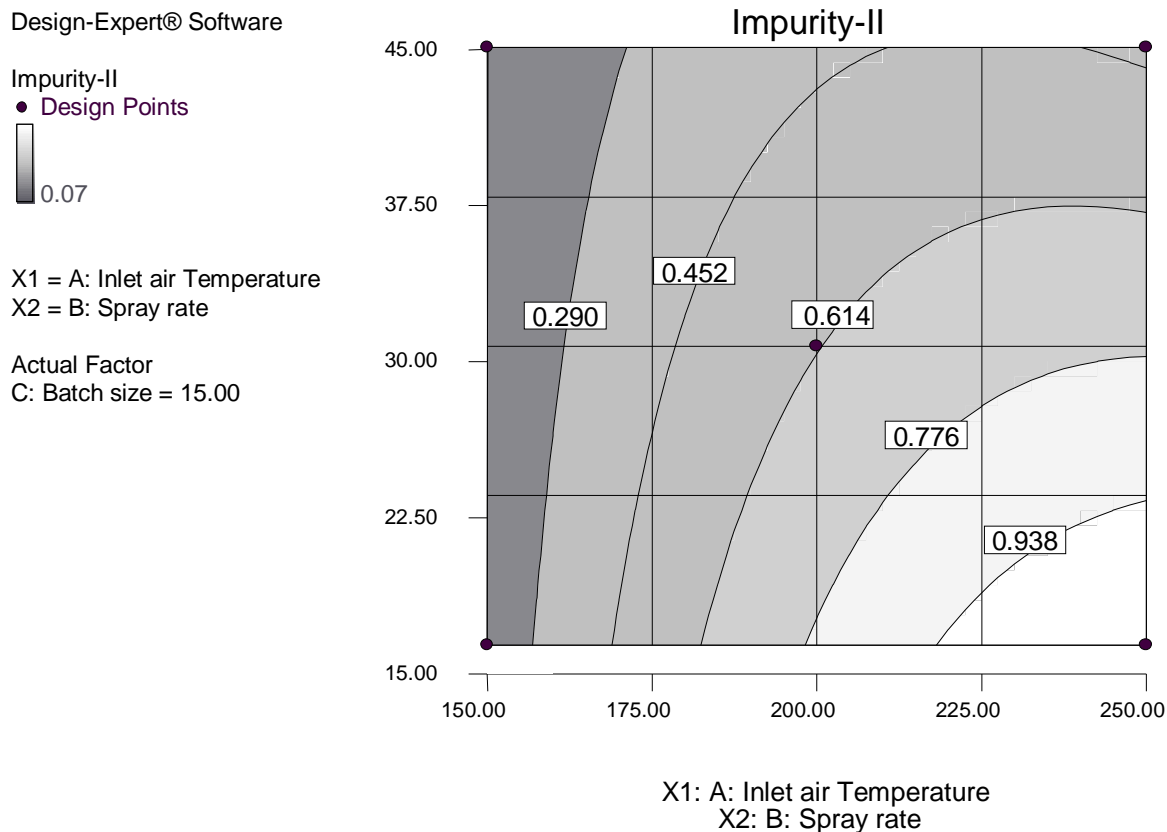


Figure 4: Typical contour plot showing effect of inlet temperature and spray rate on Impurity- II

Table 7: Comparison of Full and Partial Quadratic Model

Source	Full Model		Partial Model	
	F Value	P Value	F Value	P Value
Model	1.849365	0.2898	6.07	0.0032
X ₁	0.950121	0.3849	11.93	0.0043
X ₂	0.106633	0.7604	7.37	0.0177
X ₃	0.204545	0.6745	3.69	0.0769
X ₁ *X ₂	0.380087	0.5709	8.09	0.0138
X ₁ *X ₃	5.744537	0.0746	5.26	0.0392
X ₂ *X ₃	0.953984	0.3840	Eliminated	Eliminated
X ₁ ²	0.094694	0.7736	Eliminated	Eliminated
X ₂ ²	7.522228	0.0518	0.068	0.7987
X ₃ ²	0.075449	0.7972	Eliminated	Eliminated
Predicted R ²	-1.0395		-0.7933	
Adjusted R ²	0.7032		0.6155	
Std. Dev.	0.69		0.78	

Where X₁ is Inlet Temperature, X₂ is Spray rate and X₃ is Batch size.

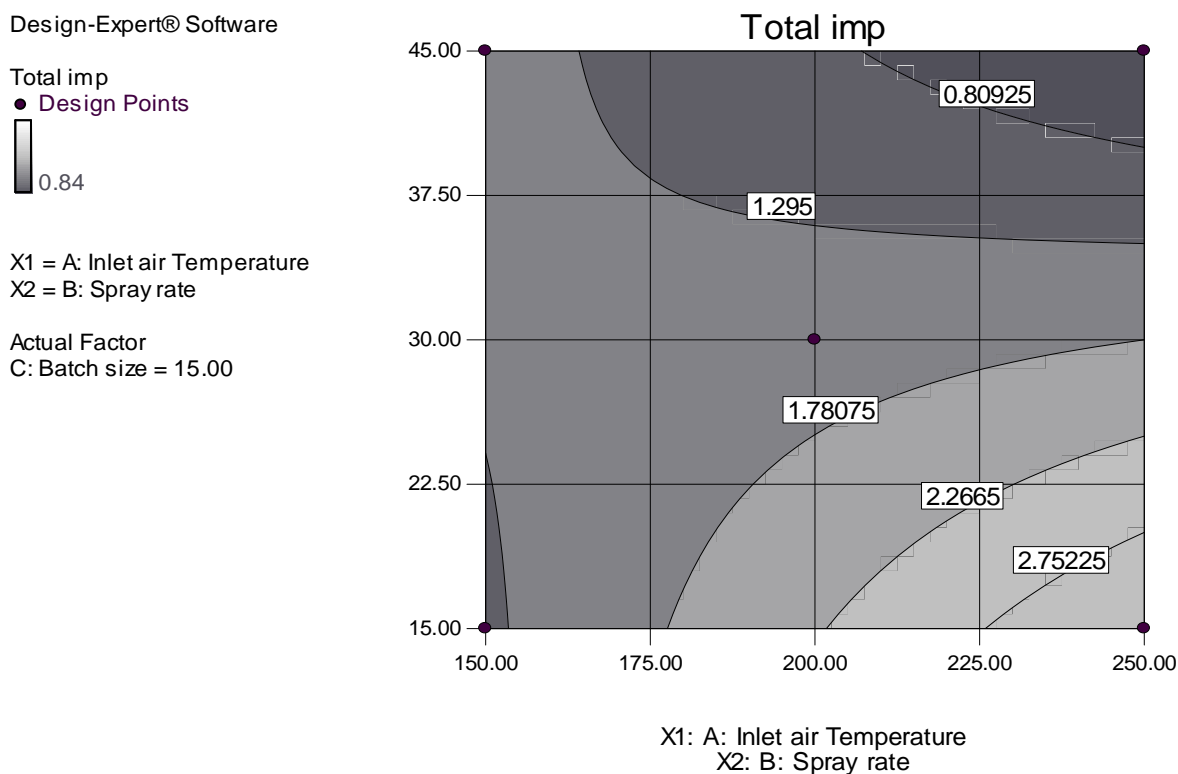


Figure 5: Typical contour plot showing effect of inlet temperature and spray rate on total impurities

Interpretations Based on Partial Quadratic Model:

- Partial quadratic model for efficiency explains better than full model.
- The model F value of 6.07 and P value of 0.0032 implies model is statistically significant relative to noise and hence can be used for further exploration and prediction.
- Interaction term of X_1 and X_2 is the significant ($P = 0.0138$) term, this implies that interaction of inlet temperature and spray rate is significantly affecting total impurities.
- Interaction term of X_1 and X_3 is significant ($P = 0.0392$) term, this implies that interaction of inlet temperature and batch size is significantly affecting total impurities.
- Adeq precision is 11.097. The value gives a measure of signal to noise ratio and a ratio greater than 4 is desirable hence this model can be used to navigate the design space.
- Adjusted R square value 0.6155 implies reasonable predictability strength of the model, thus model is improved after reduction.

F. Yield

Regression analysis of the data was carried out and a full quadratic model was fitted.

ANOVA was carried out to identify the significance of the terms of the model.

The polynomial equation obtained is as follows:

$$Y = -55.33 + 1.24 X_1 - 1.823 X_2 + 6.42 X_3 + 3.42 X_1 X_2 + 1.24 X_1 X_3 - 0.022 X_2 X_3 - 3.38 X_1^2 + 0.025 X_2^2 - 0.22 X_3^2 \quad (\text{Adjusted } R^2 = 0.8849)$$

Since the full model contains some insignificant terms, a partial quadratic model (reduced model) was fitted using regression analysis by eliminating some of the insignificant terms.

The final partial quadratic equation obtained is as follows;

$$Y = -51.21 + 1.26 X_1 - 2.04 X_2 + 6.01 X_3 + 3.4200E-003 X_1 X_2 - 3.38127E-003 X_1^2 + 0.025 X_2^2 - 0.22 X_3^2 \quad (\text{Adjusted } R^2 = 0.8849)$$

The results from full and partial quadratic model are summarized in Table 8.

Table 8: Comparison of Full and Partial Quadratic Model

Source	Full Model		Partial Model	
	F Value	P Value	F Value	P Value
Model	17.23	<0.0001	20.20	<0.0001
X ₁	0.36	0.5641	0.33	0.5760
X ₂	5.96	0.0348	5.53	0.0366
X ₃	76.97	<0.0001	71.51	<0.0001
X ₁ *X ₂	6.81	0.0260	6.33	0.0271
X ₁ *X ₃	0.10	0.7583	Eliminated	Eliminated
X ₂ *X ₃	2.82	0.1243	Eliminated	Eliminated
X ₁ ²	25.36	0.0005	23.57	0.0004
X ₂ ²	11.26	0.0073	10.46	0.0072
X ₃ ²	11.08	0.0076	10.30	0.0075
Predicted R ²	0.4328		0.6714	
Adjusted R ²	0.8849		0.8761	
Std. Dev.	2.78		2.89	

Where X₁ is Inlet Temperature, X₂ is Spray rate and X₃ is Batch size.

Interpretations Based on Partial Quadratic Model:

- Partial quadratic model for efficiency explains better than full model.
- The model F value of 20.20 and P value of <0.0001 implies model is statistically significant relative to noise and hence can be used for further exploration and prediction.
- Interaction term of X₁ and X₂ is significant (P= 0.0271), this implies that interaction of inlet temperature and spray rate is significantly affecting yield.
- Square term of inlet temperature (X₁²) is the significant (P = 0.0004) term indicating there is non-linear relationship between yield and inlet temperature
- Adjusted R square value 0.8761 implies reasonable predictability strength of the model, thus model is improved after reduction.

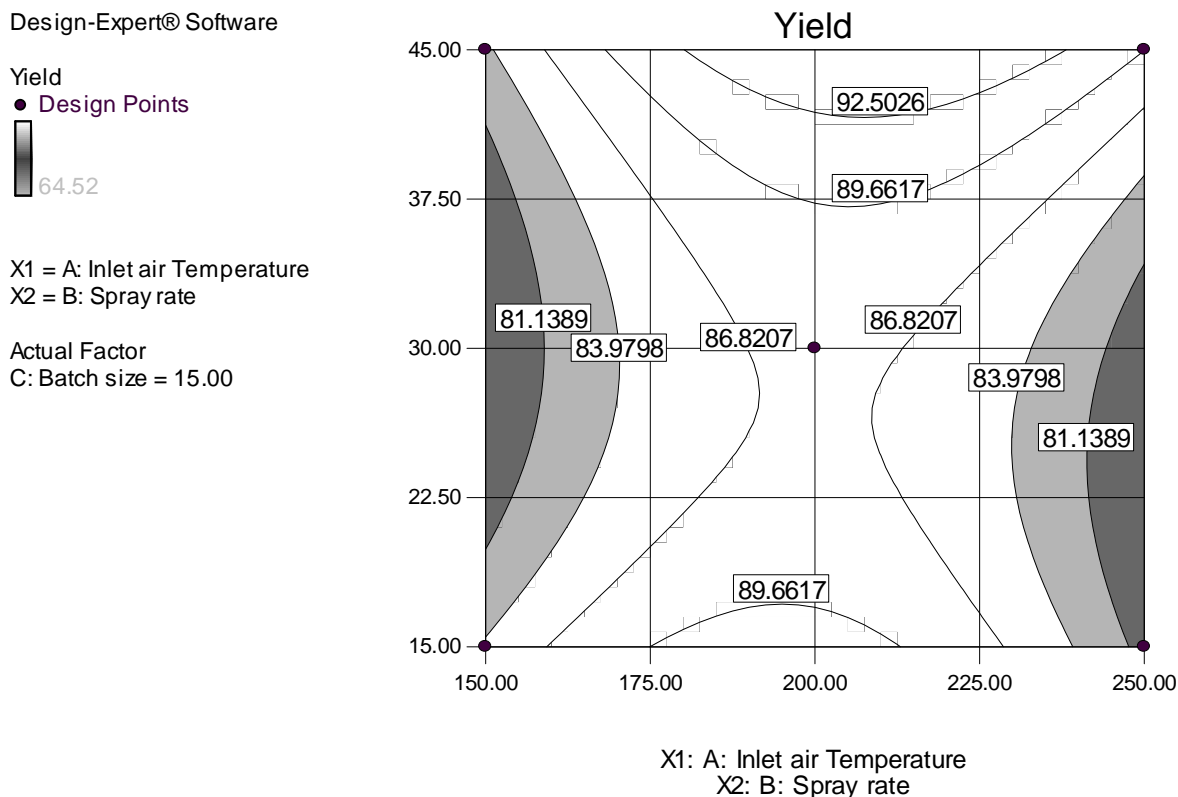


Figure 6: Typical contour plot showing effect of inlet temperature and spray rate on yield.

G. Hausner Ratio

Regression analysis of the data was carried out and a full quadratic model was fitted.

ANOVA was carried out to identify the significance of terms of the model.

The polynomial equation obtained is as follows:

$$Y = 1.726 - 7.27E-003X_1 + 6.2833E-004 X_2 - 0.0872 X_3 + 2.206 X_1X_2 + 1.575E-004 X_1X_3 + 8.24E-004 X_2 X_3 + 1.44E-005 X_1^2 - 2.069E-004 X_2^2 + 1.272E-003X_3^2$$

(Adjusted $R^2 = 0.6161$)

Since the full model contains some insignificant terms, a partial quadratic model (reduced model) was fitted using regression analysis by eliminating some of the insignificant terms.

The final partial quadratic equation obtained is as follows;

$$Y = 1.084 - 8.29E-004X_1 - 7.37E-003 X_2 - 0.061 X_3 + 1.575E-004 X_1X_3 + 8.249E-004 X_2X_3$$

(Adjusted $R^2 = 0.5533$)

The results from full and partial quadratic model are summarized in Table 9.

Table 9: Comparison of Full and Partial Quadratic Model

Source	Full Model		Partial Model	
	F Value	P Value	F Value	P Value
Model	4.39	0.0152	5.71	0.0054
X ₁	6.96	0.0248	5.98	0.0282
X ₂	0.87	0.3740	0.74	0.4028
X ₃	3.79	0.0801	3.26	0.0926
X ₁ *X ₂	1.10	0.3193	Eliminated	Eliminated
X ₁ *X ₃	6.22	0.0318	5.35	0.065
X ₂ *X ₃	15.36	0.0029	13.20	0.0027
X ₁ ²	1.80	0.2089	Eliminated	Eliminated
X ₂ ²	2.99	0.1145	Eliminated	Eliminated
X ₃ ²	1.40	0.2648	Eliminated	Eliminated
Predicted R ²	-0.2820		0.2133	
Adjusted R ²	0.6161		0.5533	
Std. Dev.	0.045		0.048	

Where X₁ is Inlet Temperature, X₂ is Spray rate and X₃ is Batch size.

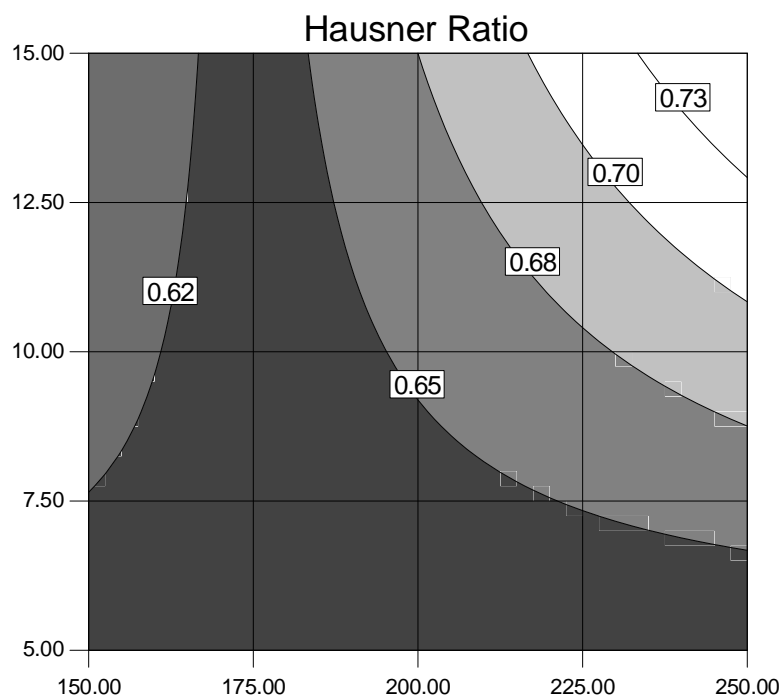
Design-Expert® Software

Hausner Ratio



X1 = A: Inlet air Temperature
X2 = C: Batch size

Actual Factor
B: Spray rate = 42.00



X1: A: Inlet air Temperature
X2: C: Batch size

Figure 7: Typical contour plot showing effect of spray rate and batch size on Hausner Ratio

Interpretations Based on Partial Quadratic Model:

- Partial quadratic model for efficiency explains better than full model.
- The model F value of 5.71 and P value of 0.0045 implies model is statistically significant relative to noise and hence can be used for further exploration and prediction.
- Adeq precision is 11.496. The value gives a measure of signal to noise ratio and a ratio greater than 4 is desirable hence this model can be used to navigate the design space
- Interaction term of X_1 and X_3 is significant ($P= 0.0365$), this implies that interaction of inlet temperature and batch size is significantly affecting Hausner ration.
- Interaction term of X_2 and X_3 is significant ($P= 0.0027$), this implies that interaction of inlet temperature and batch size is significantly affecting Hausner ration
- Adjusted R square value 0.5533 implies reasonable predictability strength of the model, thus model is improved after reduction.

H. Carr's Index

Regression analysis of the data was carried out and a full quadratic model was fitted. ANOVA was carried out to identify the significance of the terms of the model.

The polynomial equation obtained is as follows:

$$Y = 132.62 - 0.784X_1 - 0.861X_2 - 4.167 X_3 - 8.019E-004X_1 X_2 + 8.870E-004 X_1X_3 + 0.0802 X_2 X_3 + 1.948E-003 X_1^2 + 2.720E-003 X_2^2 + 0.0544X_3^2 \quad (\text{Adjusted } R^2 = 0.8347)$$

Since the full model contains some insignificant terms, a partial quadratic model (reduced model) was fitted using regression analysis by eliminating some of the insignificant terms.

The final partial quadratic equation obtained is as follows;

$$Y = 147.11 - 0.989 X_1 - 0.858 X_2 - 2.900 X_3 + 0.0802 X_1^2 X_3^2 + 2.422 X_1^2 \quad (\text{Adjusted } R^2 = 0.8546)$$

The results from full and partial quadratic model are summarized in Table 10.

Table 10: Comparison of Full and Partial Quadratic Model

Source	Full Model		Partial Model	
	F Value	P Value	F Value	P Value
Model	11.66	0.0003	23.34	<0.0001
X_1	1.88	0.1998	2.14	0.1653
X_2	1.34	0.2737	1.53	0.2372
X_3	11.39	0.0071	12.96	0.0029
$X_1 * X_2$	0.54	0.4798	Eliminated	Eliminated
$X_1 * X_3$	0.073	0.7922	Eliminated	Eliminated
$X_2 * X_3$	53.89	<0.0001	61.27	<0.0001
X_1^2	12.15	0.0059	38.81	<0.0001
X_2^2	0.19	0.6707	Eliminated	Eliminated
X_3^2	0.95	0.3527	Eliminated	Eliminated
Predicted R^2	-0.0729		0.7063	
Adjusted R^2	0.8136		0.8546	
Std. Dev.	0.030		2.17	

Where X_1 is Inlet Temperature, X_2 is Spray rate and X_3 is Batch size.

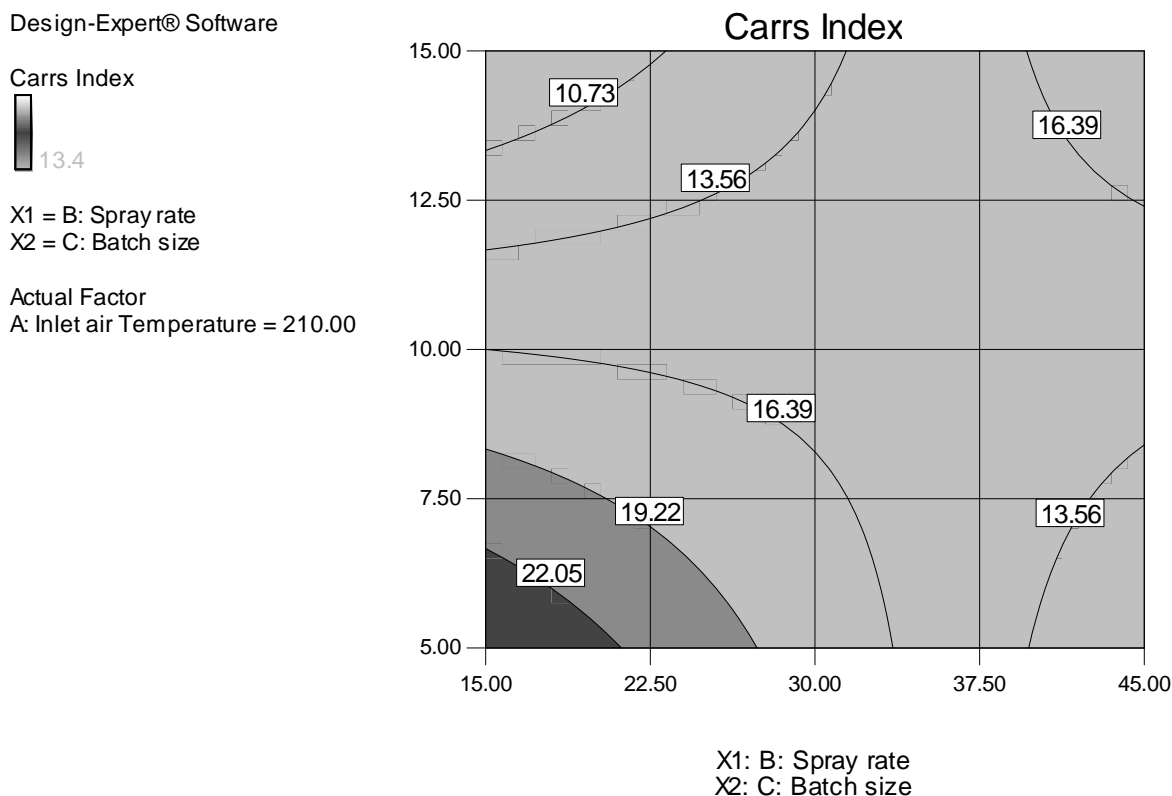


Figure 8: Typical contour plot showing effect of spray rate and batch size on Carr index

Interpretations Based on Partial Quadratic Model:

- Partial quadratic model for efficiency explains better than full model.
- The model F value of 23.34 and P value of <0.0001 implies model is statistically significant relative to noise and hence can be used for further exploration and prediction.
- Interaction term of X_2 and X_3 is significant ($P = <0.0001$) term, this implies that interaction of Spray rate and batch size is significantly affecting Carr index.
- Square term of inlet temperature (X_1^2) is the significant ($P = <0.0001$) term indicating there is non-linear relationship between Carr index and inlet temperature.
- Adjusted R square value 0.8546 implies reasonable predictability strength of the model, thus model is improved after reduction.

OPTIMIZATION

Multi response optimization with desirability function approach is carried out using above models and predicted required combination of variables to get the desired results. However, the predictions are subject to vary with true value. Variability between predicted and true value will depend on the predictability strength of the models. Some of the predicted combinations of the variables for desired responses (generated by software) are as summarized in Table No. 11:

Table 11 : Solutions for achieving maximum yield with quality product

S.No	Inlet temperature	Spray rate	Batch size	Moisture content	Assay	Impurity-I	Impurity-II	Total impurities	Yield	Desirability
1	212.40	41.21	15.00	4.37	94.11	1.00	0.511	0.96	92.12	0.792
2	210.99	41.15	15.00	4.36	94.09	0.99	0.50	0.98	92.11	0.792
3	210.40	41.12	15.00	4.35	94.09	0.98	0.50	0.98	92.11	0.792

Test batches:

Based on above predictions (solutions) three batches were executed with the set parameters given in table No.12

Table 12: Optimized process parameters based on the data analysis

S.No	Inlet temperature	Spray rate	Batch size
1	210 - 215	42.0	15.00
2	210 - 215	42.0	15.00

RESULTS:

The results of the confirmatory batches taken at FTO-III facility at optimized conditions are summarized in table No.13

Table 13: Results of confirmatory batches taken at optimized conditions (Predicted & Actual)

Batche s	Moisture Content (% w/w)		Assay mg		Impurity-I (% Area)		Impurity-II (% Area)		Total Impurities (% Area)		Yield (%)	
	Predicted	Actual	Predicted	Actual	Predicted	Actual	Predicted	Actual	Predicted	Actual	Predicted	Actual
1	4.37	4.38	94.11	97.70	1.00	1.22	0.50	0.21	0.96	0.97	92.12	90.96
2	4.37	4.34	94.09	97.12	1.00	1.10	0.50	0.18	0.96	0.97	92.12	91.12
3	4.37	4.27	94.09	96.32	1.00	0.83	0.50	0.14	0.96	0.88	92.12	90.88

CONCLUSION

The spray drying process optimization has been greatly enhanced by the use of statistically designed experiments. Traditional methods frequently will find an optimum solution, but not as efficiently as a designed experiment, and most notably, without being able to uncover important interaction effects. In addition due to advances in robotics, we are now able to exploit the power of statistically designed experiments by using more complex designs that offer much greater insight into the behavior of factors, the interactions among them, and their impact on the responses.

In this study, experimental designs have been used in order to investigate the effects of formulation and process variables on the resulting powder characteristics. Out of the three parameters tested in the experimental design, spray rate and batch size were found to affect the product yield either through non linear, quadratic or interaction effects. The optimization of process resulted in a considerable improvement of spray-dried product yield (from 55% to 90%), while minimizing the level of impurities and moisture content in the final product.

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