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Research Article

Optimization of Process Parameters for a Quasi-Continuous Tablet Coating System Using Design of Experiments

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Abstract. The aim of this study was to identify and optimize the critical process parameters of the newly developed Supercell quasi-continuous coater for optimal tablet coat quality. Design of experiments, aided by multivariate analysis techniques, was used to quantify the effects of various coating process conditions and their interactions on the quality of film-coated tablets. The process parameters varied included batch size, inlet temperature, atomizing pressure, plenum pressure, spray rate and coating level. An initial screening stage was carried out using a $2^{6-1(IV)}$ fractional factorial design. Following these preliminary experiments, optimization study was carried out using the Box–Behnken design. Main response variables measured included drug-loading efficiency, coat thickness variation, and the extent of tablet damage. Apparent optimum conditions were determined by using response surface plots. The process parameters exerted various effects on the different response variables. Hence, trade-offs between individual optima were necessary to obtain the best compromised set of conditions. The adequacy of the optimized process conditions in meeting the combined goals for all responses was indicated by the composite desirability value. By using response surface methodology and optimization, coating conditions which produced coated tablets of high drug-loading efficiency, low incidences of tablet damage and low coat thickness variation were defined. Optimal conditions were found to vary over a large spectrum when different responses were considered. Changes in processing parameters across the design space did not result in drastic changes to coat quality, thereby demonstrating robustness in the Supercell coating process.

KEY WORDS: coat quality; design of experiments; process optimization; supercell coater; tablet coating.

INTRODUCTION

Tablets are coated to mask unpleasant taste or odor (1–3), enhance stability against light and moisture (2,4,5), produce an elegant product (6), or impart a functional purpose such as the modification of drug release profiles (7,8). Tablet coats can also allow higher packaging speeds by reducing friction as well as reducing dust generation from tablets. For the consumer, colour coats besides being esthetically more pleasing also provide identity to products (9) and improve swallowability (10,11).

Commercial tablet coating is commonly carried out using the fully perforated pan coater. The Supercell coater was recently developed with the ability to rapidly and uniformly coat inert objects between 3 and 35 mm with a high degree of accuracy (12). The Supercell coater has its roots in stent coating but was later shown to be capable of applying film coating to conventional pharmaceutical tablets as well (13,14). Instead of rotating in a pan, the tablets are air-fluidized in a chamber during coating. The Supercell coater can potentially be used for quasi-continuous in-line tablet coating.

The coating zone of the Supercell coater consists of a conical coating chamber that sits on top of an air distribution plate. A two-fluid spray nozzle is located centrally below the air distribution plate and serves to atomize the coating materials. The air distribution plate is perforated with rotonozzles which direct air jets to help accelerate the tablets through the coating zone. In addition, grooves are also present on the air distribution plate, encircling the spray nozzle. Air emitted from the grooves muffles the momentum of the atomized coating materials to help reduce tablet attrition. It also aids in the modification of the air flow pattern, turning it into an upward swirling pattern. The swirling flow allows tablets to rotate rapidly as they traverse the coating zone so that uniform coating may be applied on all surfaces of the tablets. At the same time, the spray cloud is broadened and this facilitates distribution of the coating spray. The air is supplied through the plenum. Figure 1a shows the coating zone of the Supercell coater.

Coating of tablets is a multivariate process and is therefore sensitive to the properties of the tablet cores, the coating formulation applied, manufacturing techniques and changes in process conditions (15). In this study, the influence of different process conditions on the quality of Supercell-coated tablets was evaluated. In traditional experimental designs, the effects of changes to process conditions on process outcomes are often investigated by varying the process parameters one at a time. As such, interactions

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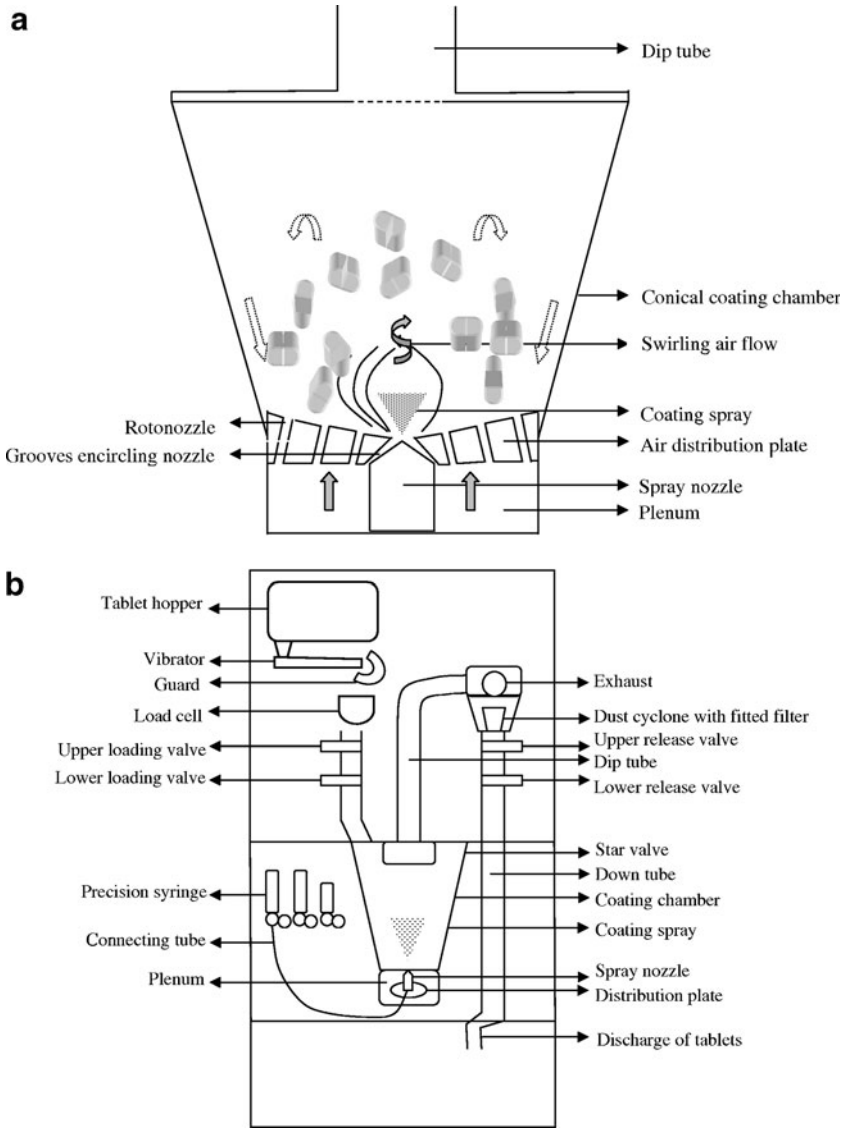

Fig. 1. (**a**) The coating zone of the Supercell coater with (⇢) representing tablet movement and (⇨) representing air flow, (**b**) Schematic representation of the Supercell coater

between process parameters are ignored and this can only lead to a local optimum during optimization. Design of experiments (DoE) is a technique whereby several process parameters are varied systematically within predefined ranges so that their effects on the response variables can be estimated and checked for significance (16). DoE, in combination with multivariate techniques, was shown to be useful in quantifying effects of changes in coating process conditions on the quality and performance of tablets coated using the conventional pan coater (15,17). Even though several studies had investigated the effects of changing various process parameters in the Supercell coater, no systematic studies focusing on the identification and optimization of critical process parameters for the Supercell coating process has been published. For example, a recent study on the Supercell coater only involved studying different spray rates for coating tablets to investigate the influence of different wetting conditions on the quality of coats formed (18). Differing coat characteristics were obtained under different wetting conditions but the interaction effects between spray rate and other process variables were not fully investigated. DoE consists of an initial screening stage, followed by subsequent optimization. For a long time, optimization has been based on the operator's experience and utilizes a black box approach that relies on final product uniformity (19). In DoE, different process parameters are varied concurrently and several responses are measured. Individual optima of the responses can be determined using response surface methodology. The eventual optimum setting of process parameters for Supercell coating will be a compromise between the individual optima.

It was hypothesized that through DoE, important process parameters for Supercell coating could be identified and optimized for the production of quality tablet coats. In addition, this study was aimed at providing better insights on the capability of the Supercell coater for better understanding of its operation and how the process parameters and their interactions could affect the quality of the tablet coats produced.

MATERIALS AND METHODS

Experimental Design

The influences of six different process parameters on the Supercell coating process were investigated. Table I indicates the various process variables and their corresponding levels together with the other conditions which were kept constant during coating. An initial screening stage was carried out using fractional factorial design (resolution VI) at two levels, with center samples. The center samples were replicated 3 times. The number of runs to be carried out was equivalent to $(2^{6-1}+3)=35$ runs. Center samples allowed the determination of experimental error and also helped predict non-linearities between design and response variables. The objective of screening was to determine which process parameters were most important. Therefore, more process parameters were included in the design and the effect that each process parameter had on the responses was roughly estimated.

Following these preliminary screening experiments, optimization design was next carried out. At the optimization stage, Box–Behnken (BB) design was built at three levels to study the effects of the process variables deemed critical to the coating process. A total of 46 experiments, including six center samples were performed. The design consisted of all combinations at the extreme levels of two or three process parameters while the levels of the remaining process parameters were kept at the center level. Various response variables were selected to characterize the quality of the coat during both screening and optimization. Apparent optimum conditions were determined by using response surface plots generated from the BB design. The data obtained from optimization could therefore cover the entire range specified. Model significance, lack of fit, residuals, and correlation coefficients were checked to assess the suitability of the model in describing the response surface adequately. From the response surface plots, the region that resulted in the best response was considered the optimum region. Sometimes, the optimum condition for a certain response variable may not be applicable to the other response variables. Hence, the final optimized condition was derived after taking into consideration the contributions of all factors. All experiments were performed in a randomized manner to minimize any systematic effects.

Table I. Process Parameters Investigated

	Settings	
Process parameters (A–F, variable; 1–5, fixed)	Low (−)	High (+)
A: Batch size (g)	40	80
B: Inlet temperature (°C)	80	120
C: Atomizing air pressure (bar)	2	4
D: Plenum pressure (mm WC[a])	1,000	1,800
E: Coating dispersion spray rate (mL/min)	4	8
F: Coating level (% *w*/*w*)	1	3
1. Hurricade size	50 mm	
2. Air distribution plate	50 mm ppr 50–02	
3. Bowl pressure (during coating)	−3 mm WC[a]	
4. Flush liquid flow rate	5 ml/min	
5. Volume of flush liquid	0.5 ml	

[a] mm WC represents mm water column, which is the pressure exerted by the equivalent height of water column

Materials

Tablet cores used for coating were composed of granules with 1% *w*/*w* magnesium stearate (M125, Productos Metallest, Spain) as tableting lubricant. The granules consisted of 74% *w*/*w* lactose (Pharmatose 200 M, DMV, Netherlands), 20% *w*/*w* microcrystalline cellulose (Avicel PH-101, FMC, UK), 1% *w*/*w* crospovidone (Polyplasdone XL-10, ISP, USA), and 5% *w*/*w* polyvinylpyrrolidone (PVP K29/32, ISP, USA).

The coating dispersion used consisted of 9% *w*/*w* hypromellose as polymer (Methocel E3 Prem LV, Dow Chemicals, USA), 1% *w*/*w* polyethylene glycol (PEG) as plasticizer (Lutrol E1500, BASF, Germany), 1% *w*/*w* yellow iron oxide as colorant (Sicopharm Yellow, Farma International, USA), and 9% *w*/*w* chlorpheniramine maleate (CPM; Merck, USA) as active. The inclusion of CPM to the coating formulation and the subsequent detection of CPM on the tablet coat allowed the evaluation of the efficiency of the coating process.

For analysis of drug content using HPLC, methanol (HPLC grade, Tedia, USA) was used as the extraction solvent. It was also employed as a 50:50 mixture with purified water (Milli-Q, Millipore Corporation, USA) to constitute the mobile phase.

Preparation of Tablet Cores

Granules were prepared using a high shear granulator (Ultima 10 L, GEA Pharma Systems, UK). The individual powder components were weighed and placed in the high shear granulator. A total of 1.2 kg of powder load was used for each granulation batch. Dry mixing was first carried out for 3 min and this was followed by addition of the liquid binder (20% *w*/*w* PVP solution) at an approximate rate of 50 g/min. The amount of water added to the powder mass was equivalent to 20% of the dry weight of the powder load for granulation.

Wet massing was then carried out for 5 min. The granules produced were collected and tray dried for 24 h at 60°C. The dried granules were forced through 500 μm sieve and were subsequently mixed with magnesium stearate before tableting using a rotary tablet press (Rimek Minipress II, Karvanati Engineering, India). The tablets were allowed to recover for at least 24 h after compaction before use.

Tablet Core Characterization

Tablets used for coating were caplet-shaped and scored on one side. At least ten tablets were evaluated for the various properties shown in Table II.

Preparation of Coating Dispersion

Hypromellose and PEG were first dispersed in distilled water which was pre-heated to 80°C. The dispersion was continuously stirred for 1 h and the mixture was then refrigerated overnight to allow hydration of the polymer. CPM and yellow iron oxide were added the following day and

Table II. Physical Characteristics of Tablet Cores Used for Coating

Tablet properties	Value	Measuring instrument
Thickness (mm)	3.919±0.065	Micrometer screw gauge (293-761-30, Mitutoyo, USA)
Length (mm)	8.167±0.007	
Width (mm)	4.100±0.005	
Weight (mg)	149.3±2.0	Weighing balance (B-220C, Fisher Scientific, Switzerland)
Hardness (*N*)	77.0±5.8	Hardness tester (HT-1, Sotax, Switzerland)
Friability (% weight load)	0.18±0.12	Friabilator USP (HT-2, Sotax, Switzerland)
Colour ([a]CIELab values)	L=95.19±0.31, a=−0.14±0.15, b=3.97±0.30	Tristimulus colorimeter (CR 241, Minolta, Japan)
Roughness (Ra) (nm)	549.665±196.696	Optical profiler (Wyko NT1100, Veeco Instruments, USA)

[a] *CIE* Commission Internationale de l'Eclairage (France)

the dispersion was homogenized at 4,000 rpm for 15 min (Silverson homogenizer, UK). The dispersion was adjusted to the required weight with distilled water. Total solids content was 20% *w*/*w*, with each tablet containing approximately 2 mg of active when coated to 3% *w*/*w* coating weight gain, which is the typical coating level employed for decorative coats. The density of the final coating dispersion prepared was approximately 1.08 g/mL.

Coating Process

Tablets were coated using the Supercell coater (GEA Pharma Systems, UK). Prior to coating, the tablets were weighed in the load cell and then transferred into the coating chamber automatically through the loading air-lock pinch valves (Fig. 1b). The coating dispersion was delivered to the spray nozzle using precision syringe pumps and atomized as the coating process began. The tablets were coated by air-fluidization with coat drying taking place concurrently. At the end of coating, the coated tablets were discharged by rapid vacuum extraction via the dip tube. All coater actions were controlled and monitored in real time by a computer system.

Evaluation of Coat Quality

Coat quality was visually inspected based on coat appearance and extent of coat defects. For each batch, tablets were examined for tablet damage and twinning. Percentage of tablets that presented each of the aforementioned defects was determined. Other coating defects such as filling in of intagliations, sticking, picking, and orange peel roughness were more qualitative in nature and therefore not considered as response variables.

Measurement of Air Flow Rate and Orifice Pressure

Values of both air-flow rate and orifice pressure changed when process conditions were altered. Understanding how the process parameters had affected these two variables had provided useful insights to understand how air flow within the coater was controlled. The air flow rate and orifice pressure were indicated by the Supercell coater's control system.

Coating Process Efficiency

The coating process efficiency (CPE) was determined from the actual amount of coating deposited on the tablets as a percentage of the theoretical amount of coating applied. The actual amount of coating deposited on the tablets was derived from the weight gained by the tablets after coating. The tablets were equilibrated at atmospheric conditions (25° C/50% RH) for at least 24 h before measurements of CPE were obtained.

Thickness

Thickness values of the tablet coat on the face (*y*-axis), central band (*z*-axis), as well as edge (*x*-axis) were estimated using a micrometer (293-761-30, Mitutoyo, Japan). Figure 2a shows the locations on the tablet where thickness measurements were taken. Thickness was derived by half the dimensional difference between corresponding locations of the coated and uncoated tablets. Thirty tablets were measured for each coating condition. Average thickness is defined as the average of thickness values obtained from the three locations. Inter-tablet thickness variation (RSD_{inter}) is the relative standard deviation (RSD) of the average thickness among tablets coated at the same condition. Intra-tablet thickness variation (RSD_{intra}) is given by the RSD of coat thicknesses at the face, central band and edge of the tablet.

Colour Uniformity

Colour uniformity was estimated based on a semi-quantitative scoring system developed internally. This method of assessment allows the rapid analysis of colour uniformity with reasonable accuracy. Fifty tablets were randomly selected from the same batch to assess inter-tablet colour uniformity. The tablets were arranged in 10 rows of five, lying on the same face and separated into two sets according to colour similarity. The number of tablets in the smaller set was determined. Figure 2b shows the diagrammatic representation of the scoring system for inter-tablet colour uniformity. The score was calculated as a ratio of the number of tablets in the smaller set with respect to denominator of 25. The maximum score possible was 1 and this occurred when the tablets were separated into two equal sets of 25 tablets each. When colour uniformity of tablets was high, fewer tablets would be present in the smaller set. Therefore, according to

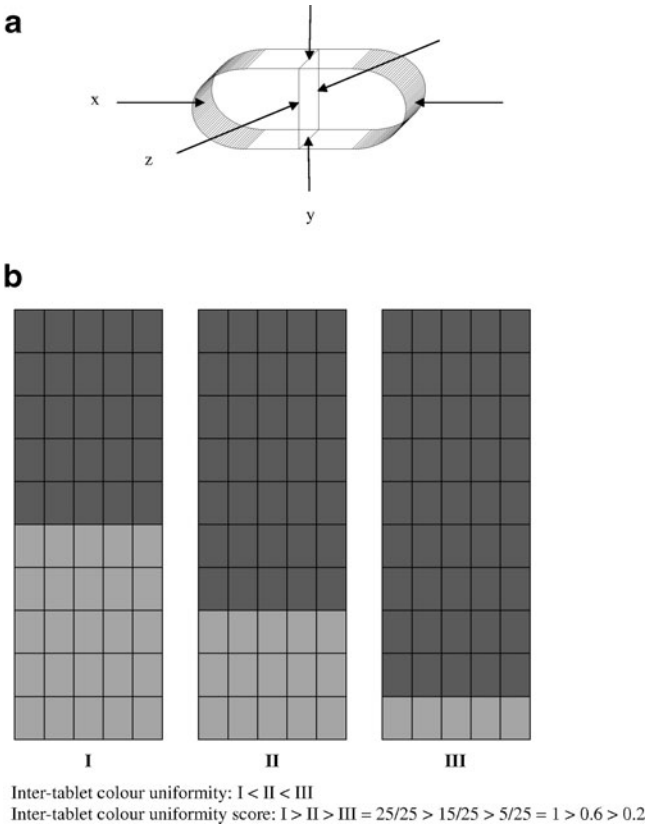

Fig. 2. **a** Diagram depicting the three directions at which thickness measurements were taken. **b** Diagrammatic representation of the scoring system for inter-tablet coating uniformity

the scoring system employed, a lower score value would indicate greater colour uniformity. The scoring system for intra-tablet colour uniformity is shown in Table III. Ten tablets were randomly selected to estimate intra-tablet colour variation. For each tablet, considerations were given to the number of surfaces that showed similar colour and also the uniformity of each tablet surface. A low score indicates increased intra-tablet colour uniformity.

Roughness

Tablet surface roughness was determined using an optical profiler (Wyko NT1100 Optical Profiling System, Veeco Instruments, USA) with an analysis software (Wyko Vision®). The measurement technique involved optical phase-shifting and white light vertical scanning interferometry. Ten tablets were randomly selected from each batch for analysis. For each tablet, two surface scans with each over an area of 100×100 μm were obtained from the tablet face. Surface roughness was defined by R_a (arithmetic mean height), which is the arithmetic mean of the absolute values of the surface deviations from the mean plane. The R_a values of 10 tablets were averaged to give the roughness value for the batch. The variation in surface topology between the tablets was determined by the RSD of the R_a values obtained.

Table III. Scoring System for Intra-tablet Colour Uniformity

Score	Number of faces showing similar colour ($N1$)	Number of faces with uniform colour ($N2$)
0	6	6
10	5	5
20	4	4
30	3	3
40	2	2
50	0	1
60	NA	0

Overall score=(score for $N1$+score for $N2$)/2×100

Drug Content, Drug Content Uniformity, and Drug-Loading Efficiency

Individual tablets were each crushed and immersed in 20 mL of methanol as extraction solvent. The mixture was sonicated for 1 min to dissolve the coats and then centrifuged (Sigma 2–5, Sartorius, Germany) at 4,000 rpm for 5 min prior to filtration through a 0.45 μm membrane filter (RC, Sartorius, Germany). Analysis of drug content was carried out using high-performance liquid chromatography (LC 2010, Shimadzu, Japan). The mobile phase used consisted of methanol and water (1:1) at a flow rate of 1 mL/min whilst the stationary phase consisted of a 5 μm BDS Hypersil C-18 column (150×4.6 mm; Thermo Electric Corp, USA). Temperature of oven was maintained at 40°C throughout the analysis. Detection of chlorpheniramine maleate was carried out at 264 nm using a variable wavelength UV detector. Ten tablets were evaluated for each batch and the results averaged to give the drug content of each tablet. The uniformity of drug content between tablets was indicated by the RSD of drug-loading efficiency (DLE). The DLE was calculated as follows:

$$\mathrm{DLE}(\%) = \frac{\text{actual amount of drug present in one table}}{\text{theoretical amount of drug sprayed on one tablet}} \times 100$$

A single, well-resolved CPM peak was obtained during analysis. The average retention time of CPM was found to be 1.61 min. The RSD of the retention time for the 460 samples tested was 2.32%, indicating excellent repeatability of the analytical method used.

Statistical Analysis

Statistical analysis was performed using Minitab Release 14 (Minitab Inc, USA). The coating conditions were optimized via response surface methodology using the same software. Response surface plots were also generated and optimized process conditions were predicted using the response optimizer function. The Unscrambler version 9.8 (CAMO Softwares, Norway) was used for multivariate data analysis.

RESULTS AND DISCUSSION

Coating Process and Duration

Various coating conditions were employed in the preliminary screening study. The flow of tablets within the

coating chamber was generally good for all the coating conditions except one. This condition consisted of the highest load (80 g), lowest plenum pressure (1,000 mm WC) and the lowest atomizing pressure (2 bar). The tablets were fluidized only up to three quarters of the whole chamber height. For all batches, coating was extremely rapid, with the coating process completed between 13 and 166 s.

During the optimization study, coating runs were completed between 43 and 172 s. Movement of tablets within the chamber was lively and reasonably unfretted for all the coating conditions employed. The time required for each coating run was dependent solely on the batch size, spray rate of coating dispersion, as well as coating level employed. The larger the batch size, more coating dispersion was needed to achieve the same coating weight gain. This corresponded to a longer coating time. However, coating time could be reduced with increased spray rate.

Appearance of Tablets after Coating

Any coat defects such as edge chipping, twinning, or colour variation could be readily identified visually. Coats of differing quality were observed during both screening and optimization studies.

Screening

Table IV shows the statistical analysis of the response variables to the process variables. When investigating a fluidized-bed tablet coater, attrition was an obvious concern. Hence, the ranges of process parameters set during a coating run were of critical importance to ensure that tablets were not damaged during the coating process. All factors with the exception of coating level were found to be significant in affecting the percentage of tablets that were damaged or chipped. This was not surprising since all the process parameters varied had a significant influence on the movement of tablets within the coater. When movement was vigorous, more tablet damage would be expected. Increased batch size and spray rate reduced the incidence of tablet damage. Larger batch sizes probably made fluidization more restricted. Hence, with shorter flight paths, high speeds were not achievable and collisions between tablets were relatively milder. Increased spray rate resulted in shorter coating duration, which could have reduced the degree of tablet damage because resident time of tablets in the coater was reduced. On the other hand, increased inlet temperature, atomizing, and plenum pressures increased tablet damage. High inlet temperature made tablets drier, with reduced moisture-related plasticizing effect and made collisions more intense. Therefore, impacts with coater surfaces or with other tablets were more liable to abrade the tablet surfaces. It was found out later, during the optimization stage, that air flow rates were increased when temperature was raised even as plenum pressure was kept constant. This increased air flow rate could also increase tablet damage due to the higher velocities imparted to the tablets. Increased atomizing and plenum pressures also affected the fluidizing capacity of the coater. Tablets were impacted with greater momentum and this resulted in a higher extent of damages when they hit the coater surfaces or with one another.

Increased batch size and coating level increased the incidence of tablet twinning due to relatively wetter conditions and increased propensity for tablets to come in contact with one another. On the other hand, the increase in plenum pressure led to less or no twinning due to better drying capacity and fluidization of tablets.

As expected, coating level strongly affected the average thickness of coats obtained. As coat thickness is related to coat density, factors affecting how the coat develops would affect the thickness of coat. Temperature and plenum pressure were also found to exert a similar effect. As temperature and plenum pressure were increased, coat thickness also increased. It was postulated that the increased temperature and better tablet fluidization resulted in faster drying and more porous coats, leading to thicker tablet coats. Spreading of droplets also became more difficult due to faster drying and this reduced incidence of tablet sticking.

For both inter-tablet and intra-tablet thickness variations, increased coating level significantly reduced the variation in coat thickness. However, inter-tablet thickness variation was found to be more significantly affected by batch size while intra-tablet thickness variation was more affected by inlet temperature.

Taking a closer look at the thickness variation within tablets, variation was higher at the faces of the tablet than the central band and edge (data not shown). Since elastic recovery is typically most pronounced in the axial than radial directions (20), the above observations could be partially attributed to the variation in tablet core thickness being more evident at the tablet face. This was further substantiated by the greater standard deviation of tablet core thickness when compared to tablet core length or breadth prior to coating (Table IV). Similar findings were reported by Okutgen *et al.* (21) in their study on tablet coating. Therefore, it might be prudent to use thickness measurements at tablet central band or edge to study the effects of process variables on coat thickness. Coat thickness was greatest on the tablet central band, followed by the face and lastly, the edge at all coating conditions tested (data not shown). It is well-known that there is greater uniformity of material deposition in a fluidized-bed system. It was apparent from the findings that even though the intra-tablet thickness variation was not significant, there were still differences in the distribution of coating materials on the tablet core and it was highly dependent on the air flow and material movement in the coater. However, to date, little is known about the distribution of spray in a fluid bed, and the mechanism of spray deposition onto particles (22). Modeling or simulations of the tablet movement in the Supercell coater may be investigated to better understand the distribution of coating materials in the coater.

Both air flow rate and orifice pressure were found to be highly dependent on plenum pressure. Plenum pressure was therefore the main contributor to fluidization of tablets within the coater. By varying plenum pressure, it was possible to control the extent of tablet fluidization within the coater.

CPE is a measure of the actual amount of coating material deposited on the substrate with respect to the theoretical quantity applied. In the screening runs, none of the process parameters were found to affect CPE significantly. In fact, for most conditions, CPE was found to be higher than 98%. The CPE responses for the pan-coater

Table IV. Statistical Analysis of Results for Experiments Conducted Based on $2^{6-1(VI)}$ Fractional Factorial Design

	Response variables														
Process parameters	Chipping/tablet damage	Twinning	Average thickness	Thickness RSD_{inter}	Thickness RSD_{intra}	Face thickness	Band thickness	Edge thickness	Inter-colour uniformity	Intra-colour uniformity	CPE	Duration of coating	Air flow rate	Orifice pressure	R_a
A	−	++	NS	−	NS	NS	NS	NS	NS	NS	NS	+++	NS	NS	NS
B	+++	NS	+++	NS	−	+++	+	++	NS	NS	NS	NS	NS	NS	NS
C	+	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
D	+++	−	++	NS	NS	NS	++	+	NS	NS	NS	NS	+++	+++	NS
E	–	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	–	NS	NS	−
F	NS	+	+++	–	–	+++	+++	+++	–	–	NS	+++	NS	NS	+
AB	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
AC	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
AD	NS	−	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
AE	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
AF	+	+	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	−	−	NS
BC	NS	NS	NS	−	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
BD	+	NS	NS	−	NS	++	NS	NS	NS	NS	NS	NS	NS	NS	NS
BE	NS	NS	NS	NS	+	NS	NS	−	NS	NS	NS	NS	NS	NS	NS
BF	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	−	NS	NS	NS
CD	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CE	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	−	NS	NS
CF	−	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
DE	NS	NS	−	NS	NS	NS	−	−	NS	NS	NS	NS	NS	NS	NS
DF	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
EF	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

NS not significant; (+/−) significant
(+/−) indicate the direction of change in response as a result of a change from low to high levels of process parameter tested
Number of +/− indicates the degree of contribution from process parameters on the responses measured

ranged from 25% to 100% when pan coating variables were altered (17). Thus, the Supercell coater, in the ranges studied, had performed well in this aspect. The high CPE values obtained inferred that loss of coating material was low regardless of the changes to the coating conditions.

R_a values were significantly affected by spray rate and coating level. Increased spray rate reduced roughness but increased coating level produced the opposite effect. The latter was also observed in other studies on film coating of tablets (23). However, roughness was excluded in the optimization studies because an 'optimum' roughness value was difficult to define. Even though it is an important response variable, visually acceptable appearance would often be sufficient for acceptance of a batch of coated tablets.

For both inter-tablet and intra-tablet colour uniformity, the process variables generally did not show any significant effects with the exception of coating level. It was apparent visually that 1% and 2% (center samples) coating levels did not provide adequate colour uniformity between tablets. On the other hand, tablets with 3% coating weight gain had generally acceptable colour uniformity. Increased coating level improved colour uniformity between and within tablets in the same batch. Therefore, coating level was fixed at 3% in the optimization studies and the number of factors investigated was reduced from six to five.

It was interesting to note that for most of the responses measured, interaction effects were extremely complex. For instance, increased atomizing pressure alone resulted in an increase in chipping tendencies but interaction effect between atomizing pressure × coating level was found to reduce chipping tendencies. Even though temperature alone did not affect coating duration and an increased coating level should have resulted in longer coating durations, interaction effect between inlet temperature × coating level was found to reduce coating time significantly. Interaction effects were difficult to comprehend and reflected the complexity of the coating process. It was therefore important to recognize that the effect of changing a certain process parameter was always dependent on the relative levels of other parameters. Hence, responses were not easily predicted. Therefore, response surface methodology became an important tool to ensure that all variables were taken into consideration when considering the ideal settings for production.

Optimization

The complexity of variable effects on critical responses made multiple response optimizations extremely difficult. This was very much the case for the Supercell coating process. During optimization, the levels of five process parameters (factors A–E) were varied according to the Box–Behnken model. This model was chosen because the screening study showed that the optimum condition did not lie at the extremes. For instance, when spray rate was high and fluidizing capacity was lowest, coating conditions became too wet and movement of tablets became increasingly sluggish as sticking took place. In addition, extension of the fractional factorial design used in the screening study to a central composite design may require the assessment of non-achievable levels. For instance, maximum achievable plenum pressure was 1,800 mm WC and could not be further increased.

The mean of average response and that of center samples measured during screening experiments should be comparable if there was a linear relationship between the test and the response variables. The results showed that several responses including percentage tablet damage, twinning and thickness variations were likely to be non-linear (Fig. 3). Hence, during optimization, a non-linear model should be

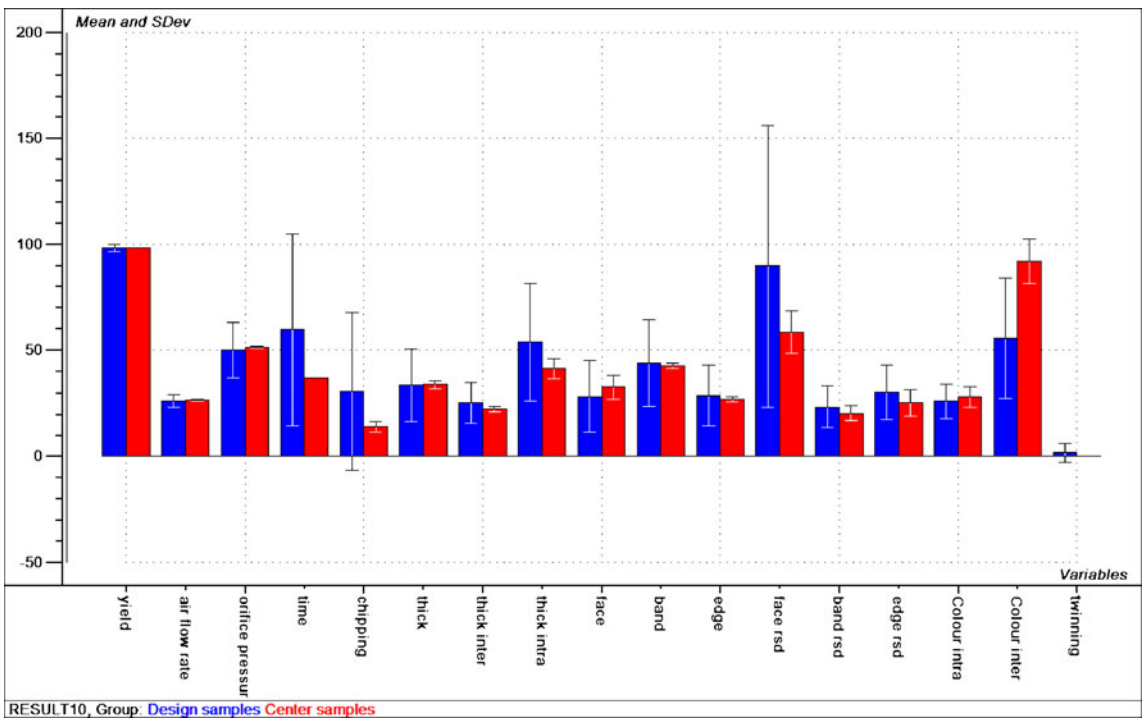

Fig. 3. Mean and SD of response variables measured during screening (excluding R_a) for non-center samples (*left*) and center samples (*right*)

used. The Box–Behnken model could be used to evaluate linear as well as quadratic or cubic relationships between the test and response variables. A total of 46 experiments were required for optimization, including six center samples. All response variables were measured as per screening study with the exception of colour and roughness which were excluded. In addition, drug content uniformity was assessed and it was determined by HPLC.

All models generated were checked for model significance in addition to lack of fit. Only significant models ($p<0.05$) and those displaying non-significant lack of fit (lack of fit $p>0.05$) were further analyzed. These models were used in the generation of response surface plots. From the response surface plots, it was possible to predict the corresponding responses when process parameters were altered. Response surface modeling described in this section would be important for subsequent response optimization.

During screening, orifice pressure and air flow rate were found to increase with increase in plenum pressure. However, the increase was non-linear and this was not detected during screening. According to response surface analysis for these two response variables, R^2 of the quadratic models describing orifice pressure and air flow rate were 0.988 and 0.967, respectively. This meant that the model was describing the orifice pressure and air flow rate very well. Temperature was also a significant contributory factor in affecting the responses. At the same plenum pressure, increase in temperature raised both air flow rates and orifice pressure, but to a lesser extent for the latter. This observation further exemplified that even though screening alone was useful in giving the broad picture, it had certain inadequacies. Since changes to temperature also affected air flow rate and orifice pressure, the effects of temperature should be considered when controlling the movement of tablets in the Supercell coater. Figure 4a and b show the effects of increasing plenum pressure on air flow rate and orifice pressure at different temperatures.

For all conditions employed, the CPE values were more than 97.5% and twinning was not observed in many of the batches. Hence, CPE and twinning were unable to be modeled satisfactorily via response surface methodology and thus were unsuitable as response variables for optimization of the coating condition.

On the other hand, temperature, plenum pressure, spray rate, atomizing air pressure, plenum pressure × spray rate were significant in affecting tablet damage or chipping. A quadratic model of chipping tendencies resulted in R^2 value of 0.823. The extent of tablet damage was considered one of the most important response variables for tablets coated using the Supercell coater. Great care must be taken to avoid tablet damage as this would severely affect the quality of the tablet batch. Chipping was therefore weighted heavily for process optimization. The response surface plot for chipping tendencies is shown in Fig. 4c.

Thickness measurements at any locations of the tablet have implications on coat uniformity. Coat thickness should be uniform at all locations and this is especially important in controlled release tablet coats. However, due to the limitations of coat thickness estimations using the micrometer screw gauge, the greatest accuracy for coat thickness measurements could be obtained from the central band or edge of the tablet. Coat thickness in these locations were less variable than that at the tablet face and were therefore more suitable for model development in coat thickness prediction (24). Higher variability at tablet face was due to elastic recovery of tablet core materials. The model based on tablet central band measurements had R^2 value of 0.837 with inlet temperature, atomizing pressure, plenum pressure, squared-effects of inlet temperature, plenum pressure × temperature, temperature × spray rate showing significant effects. On the other hand, the model based on tablet length measurements had R^2 value of 0.717, with inlet temperature, plenum pressure, squared-effects of temperature, plenum pressure × spray rate showing significant effects. Since the model based on tablet central band coat thickness had a greater R^2, it was a better fit compared to the model built on tablet length measurements. There was a significant lack of fit for the model built on coat thickness at tablet face. Figures 4e and f showed response surface plots of coat thickness at tablet edge and tablet central band, respectively.

The model for RSD of face and central band coat thickness fitted the data obtained but this was not so for the RSD of coat thickness at tablet edge. The model for RSD of coat thickness at the tablet face had R^2 value of 0.717. This was slightly higher than the R^2 value of coat thickness RSD at the tablet central band which was 0.680. However, tablet central band thickness variation would reflect the actual coat thickness variation more accurately. Batch size, plenum pressure, spray rate, squared effects of atomizing pressure, and squared effects of spray rate were significant in affecting RSD of coat thickness at the tablet central band. Conversely, batch size, temperature, squared effects of atomizing pressure, and squared effects of spray rate were significant in affecting RSD of coat thickness at the tablet face. Figure 4g shows the response surface plot for RSD of coat thickness at the tablet central band. Model for inter-tablet coat thickness RSD had R^2 value of 0.688 with batch size, squared effects of batch size, squared effects of atomizing pressure, squared effects of spray rate, and squared effects of plenum pressure showing significant effects. Figure 4h shows the response surface plot for inter-tablet RSD of coat thickness. On the other hand, the model for intra-tablet coat thickness variation did not fit the data well.

Figure 4d shows the response surface plot for DLE. A quadratic model was used to generate the plot and it was found to have R^2 value of 0.869. Data was log-transformed prior to response surface analysis to reduce skewness of the data. An ideal DLE was expected to be as close to 100% as possible. In-process losses of the active ingredient had to be minimal for the process to be economically viable (25). Content variation would also be of critical importance when actives were coated onto the tablets. Only batch size was shown to be significant in affecting DLE. A trough was observed in the response surface plot for DLE, indicating greater drug deposition when the batch size was near the lower and higher levels. At higher batch sizes, this was probably due to the presence of a greater surface area to capture the coating spray with lesser material being lost as exhaust. At lower batch sizes, the predominating factor could be due to the faster turnaround for coating of tablets. Since the tablet cycling time was lower, tablets made more passes through the coating zone and this mitigated the reduction in surface area. All squared effects were significant. The RSD of

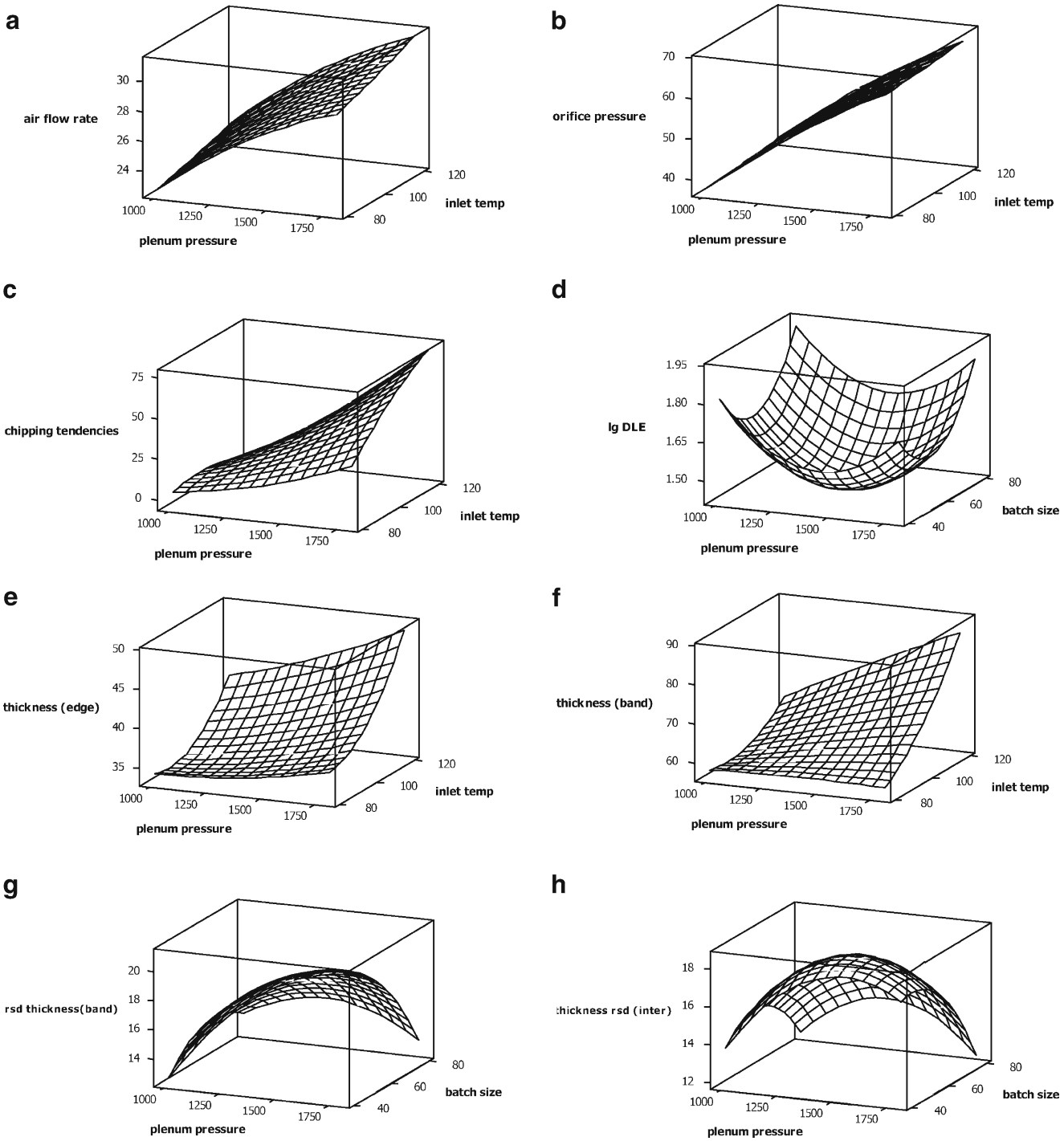

Fig. 4. Response surface plots for **a** air flow rate, **b** orifice pressure, **c** chipping/tablet damage, **d** Log (DLE), **e** coat thickness at tablet edge, **f** coat thickness at tablet band, **g** RSD of coat thickness at tablet band, and **h** inter-tablet coat thickness RSD. Hold values for process parameters not included in the response surface plots were defined as the center values of the studied range for that particular process parameter

DLE was found to range between 4.97% and 37.65% for the coating conditions studied (data not shown). The RSD of DLE would be important in process optimization for the coating of actives. However, response surface analysis of the RSD of DLE obtained in this study did not display adequate model fit. Hence, this response was not used for subsequent optimization.

The response surface models for DLE, chipping tendencies and RSD of coat thickness at tablet central band were used for optimization. Optimized conditions should maximize DLE while minimizing the incidences of tablet damage and variations in coat thickness.

Response Optimizer

The simultaneous optimization of the individual responses resulted in an optimum value whereby trade-offs

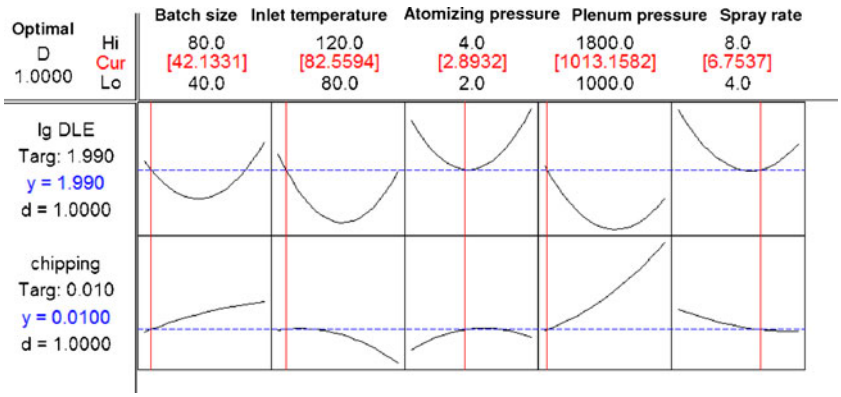

Fig. 5. Response optimization of drug-loading efficiency (DLE) and chipping tendencies with optimized conditions in brackets

between individual optima were used to obtain the best compromise. MINITAB calculates individual desirabilities for the responses and combines them to provide a measure of the overall desirability of the multi-response system. Composite desirability (D) is a measure of how the solution has satisfied the combined goals for all the responses and range from zero to unity. Unity represents the ideal case while zero indicates that one or more responses are outside their acceptable limits. The optimal operating conditions were determined by maximizing D. Through the response optimizer function in MINITAB, it was possible to optimize the process conditions (A–E) which would lead to the highest DLE (i.e., highest coating yield) and minimal chipping tendencies. Figure 5 shows the recommended solution for the target response values. D was found to be 1. When RSD of coat thickness at the tablet central band was added as response variable for optimization, optimal D was lowered to 0.821 (Fig. 6). However, it was interesting to note how the optimal parameters had shifted to the other end of the design space. This was due to the quadratic nature of most of the response variables with respect to the process variables. Many squared effects of process variables were significant, which indicated significant curvature in the response surfaces. In both figures, values in brackets were the optimized conditions. Each graph on the figures represented individual response surfaces for the range of process parameter settings examined (x-axis) against the responses measured (y-axis). The horizontal dotted lines on the figures signified the achieved values of response at the predicted optimum of each process parameter which was in turn indicated by the vertical lines.

When carrying out response optimization, greater importance and weight was placed on DLE and chipping tendencies, while keeping variation tablet thickness to a minimum. This response optimizer function may also be used for predicting the responses when new process conditions were employed. Results for optimization could only be accurately extrapolated to tablets of the same shape and dimensions as used in this study. This was because flow properties of tablets in the coater could change when tablets were of different physical dimensions. Results were also only fully applicable when a similar coating formula was used. However, these findings would allow better choice of working range settings for process parameters in optimization studies. The process of response optimization becomes increasingly difficult when

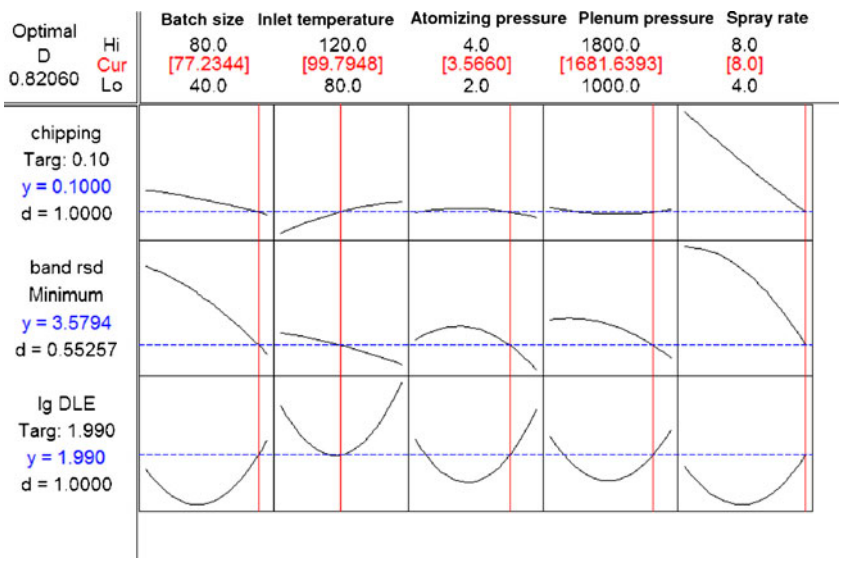

Fig. 6. Response optimization of drug-loading efficiency (DLE), chipping tendencies and coat thickness RSD at tablet central band with optimized conditions in brackets

more response variables were included. The optimal conditions predicted will also be altered. The selection of response variables for optimization should depend on the main purpose of coating. Chipping tendencies should always be weighted heavily for optimization in Supercell coating. The yield and inter-tablet RSD of drug distribution will be important in active coating. On the other hand, RSD of coat thickness will be more critical for controlled release coatings.

Principal Component Analysis

Principal component analysis (PCA) is a projection method whereby information carried by the original variables were projected onto a smaller number of underlying ("latent") variables called principal components. In this study, the data from both the screening and optimization designs were pooled together for the generation of a PCA model. The first principal component (PC1) covers as much of the variation in the data as possible. The second principal component (PC2) is orthogonal to the first and covers as much of the remaining variation as possible, and so on. By plotting the principal components, interrelationships between different variables, sample patterns, groupings, similarities, or differences may be detected. Before generating the PCA model, data was first normalized. Different responses were measured using different instruments, with different measurement units and under different conditions. Application of weights allowed data to be transformed to approximately the same scaling and allowed a more even distribution of variances and average values. Besides DLE which was already log-transformed, weights (1/SD) were applied to all the other variables. All data from experiments carried out during screening and optimization were pooled to give additional data for PCA modeling. Colour tests were not performed during optimization study and drug content tests were not performed on screening batches. Thus, colour and content tests were not used to build the PCA model.

In this study, PC1 and PC2 together explained 55% of total X variation. Figure 7 shows the correlation loadings plot for all process and response variables. The outer ellipse indicates 100% explained variance. The inner ellipse indicates 50% of explained variance. Variables which were found within the inner circle of the loadings plot and close to the origin were not significant factors. An interesting observation was seen from the PCA loadings plot of this study. The varied processing factors did not appear to explain much of the variances present in the data as they were located in the inner ellipse near the origin of the loadings plot (region A). This means that these variables were poorly explained by the plotted PCs and cannot be interpreted in the plot. Only plenum pressure appeared to be correlated strongly to other response variables. Plenum pressure was positively correlated to air flow rate, orifice pressure and chipping tendencies (region C). Region C and region B or D have independent variations since they were orthogonal to one another. Regions B and D were explained mainly by PC1 but region C was to a greater extent explained by PC2. Coating level, coating time, and coat thickness at tablet central band were positively correlated (region D). Inter-tablet coat thickness RSD was also positively correlated to coat thickness RSD at tablet central band (region B). Regions B and D were negatively correlated to each other. With increasing coating times and coat thickness, inter-tablet variation would certainly be reduced.

Many of the findings from the PCA were not unexpected. PCA was useful to give a broad picture of the inter-relationships between different variables. The fact that many of the processing variables were poorly explained by the model was believed to be due to insufficient sensitivity of the response variables in detecting the difference or that they were insufficiently correlated to the process variables. However, it could also mean that changes to the levels of the processing variables across the design space did not result in drastic changes to the outcome which concludes that the Supercell coating process was quite robust.

CONCLUSION

This study had enabled a greater understanding on the operation of the Supercell coater. The effects of process parameters and their interactions on response variables were investigated. Screening study had shown that for most of the response variables measured, changes to process parameters resulted in a non-linear change in response. Interaction effects between process parameters were also found to be complex. Film coating in the Supercell coater is a very

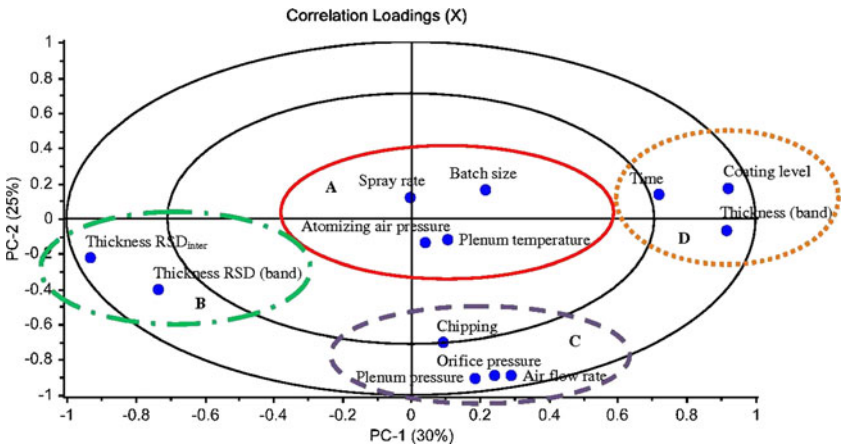

Fig. 7. PCA correlation loadings plot for process and response variables

complicated process and many factors could inter-play to affect the process as well as the response variables studied. Thus, optimization based empirically on various tests and response variables is extremely challenging. This study had shown the immense prospects of using statistically designed experiments to optimize the Supercell coating process. By using response surface methodology and optimization, coating conditions which produced coated tablets of high drug-loading efficiency, low chipping tendencies, and low-coat thickness variation were defined. Optimal conditions were found to vary over a range when different responses were considered. Changes in processing parameters across the design space did not result in drastic changes to coat quality, thereby demonstrating robustness in the Supercell coating process. It was possible to use DoE for future optimizations of formulations in the investigation on the Supercell coater. Moreover, since the optimization study took into consideration the various quality aspects of a coated tablet, results were also likely to be more accurate at predicting an optimized set of process conditions for coating.

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