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Spray-drying process optimization for manufacture of drug–cyclodextrin complex powder using design of experiments

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Abstract

Background: Design of experiments (DOE), a component of Quality by Design, is systematic and simultaneous evaluation of variables (process or formulation) to develop a product with predetermined quality attributes. This study presents a case study to understand the effects of process variables in a spray-drying process used in the manufacture of drug-cyclodextrin complex for a drug that is prone to chemical instability at elevated temperature conditions encountered during processing. *Methods*: Experiments were designed, and data were collected according to a three-factor, three-level face-centered central composite design. The factors investigated were inlet temperature, spray rate, and batch size. Responses analyzed for computing the interaction effects were drug content, impurities, moisture content, and process yield. The spray-drying process conditions were optimized using DOE to maximize production yields while minimizing moisture content and drug-related impurities. Process validation batches were executed using the optimum process conditions obtained from software Design-Expert® to evaluate both the repeatability and reproducibility of spray-drying technique. *Results*: Optimization of process variables using DOE resulted in a significant improvement of process yields, above 90% and moisture content below 6% (w/w). The impurities were controlled within acceptable limits. The desirability function used to optimize the response variables and observed responses were in agreement with experimental values. These results demonstrated the reliability of selected model for manufacture of powder complex with predictable quality attributes. *Conclusion*: The study indicates the general applicability of DOE approach to optimize critical process parameters in the manufacture of drug product with desired quality attributes.

Key words: *Central composite design; design of experiments; process optimization; QbD; spray drying*

Introduction

DRL001, a compound with low solubility ($S < 100$ μg/mL) in physiologically relevant pH range, is an example of class II compound wherein its oral bioavailability is dependent on rate of dissolution in the gastrointestinal (GI) tract[1,2]. Because of its low solubility and dissolution in physiologically relevant media, DRL001 has poor bioavailability following oral administration. To overcome poor solubility and enhance its oral bioavailability, a drug complex with cyclodextrin was developed. Cyclodextrins have been used in pharmaceutical product development and presently there are about 30 commercialized products containing cyclodextrins[3,4].

Cyclodextrins have mainly been used as complexing agents to enhance the aqueous solubility of poorly water-soluble drugs to improve bioavailability. Cyclodextrin encapsulation of a drug affects the drug's physicochemical properties including its aqueous solubility

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and chemical stability. In a drug complex, the cyclodextrin molecule forms a hydrophilic shield around the lipophilic moiety of drug molecule. This will, in general, increase the apparent aqueous solubility and stability of the drug. Despite these advantages, incorporating cyclodextrins in solid dosage forms usually results in increased formulation bulk, and, therefore, its use has been limited in developing solid dosage forms of relatively potent compounds.

Drug–cyclodextrin complex powder can be prepared by various methods such as freeze drying and spray drying[5–7]. Freeze-drying technique has successfully been used to prepare drug–cyclodextrin complex powder for various formulations including solid and injectable dosage forms. However, this technique is expensive and reserved for product with high added value. The spray-drying process has been used as an alternative to freeze drying to prepare drug–cyclodextrin complex in the form of powder[7,8]. Spray drying has been used extensively in the pharmaceutical industry for production of bulk drugs, excipients, and in microencapsulation[9–11]. This technique transforms a liquid feed into dry powder in a single step and can be used for continuous processing. The process exhibits advantages including rapid transformation of a liquid feed into powder in a single step, possibility to modulate physicochemical characteristics of resulting powders thus synergizing the scale-up potential, and the flexibility to operate in a continuous mode resulting in high throughput. Compared to freeze-drying process, spray drying requires less time and thus economical[9,12]. Despite these advantages, in a spray-drying process, the variables must be controlled adequately to avoid low yields, sticking, and moisture content, usually encountered with laboratory-scale spray driers[13]. The optimization of spray-drying process therefore involves evaluation of parameters concerning both spray drier and feed formulation[14–16]. To date, the impact of process variables on spray drier performance and product characteristics of compounds that are chemically unstable—at elevated temperature conditions—has not been thoroughly investigated using a systematic approach. This article presents an extensive investigation on the effect of process variables in a spray-drying process on product characteristics using design of experiments (DOE).

DOE, a component of Quality by Design (QbD), is systematic and simultaneous evaluation of variables (process or formulation) to develop a product with the desired quality attributes[17]. QbD is a broad term that encompasses predefined target quality, physicochemical, physiological, pharmacological, and clinical considerations to obtain a product with the desired quality attributes that are safe and effective. For practical considerations, it is expected that variables associated with raw material characteristics, product design, process, and scale-up issues will be thoroughly investigated. Therefore, a very useful component of QbD is the understanding of factors and their interaction effects using a desired set of experiments. To understand the variables and their interactions, many statistical experimental designs have been recognized as useful techniques.

Central composite design (CCD) is a response surface design that provides information on direct effects, pairwise interaction effects, and curvilinear variable effects and is widely used for formulation and process optimization in the field of pharmaceutical product development[16,18,19]. High shear manufacturing process of theophylline-containing pellet has been evaluated successfully using a face-centered CCD[20]. This design is efficient and flexible, providing extensive information on experiment variable effects and overall experimental error in a minimal number of trials. Therefore, face-centered CCD is a suitable tool for optimization of process variables in spray drying used in the manufacture of powder complex.

The aim of this study was to evaluate the effects of spray-drying process parameters (spray rate, inlet air temperature, and batch size) on product characteristics of compounds that are chemically unstable (epimerization and decarboxylation) at elevated temperature conditions encountered during processing. The powder characteristics that were evaluated include moisture content, impurity levels, assay, flowability, and yield. The studies were conducted at pilot scale to optimize the process to enable commercial manufacturing. The repeatability and reproducibility of spray-drying technique for manufacture of drug complex with desired quality attributes was assessed by performing validation at optimal conditions.

Materials and methods

Materials

All chemicals used in this study were of standard pharmaceutical grade. The test compound, DRL001, was provided by Dr. Reddy's Laboratories Limited (Hyderabad, India).

Methods

Preparation of spray-dried drug–complex powder

Drug–cyclodextrin complex solution was prepared using laboratory-scale high-shear mixer (Ultra Turrax; IKA, Wilmington, DE, USA). DRL001 [~10% (w/v)], cyclodextrin [~60% (w/v)], mannitol [~10% (w/v)], sodium lauryl sulfate [~1% (w/v)], and L-arginine [~19.0% (w/v)] were dissolved in distilled water. Stirring

was continued until a clear solution was obtained. The solution was filtered using 0.45-μm pore size membrane filter (Millipore, Bedford, MA, USA) and the filtrate was placed in the feed tank of spray drier.

A pilot-scale spray drier (PSD01; Lab India, Mumbai, India) with 5.0 kg/h water evaporation capacity was used in this study. The preparations were spray-dried using rotary nozzle of narrow diameter (0.5 mm). The operating parameters were set as follows: drying air rate 85 m^2/h, atomizing air pressure 8 bar. Inlet temperature, spray rate, and batch size settings were dependent on the experiment. The dried powder was appropriately recovered, weighed, and stored in a well-closed glass container at room temperature.

Spray-dried powder characterization

Drug content by high-performance liquid chromatography. The drug content in the spray-dried powder was determined using an appropriate high-performance liquid chromatography (HPLC) method. The analysis was performed using an Agilent HPLC system (Agilent, Santa Clara, CA, USA). The column used was Waters symmetry 5 μm C18 (250 × 4.6 mm; Waters, Los Angeles, CA, USA). The mobile phase consisted of 0.025 M phosphate buffer (pH 6.8) and acetonitrile (70:30). The flow rate was 1 mL/min, the injection volume was 10 μL, and the UV detector was set at 257 nm.

A certain amount of spray-dried powder (30 mg) was accurately weighed, added to a 50 mL volumetric flask containing 12 mL methanol, 24 mL phosphoric acid (50%), and 4 mL acetonitrile; and sonicated for 20 minutes. Following this, the volume was adjusted to 50 mL by diluting the solution using mobile phase. Precisely, 2 mL of solution was taken from the flask and filtered through a 0.22-μm pore size membrane filter and diluted using mobile phase to obtain a volume of 20 mL. The sample solution was then examined using an HPLC method as described earlier in the text.

Impurities by HPLC. The procedure and system conditions are same as described in the HPLC analysis for drug content. The relative response factors (RRFs) for the two impurities, impurity I (epimer) and impurity II (decarboxylated), with respect to parent compound were 0.94 and 0.935, respectively. The weight percent of impurity present in DRL001 sample was calculated using its RRF value and peak response.

Moisture content. The residual moisture content of the spray-dried powders was measured using Karl Fisher titration in dry methanol using a DL38 titrator (Mettler-Toledo, Schwerzenbach, Switzerland). The sample weight was approximately 30 mg and Hydranal composite 5 (Riedel-de-Haen, Seelze, Germany) was used as the titration reagent.

Batch yield. The process yields (w/w) was calculated by subtracting the water content from the weight of the spray-dried powder and dividing the resulting value by the amount of dry solids in the spray-dried dispersion.

Density. The bulk density of spray-dried powder was determined by placing a known amount of powder (approximately 5 g) under gravity into a calibrated measuring cylinder and recording the volume occupied by the powder. The tapped density of the spray-dried powder was determined by measuring the volume occupied by the powder following tapping using a tamping volumeter (Tapped Density Assessor; Copley Scientific Ltd., Nottingham, UK) until no further change in the powder volume was observed. Carr's index values for each spray-dried powder were derived from bulk density and tapped density data, according to the following equation:

$$\text{Carr's index}\,(\%)=\frac{(\text{Tapped density}-\text{Bulk density})}{\text{Tapped density}}\times 100. \quad (1)$$

The Carr's index value gives an indication of powder flow; a value less than 25% indicates a fluid powder (good flow) whereas a value greater than 25% indicates a cohesive powder with poor flow. Hausner ratio was calculated from tapped and bulk density using the following equation:

$$\text{Hausner ratio}=\frac{\text{Tapped density}}{\text{Bulk density}}. \quad (2)$$

A Hausner ratio value less than 1.20 is indicative of good flow, whereas a value less than 1.5 indicates poor flow.

Experimental design. CCD (face centered of α1) was used to optimize and evaluate main effects, interaction effects, and quadratic effects of the process parameters on spray-dried powder complex. α1 indicates a face-centered design with only three levels for each factor. Setting α1 = 1 in CCD ensures that the axial runs will not be any more extreme values than the factorial portion. A three-factor, three-level design was used and found suitable for exploring quadratic response surfaces and constructing second-order polynomial models. It contains an embedded factorial or fractional factorial matrix with center points augmented with a group of 'star points' or 'axial points' that allow estimation of curvature. The distance from the center of the design space to a factorial point is ±1 unit for each factor, the distance from center of the design space to an axial point is ±α′, where |α′| > 1. The precise value of α′ depends on certain properties desired for the design and on the number of factors involved. In central composite face-centered (CCF) design, the star points are at the center of each face of the factorial space, so that α′ = ±1. This variety requires three levels of each factor. The externally

studentized residual (sometimes referred to as outlier *t*) test was used to check whether a run is consistent with other runs in a chosen model. The model coefficients are calculated based on all design points except one. A prediction of the response at this point is made and the residual evaluated using *t*-test. A value greater than 3.5 indicates that this point is a potential outlier. The measure of the amount of variation around the mean explained by the model is given by adjusted R^2 and predicted R^2. The adjusted R^2 decreases as the number of terms in the model increases if those additional terms do not add value to the model. The predicted R^2 and the adjusted R^2 should be within 0.20 of each other, else there may be a problem with either the data or the model. The CCF allows estimation of first-order linear terms and two-factor interactions and results in resolution, R = V [19,21], where R refers to resolution of the experimental design and V refers to five in roman letter, denoting that this design enables the study of main effects as well as two-factor interactions without confounding. Thus the estimates of the main effects are not confounded with two-factor interactions, and the two-factor interactions are not confounded with each other; however, two-factor interactions do confound with three-factor interaction[21].

DRL001–cyclodextrin powder complex was produced at different settings of process variables. The ranges of process variables to be applied for pilot-scale spray-drying process were fixed using preliminary experimentation. The three factors as well as their levels are shown in Table 1. The levels for each parameter are represented by a (–) sign for the lower level, a (+) sign for the higher level, and by (0) for the center level. As shown in Table 1, the high level for liquid spray rate was the maximum that could be used without condensation appearing in the drying chamber. As for batch size, the low level corresponds to the minimum acceptable to obtain sufficient yield. The range for inlet temperature was chosen based on the maximum drying capacity of the equipment. A Design-Expert® (version.7.3.1; Stat-Ease Inc., MN, USA) program was used to calculate the expected form of the polynomial equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + \boldsymbol{b}_{33}X_3^2,$$

Table 1. Independent process variables and their variation interval: factors and their coded levels.

	Variation intervals		
Factors	Low (–1)	Base (0)	High (+1)
Inlet temperature (°C)	150	200	250
Spray rate (mL/min)	15	30	45
Batch size (L)	5	10	15

where Y is the response, X are factors, and the 'b' parameters denote coefficients characterizing the main (b_1, b_2, b_3), the interaction (b_{12}, b_{13}, b_{23}), and the quadratic (b_{11}, b_{22}, b_{33}) effects.

Process validation. Three replicates were produced on three different days to evaluate conformity of the technique. For these experiments the processing parameters used were optimal conditions determined from the response surface designs. The spray-dried powders were characterized using different techniques as described earlier, and statistical analysis was performed.

Results and discussion

Experimental design

The process parameters during pilot-scale spray-drying process were optimized for manufacture of DRL001–cyclodextrin powder complex using three-factor, three-level CCD (face centered of α1) as the response surface methodology. The observed responses for 20 trials are summarized in Table 2. Based on the experimental design generated, the factor combinations resulted in different responses. From these results, it can be concluded that all trials resulted in a powder complex with <2.0% (w/w) of impurity I (epimer) and <1.0% of impurity II (decarboxylated), except for trial 2 that showed slightly higher levels. The process yield was >70% (w/w), except for trials 1 and 2 where yields were 65.22% (w/w) and 64.52% (w/w), respectively. These variations in results are due to experimental errors (spray nozzle blockage during execution of trials) and they are considered as outliers. The drug content varied from 90.07% to 97.47% (w/w) and moisture content ranged from 3.54% to 5.42% (w/w), respectively.

Regression and modeling

A stepwise regression was used to generate quadratic equations for each response variables. Each response variable listed in Table 2 was fitted to a second-order polynomial model and the regression coefficients for each term in the regression model is summarized in Table 3 along with R^2 of regression model. The default value of 0.10 was selected for both α-in and α-out during stepwise regression. The six replicated center points in the experimental design provided the design ability to assess the pure error of experiment and enabled evaluation of the model's lack of fit (LOF). In this case, the LOF evaluated using Design-Expert® indicated that the model was adequate; the results from this evaluation for LOF are summarized in Table 4. If the $P > F$ value is very small (<0.05) then LOF is significant. If we have an LOF term and it is significant, then it indicates that the model that is considered

Table 2. Matrix of the three-factor, three-level face-centered central composite design and observed responses.

	Factors				Responses			
	Inlet air temperature (X_1)	Spray rate (X_2)	Batch size (X_3)	Drug content (Y_1)	Impurity I (Y_2)	Impurity II (Y_3)	Moisture content (Y_4)	Yield (Y_5)
Run	°C	mL/min	L	% (w/w)	% area	% area	% (w/w)	% (w/w)
1	250 ± 5	45 ± 1	5	93.05	0.68	0.12	4.96	65.22
2	150 ± 5	45 ± 1	5	90.38	3.41	1.18	4.17	64.52
3	200 ± 5	30 ± 1	10	91.18	1.52	0.18	4.27	71.21
4	200 ± 5	30 ± 1	10	91.6	0.61	0.4	3.54	76.32
5	200 ± 5	30 ± 1	5	90.07	1.67	0.3	3.86	84.53
6	150 ± 5	45 ± 1	15	92.26	1.89	0.98	3.65	80.61
7	150 ± 5	30 ± 1	10	91.11	1.05	0.07	5.36	79.45
8	150 ± 5	15 ± 1	5	93.32	1.51	0.41	5.16	92.12
9	250 ± 5	30 ± 1	10	97.47	1.9	0.16	5.42	80.62
10	200 ± 5	15 ± 1	10	96.35	1.92	0.85	5.11	80.28
11	250 ± 5	45 ± 1	15	95.18	1.52	0.8	4.72	74.56
12	200 ± 5	30 ± 1	10	91.56	1.03	0.53	4.83	91.23
13	200 ± 5	30 ± 1	10	96.41	1.45	0.67	4.16	70.64
14	250 ± 5	15 ± 1	5	97.26	1.45	0.68	4.03	90.27
15	200 ± 5	45 ± 1	10	95.2	1.44	0.67	3.74	84.29
16	250 ± 5	15 ± 1	15	93.24	0.55	0.59	3.86	84.67
17	200 ± 5	30 ± 1	10	95.04	1.04	0.58	3.8	85.21
18	150 ± 5	15 ± 1	15	93.63	1.03	0.58	3.83	84.53
19	200 ± 5	30 ± 1	10	96.23	1.04	0.53	3.7	84.62
20	200 ± 5	30 ± 1	15	95.93	1.07	0.54	3.58	84.00

Impurity I, epimer; impurity II, decarboxylated.

Table 3. Regression coefficients for the response variables.

$Y_1 = 87.24 - 0.03X_1 + 0.97X_2 - 0.63X_3 + 3.32500\text{E}{-}003X_1X_3 - 0.016X_2^2$
$R^2 = 0.6960$

$Y_2 = -3.80 + 0.035X_1 + 0.028X_2 - 1.40000\text{E}{-}003X_3 - 2.03333\text{E}{-}004X_1X_2 - 5.92000\text{E} - 005X_1^2$
$R^2 = 0.9514$

$Y_3 = 4.72 - 0.05X_1 + 0.09X_2 - 2.00000\text{E}{-}003X_3 - 5.66667\text{E}{-}004X_1X_2 + 1.81600\text{E} - 004X_1^2$
$R^2 = 0.5699$

$Y_4 = 14.93 - 0.088X_1 - 0.060X_2 - 0.197X_3 + 7.21667\text{E}{-}003X_2X_3 + 2.10000\text{E}{-}004X_1^2$
$R^2 = 0.5930$

$Y_5 = -51.21 + 1.26X_1 - 2.04X_2 + 6.01X_3 + 3.42500\text{E}{-}003X_1X_2 - 3.38127\text{E}{-}003X_1^2 + 0.025X_2^2 - 0.22X_3^2$
$R^2 = 0.9218$

for fitting the response is not adequately explaining variation in response. We may need a higher order model or perhaps a transformation. In some instance, it may indicate that a polynomial may be inadequate to describe the system. In our analysis from Table 4, the LOF is not significant since probability values are more than 0.05.

The data of pure error and LOF provide a mean response and estimate of pure experimental uncertainty[22]. Clustering and overlapping of the response summarized in Table 2 indicated that the experimental errors caused by the procedure were small enough to generate meaningful fittings for the response variables. The model parameters for studied response variables are summarized in Table 5. All the models generated for the responses Y_1–Y_5 had significantly improved after excluding some of the nonsignificant terms. The nonsignificant terms pertaining to interaction and quadratic terms are eliminated in relevant cases to strengthen the model. The significance of terms is dependent on the model *P*-value, which should be less than 0.05 to be strongly significant and between 0.05 and 0.10 to be marginally significant. If a term is not significant, it is removed from the model unless it is needed to satisfy hierarchy (i.e., it is a parent term of a significant interaction). A *P*-value less than 0.05 indicates significant effect on prediction efficacy of the model for the measured responses and these effects are briefly described as follows; all factors except inlet temperature (X_1) were found to be significant for process yield (Y_5). Similarly, inlet temperature (X_1), spray rate (X_2), interaction effect of inlet temperature and spray rate ($X_1 \times X_2$), and quadratic effect of inlet temperature (X_1^2) were found to be significant for impurity I (Y_2). The spray rate and interaction effect of inlet temperature and spray rate were found to be significant for impurity II (Y_3). The interaction of spray rate and batch size ($X_2 \times X_3$) and quadratic effect of inlet temperature (X_1^2) were found to significant for moisture content (Y_4). The quadratic effect of spray rate (X_2^2) was the only factor found significant for drug content (Y_1). The above results indicted that all the factors play an important role

Table 4. Summary of ANOVA results in analyzing lack of fit and pure error.

Source	SS	df	MS	*F* value	*P*
Drug content (%)					
Model	74.94	5	14.99	6.41	0.0027
Residual	32.73	14	2.34	—	—
Total	107.66	19	—	—	—
Lack of fit	25.42	9	2.82	1.93	0.2421
Pure error	7.31	5	1.46	—	—
Impurity I (%)					
Model	1.55	5	0.31	54.78	<0.0001
Residual	0.079	14	5.656E–003	—	—
Total	1.63	19	—	—	—
Lack of fit	0.067	9	7.433E–004	3.03	0.1178
Pure error	0.012	5	2.457E–003	—	—
Impurity II (%)					
Model	4.30	5	0.86	3.71	0.0239
Residual	3.25	14	0.23	—	—
Total	7.55	19	—	—	—
Lack of fit	2.85	9	0.32	3.95	0.0723
Pure error	0.40	5	0.080	—	—
Moisture content (%)					
Model	4.64	5	0.93	4.08	0.0170
Residual	3.18	14	0.23	—	—
Total	7.82	19	—	—	—
Lack of fit	3.13	9	0.35	33.15	0.0846
Pure error	0.052	5	0.010	—	—
Process yield (%)					
Model	1178.94	7	168.42	20.20	<0.0001
Residual	100.06	12	8.34	—	—
Total	1279	19	—	—	—
Lack of fit	99.24	7	14.18	85.88	0.1224
Pure error	0.83	5	0.17	—	—

Table 5. Model parameters for the studied response variables.

Source	SS	df	MS	*F* value	*P*
Drug content (%)					
X_1	11	1	0.11	0.045	0.8344
X_2	0.47	1	0.47	0.20	0.6604
X_3	0.20	1	0.20	0.084	0.7764
$X_1 \times X_3$	5.53	1	5.53	2.36	0.1464
X_2^2	68.64	1	68.64	29.36	<0.0001
Impurity I (%)					
X_1	0.92	1	0.92	162.33	<0.0001
X_2	0.33	1	0.33	59.21	<0.0001
X_3	4.900E–004	1	4.900E–004	0.087	0.7728
$X_1 \times X_2$	0.19	1	0.19	32.90	<0.0001
X_1^2	0.11	1	0.11	19.36	0.0006
Impurity II (%)					
X_1	0.64	1	0.64	2.74	0.1202
X_2	1.19	1	1.19	5.13	0.0399
X_3	1.000E–003	1	1.000E–003	4.313E–003	0.9486
$X_1 \times X_2$	1.45	1	1.45	6.23	0.0256
X_1^2	1.03	1	1.03	4.44	0.0535
Moisture content (%, w/w)					
X_1	0.50	1	0.50	2.21	0.1596
X_2	0.32	1	0.32	1.42	0.2525
X_3	0.09	1	0.09	0.41	0.5347
$X_2 \times X_3$	2.34	1	2.34	10.30	0.0063
X_1^2	1.38	1	1.38	6.06	0.0274
Process yield (%, w/w)					
X_1	2.76	1	2.76	0.33	0.5760
X_2	46.14	1	46.14	5.53	0.0366
X_3	596.29	1	596.29	71.51	<0.0001
$X_1 \times X_2$	52.79	1	52.79	6.33	0.0271
X_1^2	196.50	1	196.50	23.57	0.0004
X_2^2	87.22	1	87.22	10.46	0.0074
X_3^2	85.88	1	85.88	10.30	0.0054

in the manufacture of DRL001–cyclodextrin powder complex. Therefore, an appropriate range of process variables results in higher yields with low moisture content and minimal increase in drug-related impurities.

In order to determine the levels of factors that yield optimum responses, mathematical relationships were generated between the dependent and independent variables using statistical package Design-Expert®. A dependent variable is what is measured and affected during the experiment. The dependent variable responds to the independent variable. An independent variable is the one that might influence the outcome measure. The resulting equations for all responses are summarized in Table 3. This table represents the quantitative effect of the process variables on five responses Y_1–Y_5. The values of coefficients X_1–X_5 relate to effects of these variables on the corresponding responses. Coefficients with more than one-factor term represent the interaction terms and coefficients with higher order terms indicate the quadratic (nonlinear) nature of the relationship. A positive and negative sign in polynomial equations indicates a synergistic and antagonistic effect, respectively. To justify the use of polynomial equations, values of X_1–X_5 were substituted in equations (Table 3) to obtain the theoretical values of Y_1–Y_5.

Figures 1–5 show the two-dimensional contour plots and three-dimensional response surface, and the interaction effect of factors on responses. These plots show effects of two factors on the response at any given time. All relationships among the three factors were nonlinear, indicating potentially strong interaction between variables.

In the model for drug content, spray rate had a quadratic negative effect. The effects of X_1 and X_3 and their interaction on Y_1 are presented in Figure 1. At lower levels of X_1, Y_1 was directly proportional to second variable, X_3. Conversely, at high levels of X_1, the Y_1 increased with increase of X_3. This may be attributed to the fact that when the batch size is high the drying capacity of inlet air at a given flow rate was sufficient to

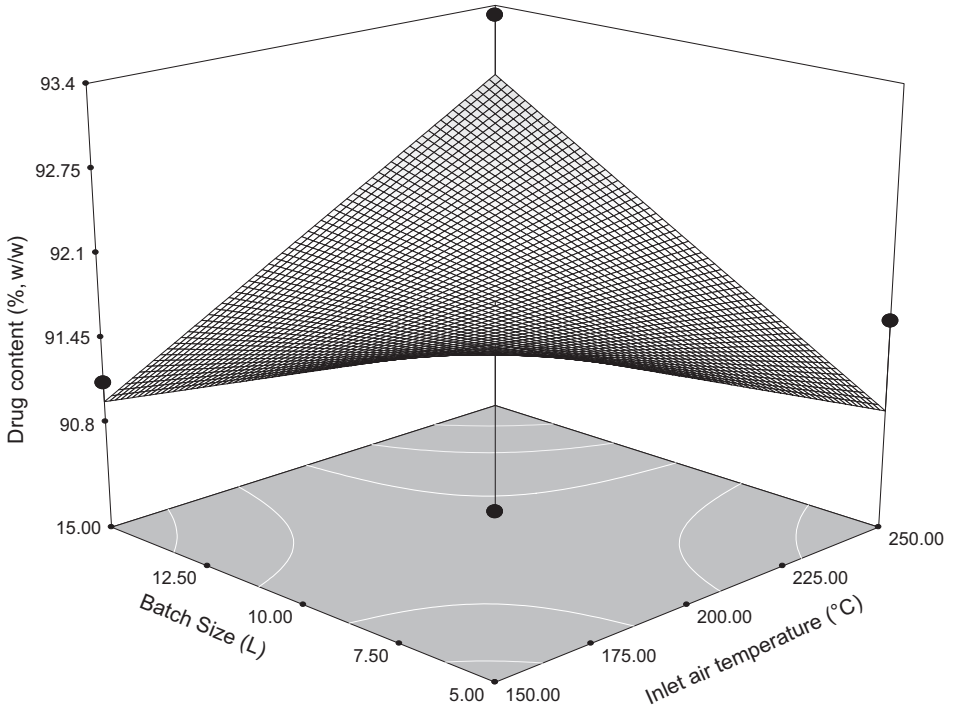

Figure 1. The response surface plot showing effects of inlet temperature (X_1) and batch size (X_3) on response, drug content (Y_1).

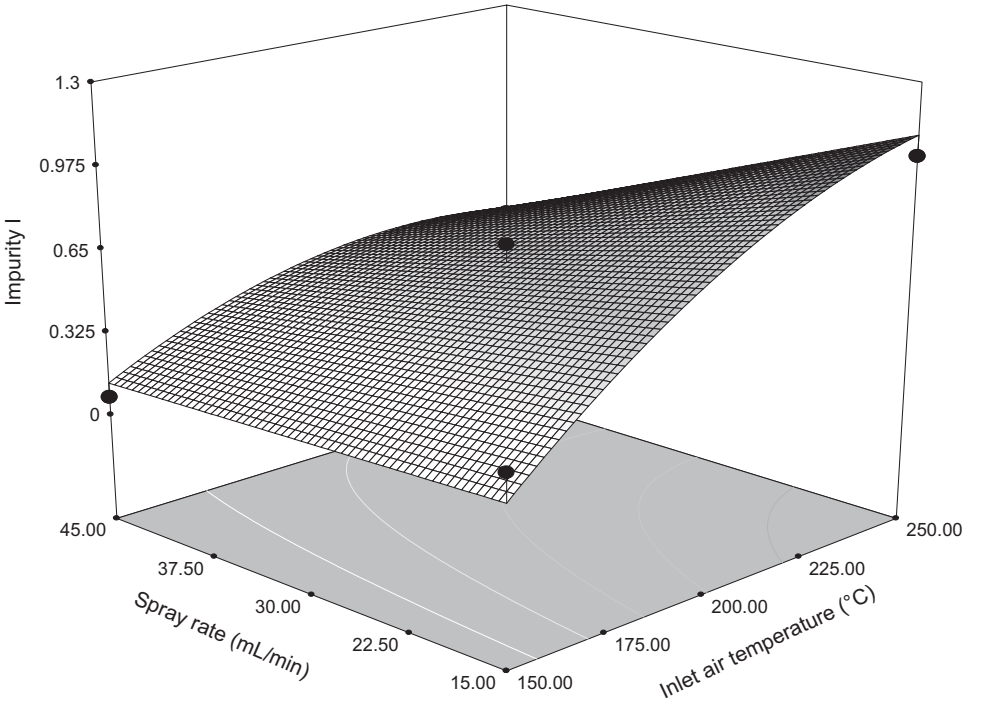

Figure 2. The response surface plot showing effects of inlet temperature (X_1) and spray rate (X_2) on response, impurity I (Y_2).

obtain a powder complex with low moisture content and minimal increase in drug-related impurities.

The response surface and interaction plot developed by the model for impurity I is shown in Figure 2. When the temperature and spray rate were increased the impurity I level increased significantly whereas their interaction resulted in a significant reduction. The significant quadratic effect of inlet temperature also

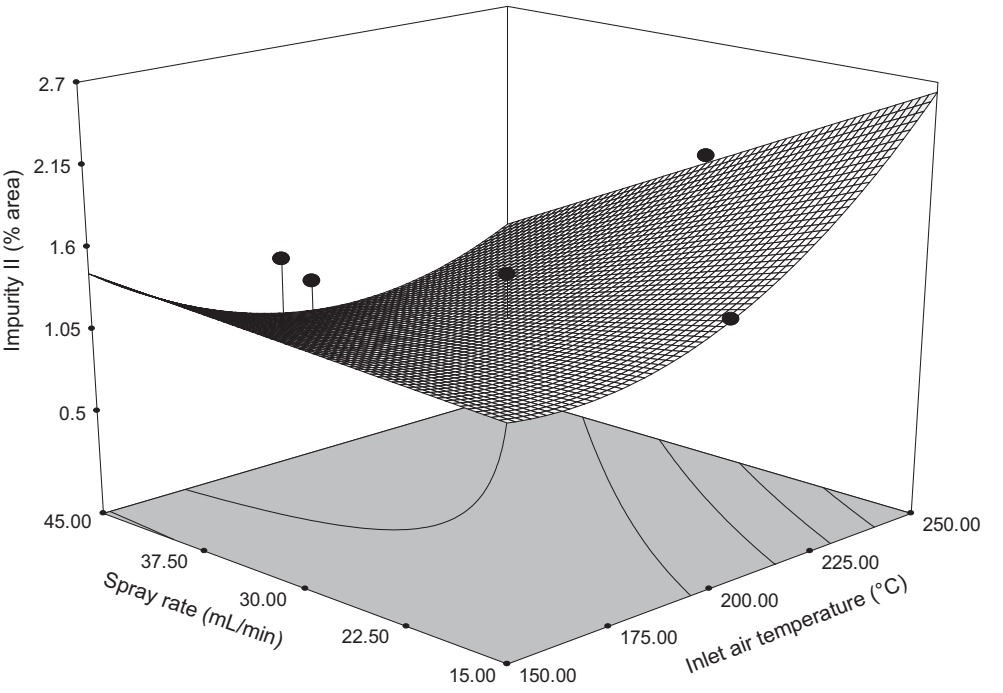

Figure 3. The response surface plot showing effects of inlet temperature (X_1) and spray rate (X_2) on response, impurity II (Y_3).

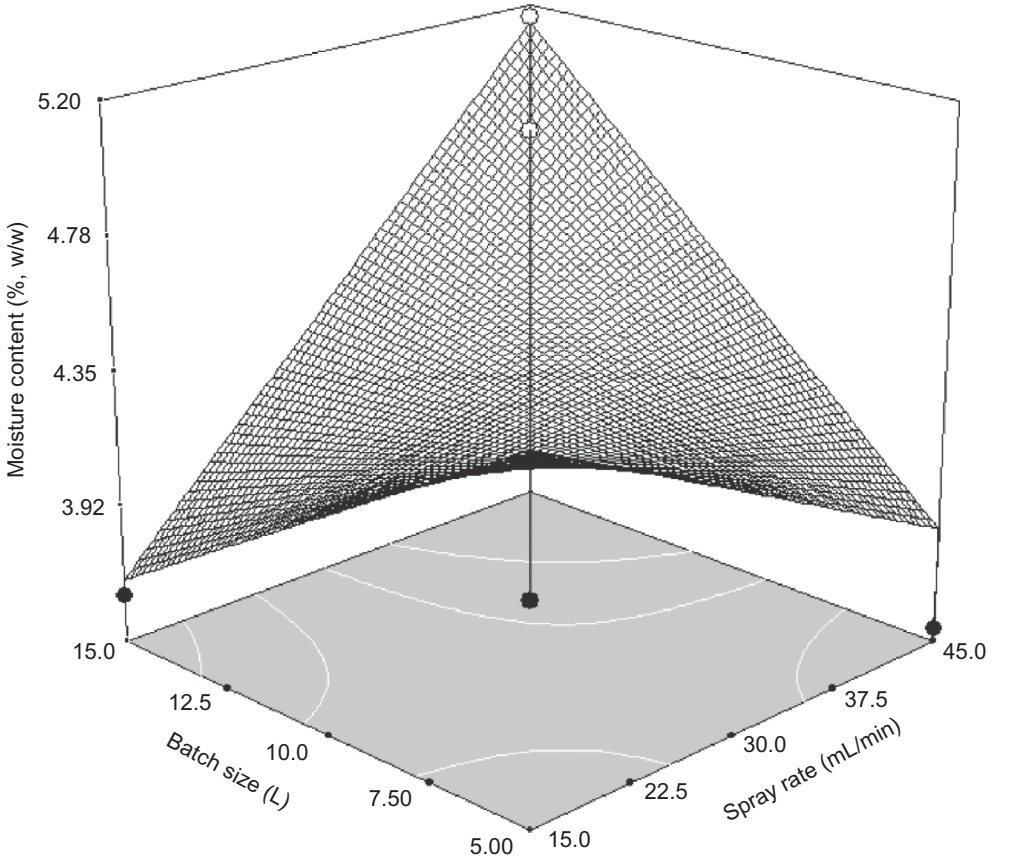

Figure 4. The response plot showing effects of spray rate (X_2) and batch size (X_3) on response, moisture content (Y_4).

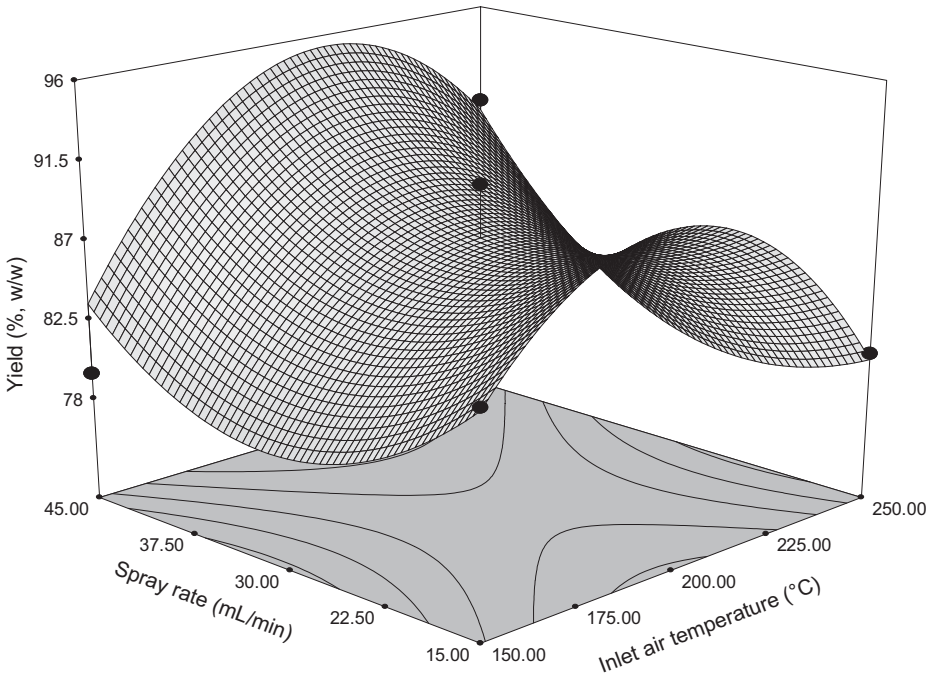

Figure 5. The response surface plot and interaction plot (b) showing effects of temperature (X_1) and spray rate (X_2) on response, process yield (Y_5).

favored this response. Increasing the temperature of inlet air at low spray rate led to a significant increase in the level of impurity I. Similar trend was seen at higher spray rate, but the magnitude of increase was less pronounced. Both temperature and spray rate have an effect on impurity with temperature having a significant impact in controlling the level of impurity I. This observation may be attributed to the fact that the chemical structure of drug is susceptible to epimerization in presence of moisture at higher temperature leading to an increase in the level of impurity.

Similar to impurity I, the spray rate ($P < 0.05$) affected impurity II levels significantly, and the interaction of inlet temperature and spray rate was found to reduce the impurity II level. The effects of temperature and spray rate and their interaction on impurity II are shown in Figure 3. At low spray rate, impurity II increased when the inlet temperature increased from 150°C to 250°C. Conversely, at a higher spray rate, impurity II reduced as temperature was increased up to 200°C. Further, increase in temperature beyond 200°C led to an increased level of impurity II. This increase could be explained by the fact that at low spray rate the drying capacity of inlet air was sufficient to dry the liquid spray completely, and further increase in the inlet air temperature above the drying capacity results in thermal instability leading to an increase in the level of impurity II. Alternatively, the excess drying capacity can be compensated by increasing spray rate, from 15 to 30 mg/mL, while minimizing thermal instability and the level of impurity II. It is observed that increase in spray rate above the drying capacity resulted in insufficient drying, leading to an increase in level of impurity II.

Generally in a drying operation, lower moisture content results in improved product characteristics and stability. The values measured for moisture content were very weak with a low variation (3.54–5.42%). It was found that none of the main factors tested were responsible for controlling the moisture content. The interaction between the spray rate and the batch size and quadratic effect of inlet temperature are the principal parameters affecting moisture content. The lesser the interaction and quadratic effect, lower is the moisture content. The effects of spray rate and batch size and their interaction on moisture content are shown in Figure 4. For a larger batch size, moisture content increased with increasing spray rate and for a smaller batch size, the moisture content decreased at higher spray rate. This can be attributed to the fact that the equipment used for spray drying of both smaller and larger batches is the same. In case of smaller batch, the efficiency of the equipment is much higher and even at higher spray rate, efficient drying is accomplished resulting in lower moisture content. As the batch size increases, the drying efficiency of the spray drier decreases resulting in higher moisture content.

The effect of factors on process yield is shown in Figure 5. The yields obtained ranged from 64.52% to 92.12% (w/w). The values obtained are an indication of the process performance. The yield was significantly

influenced by batch size and quadratic effect of spray rate. The larger the batch size and quadratic effect of spray rate, the better was the yield. In addition, reducing the spray rate can also result in improved yields irrespective of the drying temperature. An increase in inlet temperature improves yields only when spray rate is high. High spray rate requires more thermal energy to ensure complete solvent evaporation, the energy for which is supplied by inlet temperature. These observations are in agreement with published reports[18]. Spray-drying operation frequently results in unsatisfactory yields because of difficulties in collecting finer particles with low mass. In few publications involving experimental design, yields up to 70% (w/w) have been reported for pilot-scale spray-drying operation. The yields obtained from our experimental design were higher than reported values[18,23–25].

Optimization

A numerical optimization technique utilizing the desirability approach was used to generate the optimum settings for process conditions. The process was optimized for response variables Y_1–Y_5. The targets set for process yield, moisture content, and impurity levels are >50.0%, <8.0%, and <5.0%, respectively, and for drug content it is between 90.0% and 110.0%. In order to evaluate the optimization capability of the models generated according to the results of the face-centered CCD, drug–complex powders with similar formula composition were prepared at the optimal process variable settings. The values for drug content, moisture content, yield, and impurity of the drug–complex were comparable to those predicted by the model and are summarized in Table 6. The results showed good agreement for product properties with theoretical predictions, justifying the predictability and validity of model used in our experimental design.

Flowability parameters

The flowability parameters were evaluated for all the batches of spray-dried powder and the results are summarized in Table 7. The tapped density is a measure of the degree of packing or conversely the amount of space between the particles in the powder bed. According to Gonnissen et al.[26], the value of Carr's index and Hausner ratio of spray-dried powder obtained indicated poor to moderate flow resulting from finer particles and interparticle cohesiveness, a constraint to be considered in future experiments for potential improvement.

Table 6. Validation of model optimization.

	Trial 1		Trial 2		Trial 3	
Responses	Exp	Pre	Exp	Pre	Exp	Pre
Drug content	97.70	94.11	97.12	94.09	96.32	94.09
Impurity I	1.22	1.0	1.10	1.00	0.83	1.00
Impurity II	0.21	0.50	0.18	0.50	0.14	0.50
Moisture content	4.38	4.37	4.34	4.37	4.27	4.37
Yield	90.96	92.12	91.12	92.12	90.88	92.12

Exp, experimental values; Pre, predicted values.

Table 7. Flowability parameters of the spray-dried powders.

Run	Bulk density (g/mL)	Tapped density (g/mL)	Hausner ratio	Carr's index (%)
1	0.32	0.42	1.31	15.41
2	0.35	0.47	1.34	20.36
3	0.22	0.36	1.64	15.41
4	0.17	0.27	1.59	15.35
5	0.17	0.33	1.94	16.50
6	0.15	0.24	1.60	23.28
7	0.25	0.43	1.72	23.40
8	0.26	0.33	1.27	30.69
9	0.25	0.40	1.60	15.53
10	0.17	0.25	1.47	14.94
11	0.17	0.35	2.06	24.73
12	0.17	0.26	1.53	16.50
13	0.18	0.27	1.50	15.53
14	0.17	0.27	1.59	33.66
15	0.18	0.27	1.50	15.47
16	0.17	0.25	1.47	13.40
17	0.16	0.26	1.63	14.38
18	0.17	0.27	1.64	15.06
19	0.17	0.26	1.53	15.47
20	0.17	0.27	1.59	15.41

Conclusions

A CCD was performed to study the effect of process variables on the resulting powder characteristics by applying the statistical optimization technique. Within the studied experimental conditions, it has been found that the presence of strong interaction contributions on the quantitative results and a better interaction between inlet temperature and spray rate is determinant of both process yield and impurities. As described earlier, with well-controlled process variables, powders of interest as intermediary pharmaceutical powder convenient for handling and future manipulations can be prepared. The optimization of process resulted in a considerable improvement of spray-dried product yield, while minimizing impurities and moisture content. Observed responses were in close agreement with the predicted values of the optimized formulation, thus demonstrating the feasibility of the optimization procedure in manufacturing DRL001–cyclodextrin powder complex. Finally, it can be concluded that with limited

number of experiments, an optimal process that provides a drug product with the desired attributes can be obtained using appropriate statistical experimental design and optimization technique.

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References

1. Amidon GL, Lennernas H, Shah VP, Crison JR. (1995). A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res, 12:413–20.
2. Dressman JB, Amidon GL, Reppas C, Shah VP. (1998). Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms. Pharm Res, 15:11–22.
3. Davis ME, Brewster M. (2004). Cyclodextrin-based pharmaceutics: Past, present and future. Nat Rev Drug Discov, 3:1023–35.
4. Brewster ME, Loftsson T. (2007). Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev, 59:645–66.
5. Lin SZ, Wouessidjewe D, Poelman MC, Duchene D. (1991). Indomethacin and cyclodextrin complexes. Int J Pharm, 69:211–9.
6. Ramprakash G, Nagarsenker MS. (2001). Cyclodextrin based oral delivery of flurbiprofen: Effect of method of preparation on drug release and studies on in-vivo performance. Proceedings of the 28th international symposium on controlled release of bioactive materials and 4th consumer & diversified products conference, vol. 28, Controlled Release Society, Inc., San Diego, CA, 772–3.
7. Miller LA, Carrier RL, Ahmed I. (2007). Practical considerations in development of solid dosage forms that contain cyclodextrin. J Pharm Sci, 96:1691–707.
8. Sinha VR, Anitha R, Ghosj S, Nanda A, Kumaria R. (2005). Complexation of celecoxib with beta-cyclodextrin: Characterization of the interaction in solution and in solid state. J Pharm Sci, 94:676–87.
9. Broadhead J, Edmond Rouan SK, Rhodes CT. (1992). The spray drying of pharmaceuticals. Drug Dev Ind Pharm, 18:1169–206.
10. Muller CR, Bassani VL, Pohlmann AR, Michalowski CB, Petrovick PR, Guterres SS. (2000). Preparation and characterization of spray-dried nanocapsules. Drug Dev Ind Pharm, 26:343–7.
11. Desai KGH, Park HJ. (2005). Encapsulation of vitamin C in tripolyphosphate cross-linked chitosan microspheres by spray drying. J Microencapsul, 22:179–92.
12. Oakley DE. (1997). Produce uniform particles by spray drying. Chem Eng Prog, 93:48–54.
13. Masters K. (1991). Spray drying handbook. New York: Longman Scientific and Technical.
14. Conte U, Conti B, Giunchedi P, Maggi L. (1994). Spray dried polylactide microsphere preparation: Influence of the technological parameters. Drug Dev Ind Pharm, 20:253–8.
15. Wendel S, Celik M. (1997). An overview of spray drying applications. Pharm Technol, 10:124–56.
16. Tagne PT, Briancon S, Fessi H. (2006). Spray-dried microparticles containing polymeric nanacapsules: Formulation aspects, liquid phase interactions and particle characteristics. Int J Pharm, 325:63–74.
17. FDA guidance of industry. (2006). ICH Q8 Pharmaceutical development. U.S. Department of Health and Human Services, FDA/CDER/CBER. http://www.fda.gov/ [accessed April 2, 2009].
18. Billon A, Bataille B, Cassanas G, Jacob M. (2000). Development of spray dried acetaminophen microparticles using experimental designs. Int J Pharm, 203:159–68.
19. Vaithiyalingam S, Khan MA. (2002). Optimization and characterization of controlled release multi-particulate beads formulated with a customized cellulose acetate butyrate dispersion. Int J Pharm, 234:179–93.
20. Devay A, Mayer K, Pal S, Antal I. (2006). Investigation on drug dissolution and particle characteristics of pellets related to manufacturing process variables of high-shear granulation. J Biochem Biophys Methods, 69:197–205.
21. Box GEP, Hunter WG, Hunter JS. (1976). Statistics for experimenters, an introduction to design, data analysis, and model building. New York: Wiley.
22. Lieberman HA, Rieger MM, Banker GS. (1988). Pharmaceutical dosage form—Disperse systems. New York: Marcel Dekker, 438–64.
23. Giunchedi P, Juliano C, Gavini E, Cossu M, Sorrenti M. (2002). Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres. Eur J Pharm BioPharm, 53:233–9.
24. Prinn KB, Costantini RH, Tracy M. (2002). Statistical modeling of protein spray drying at the lab scale. AAPS PharmSciTech, 3:1–8.
25. Martinac A, Filipovic-Grcic J, Perissuti B, Voinivich D, Pavilic Z. (2005). Spray-dried chitosan/ethylcellulose microspheres for nasal drug delivery: Swelling study and evaluation of in vitro drug release properties. J Microencap, 22:549–61.
26. Gonnissen Y, Remon JP, Vervaet C. (2008). Effect of maltodextrin and superdisintegrant in directly compressible powder mixtures prepared via co-spray drying. Eur J Pharm BioPharm, 68:277–82.