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Identification of critical process variables for coating actives onto tablets via statistically designed experiments

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Abstract

The objective of this work was to identify, using a statistical experimental design, the critical processing variables that affect content uniformity and loading of active agent coated on tablets in a 24″ Accela-Cota. United States Pharmacopeia (USP) specifies that the % relative standard deviation (RSD) of drug content within a batch should be less than 6%. A Plackett–Burman experimental design was used to identify the process variables that influence the content uniformity and loading efficiency of the drug in the aqueous-based film coat of the tablets. The process variables investigated were inlet airflow, pan speed, inlet air temperature, coating time, atomization pressure, and fan pressure. Atomization pressure was identified as a major variable with respect to content uniformity ($P < 0.01$). Pan speed and coating duration were also identified as variables significantly affecting content uniformity ($P < 0.05$). Fan pressure was identified as a critical variable affecting recovery ($P \ll 0.01$). Temperature also significantly affected recovery ($P < 0.05$). A good correlation was obtained between observed and predicted values for content uniformity ($r^2 = 0.85$) and recovery ($r^2 = 0.95$). It was possible to achieve % RSD less than 6% while maintaining the recovery at 80% or higher.

Keywords: Accela-cota; Coating; Experimental design

1. Introduction

Aqueous film coating of tablets is generally performed in different kinds of coating pans. The uniformity of tablet coating is very important as it affects the organoleptic quality of tablets and functionality of the coating, especially in the case of modified release formulations (Fourman et al., 1995). Aqueous film coating is a sensitive process in which a number of variables can affect the quality of the final product. Nature of coating, uniformity of coating and quantity applied affect release rates of the active drugs in the tablet core. There is also a growing interest in incorporating active ingredients in the coating. This approach can be used to load an immediate release dose in a sustained release formulation of one or more drugs or to separate incompatible drugs in combi-

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nation therapy. For this technique to be useful, the maximum variation in the drug content permitted by United States Pharmacopeia (USP 24, 2000) is less than 6% relative standard deviation (RSD). Content variation may result from formulation variables such as drug solubility, environmental variables like evaporation, settling, temperature changes or processing variables. Hence it is very important to identify the critical process variables, which affect the content uniformity when actives are coated on tablets. Another aspect that must be considered is drug loading efficiency of the process. In-process losses of the active ingredient have to be minimal if the process is to be economically viable.

Accela-Cota is a type of side-vented coating pan in which drying efficiency is improved by perforated design of the pan resulting in better coating uniformity (Mehta, 1997). It offers an alternative to fluid bed coating apparatus for incorporating actives in the tablet coat. Some of the early literature on Accela-Cota focused on process variables critical for movement of tablets in the pan (Leaver et al., 1985), material carryover and process efficiency (Kara et al., 1982), and drug/excipient migration into the film (Dansereau et al., 1993). One report focused on identification and optimization of some process parameters for improved physical properties of aqueous film coat in a side vented coating pan similar to Accela-Cota (Heinamaki et al., 1997). The importance of some process variables on uniformity of coating was investigated by quantifying a dye included in the tablet coat (Skultety et al., 1988). Although, this study resulted in identifying some of the variables important for coating uniformity, the variability remained higher than accepted value ($>6\%$ RSD). Also this study did not take into consideration the target dose and therefore, drug loading efficiency in the coating could not be quantified. However, coating efficiency and content uniformity are the two most important considerations in a commercial coating process, especially if drug active is to be coated onto tablets. Hence, it was thought to be necessary to investigate both of these response factors via statistically designed experiments to enable the use of a 24″ Accela-Cota. F, D and C Yellow # 6 dye was chosen as a surrogate marker for a water-soluble active agent. This dye was chosen because it can be analyzed easily by visible spectroscopy, none of the excipients used interfered in the assay, and it had no incompatibilities with the excipients. Plackett–Burman screening design consisting of 16 runs with three replicates was constructed and the data was analyzed by the software Echip version 6.0.

Table 1
Coating composition of subcoat and active coat

Ingredient	Quantity per tablet (mg)
(A) Composition of subcoat	
HPMC 2910, 6 cps	16.07
PEG 3350	3.16
Purified water[a]	141.09
(B) Composition of active coat	
HPMC 2910, 6 cps	17.00
PEG 3350	4.25
F, D and C Yellow # 6	5.00
Purified Water[a]	205.25

[a] Water is evaporated during coating.

2. Materials and methods

2.1. Materials

F, D and C Yellow # 6 was obtained from Warner Jenkinson (St. Louis, MO). Lactose anhydrous was procured from Sheffild Products (Norwich, NY). Microcrystalline cellulose PH102 (MCC) was obtained from FMC Corp. (Princeton, NJ). Magnesium stearate was obtained from Mallinckrodt (St. Louis, MO). HPMC 2910 (6 cps) and PEG 3350 were obtained from Shi-Etsy Chemicals (Tokyo, Japan) and Union Carbide Corporation (Danbury, CT), respectively.

2.2. Preparation of coating solution

Coating composition of subcoat and color coat is given in Table 1A and B, respectively. Coating solutions were prepared by dispersing polyethylene glycol and HPMC in half the quantity of purified water heated to 70 °C and gradu-

Table 2
Plackett–Burman design showing levels of process variables and observed and fitted values of response variables

Trial	X_1	X_2	X_3	X_4	X_5	X_6	Y_1	Y_2	Y_1^*	Y_2^*
2	10	30	20	200	4	70	4.3	62.14	5.46	63.55
3	30	10	20	400	2	70	8.09	76.98	9.00	77.64
2	10	30	20	200	4	70	3.33	64.69	5.46	63.55
12	10	10	12	200	2	50	6.44	82.92	6.86	84.42
13	10	20	20	200	4	60	5.48	73.78	4.71	73.75
8	30	30	12	200	2	70	11.46	62.12	11.58	63.13
13	10	20	20	200	4	60	6.48	70.10	4.71	73.75
1	30	30	12	400	4	70	9.26	63.23	8.85	63.84
9	30	30	20	200	2	50	10.65	68.34	9.61	64.43
10	10	30	20	400	2	50	5.48	62.13	5.46	64.60
4	10	30	12	400	4	50	4.3	70.82	4.72	67.97
5	10	10	20	200	4	70	6.04	83.91	4.87	80.72
11	30	10	20	400	4	50	5.72	82.14	6.29	82.31
7	30	10	12	200	4	50	7.36	84.17	8.28	84.96
6	10	10	12	400	2	70	7.23	82.21	6.84	80.47
1	30	30	12	400	4	70	9.93	63.17	8.85	63.84

Process variables: X_1, atomization pressure (psi); X_2, fan pressure (psi); X_3, pan speed (RPM); X_4, inlet air flow (cfm); X_5, spray time (h); X_6, inlet air temperature (°C). Response variables: Y_1, % RSD (observed); Y_1^*, % RSD (fitted); Y_2, % recovery (observed); Y_2^*, % recovery (fitted).

ally diluting with remaining amount of water at room temperature. The dye was added to the clear coating solution when required.

2.3. Qualitative evaluation of spray pattern

Active coat solution was sprayed on a blank sheet fixed at a distance of 9″ from spray gun using the combinations of atomization air pressure and fan air pressure given in Table 2. The shape of the resulting spray pattern was recorded. The color intensity of the spray pattern was inspected visually.

2.4. Preparation of core tablets

Lactose (69%), MCC (30%) and magnesium stearate (1%) were mixed in a planetary mixer for 10 min and tablets were compressed by direct compression technique on a high speed Elizabeth-Hata tablet press using oval biconvex punches. Average weight and hardness of tablets were 800 mg and 20 scu (Strong-Cobb unit), respectively. It is noted that 1 scu = 0.71 kilopounds (Diem et al., 1970).

2.5. Statistical experimental design

Six processing variables with potential to influence content uniformity and percent drug loading, were examined. They were atomization pressure (X_1), fan pressure (X_2), pan speed (X_3), inlet airflow (X_4), coating time (X_5) and inlet air temperature (X_6). A Plackett–Burman screening design with 16 experiments including three replicates was constructed using the software, Echip version 6.0. Using this design the magnitude of each variable on each resulting product property can be estimated independently of all other tested variables. Each variable was tested at two levels, low and high. This is depicted in Table 2 along with the response variables. Response variables were content uniformity (% RSD) and % recovery. The effects of independent process variables were analyzed by the linear model, $y = a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_4X_4 + a_5X_5 + a_6X_6$. The pan load was 8 kg per run (approximately 10 000 tablets). The exhaust airflow rate were 400 and 550 cfm adjusted for low and high levels, respectively of the inlet airflow. Other variables like baffles, tablet bed weight, application rate and distance of the gun from tablet bed were kept

constant (Skultety et al., 1988). The coating solution was sprayed from a distance of 9 in. onto the tablet bed at a rate of 20 ml/min. The tablets were dried in the coating pan at 60 °C for 15 min and then overnight at room temperature.

2.6. Determination of dye content

Twenty tablets were selected randomly from different locations in the coating pan. The dye was extracted from individual tablet in distilled water by sonication. The extract was filtered, suitably diluted and the absorbance was read at 482 nm.

3. Results and discussion

3.1. Qualitative evaluation of spray pattern

A combination of higher atomization and lower fan pressure resulted in a narrow and non-uniform, circular spray pattern with decreasing intensity outward. Low atomization and low fan pressure resulted in broader and uniform spray. Lower atomization and higher fan pressure resulted in uniform spray pattern, elliptical in shape and covering the largest area. High atomizing pressure and high fan pressure resulted in a non-uniform and elliptical spray pattern. In general the combinations with low atomization pressures gave the most uniform spray pattern with respect to color intensity. The combinations containing higher atomization pressures gave non-uniform color intensity.

Table 3
Statistical analysis of results obtained from Plackett–Burman design

Process variables	Response variables	
	% RSD	% Recovery
Atomization pressure (psi)	3.24[a]	NS
Fan pressure (psi)	NS	−17.17[c]
Pan speed (RPM)	−1.07[b]	NS
Inlet air flow (cfm)	NS	NS
Spray time (h)	−1.81[b]	NS
Inlet air temperature (°C)	NS	−3.23[b]

The values are estimated mean % effects. NS, not significant.
[a] $P < 0.01$.
[b] $P < 0.05$.
[c] $P \ll 0.01$.

3.2. Evaluation of process variables using experimental design

In order to achieve content uniformity of active agent present in tablet coat within USP requirements, the coating process must be adequately controlled. Critical process variables are those parameters that have potential to affect the uniformity and efficiency of coating process. These critical process variables can either affect mixing pattern of tablets or spray pattern of coating solution, which can individually or collectively affect coating process. This study was undertaken with a specific aim of identifying those variables, which can be controlled in order to make Accela-Cota suitable for coating actives on tablets. The target dose per tablet was fixed at 5 mg. In this study, six variables potentially affecting mixing pattern of tablets and/or spray pattern of coating solution in Accela-Cota were selected. Atomization pressure, fan pressure, inlet airflow, and inlet air temperature can potentially affect the spraying, whereas pan speed, and coating time have the potential to affect tablet mixing. Statistical analysis of the results showing the estimated effects is presented in Table 3.

Atomization pressure of the spray was identified as the most influencing variable with respect to content uniformity ($P < 0.01$). Increasing atomization pressure from 10 to 30 psi resulted in mean relative increase of 3.24% in % RSD. This result is in agreement with the earlier qualitative analysis of spray pattern in which visible non-uniformity was observed when coating solution was sprayed at a high atomization pressure. Pan speed and coating time also influenced uniformity positively to a lesser extent ($P < 0.05$). Increasing pan speed from 12 to 20 rpm and coating time from 2 to 4 h reduced % RSD by 1.07 and 1.81%, respectively. Increasing pan speed probably results in better mixing of tablets and hence better content uniformity. Increasing coating time also helps in improving content uniformity by increasing mix-

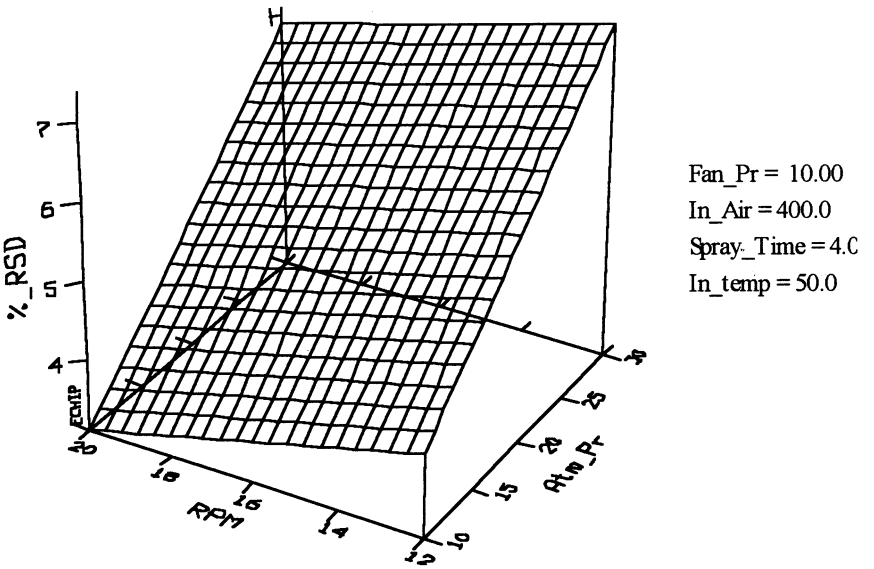

Fig. 1. Response surface plot showing effect of atomization pressure and pan speed on % RSD (content uniformity). Atm_Pr, atomization pressure in psi; Fan_Pr, fan pressure in psi; In_Air, inlet airflow in cfm; Spary_Time, coating time in hours; In_Temp, inlet air temperature in °C; and RPM, pan speed in rotations per minute.

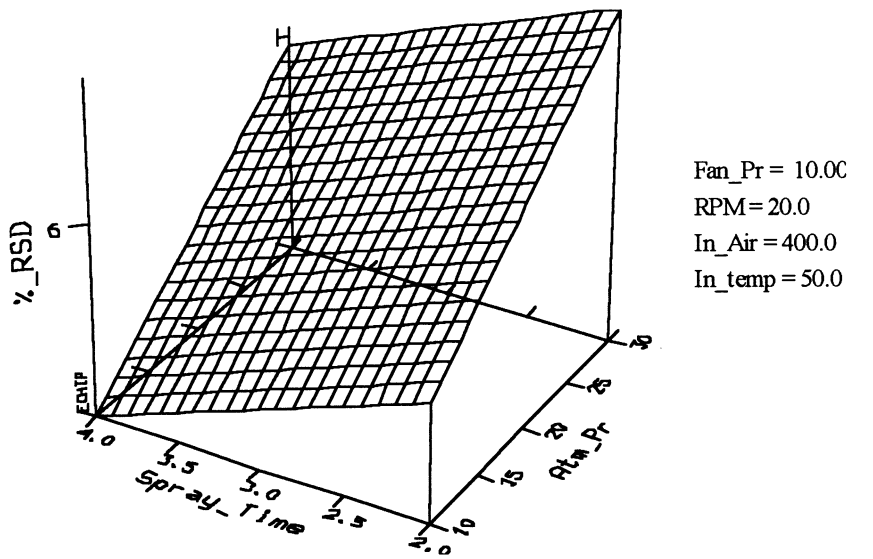

Fig. 2. Response surface plot showing effect of atomization pressure and coating time on % RSD (content uniformity). Atm_Pr, atomization pressure in psi; Fan_Pr, fan pressure in psi; In_Air, inlet airflow in cfm; Spary_Time, coating time in hours; In_Temp, inlet air temperature in °C; and RPM, pan speed in rotations per minute.

ing time. Figs. 1 and 2 show the response surface plots for % RSD. These three process parameters are clearly the most important in improving uniformity. A good correlation was obtained in observed versus fitted values ($r^2 = 0.85$). The other three variables viz. fan pressure, inlet airflow and

temperature did not significantly affect content uniformity ($P > 0.05$).

The second response variable was % recovery of the dye on tablets indicating the drug loading efficiency of the process. For the process of coating actives on tablets to be economically viable, the loading efficiency has to be adequate. As the data suggests, only two out of six variables influenced % recovery. Fan pressure had the greatest impact on the recovery of the dye ($P \ll 0.01$). The mean % recovery decreased by 17.17% with increased fan pressure. Increased fan pressure caused the spray pattern to elongate in the direction perpendicular to the axis of the pan. Although, this resulted in more uniform spray (as was evident from qualitative studies) covering larger area, it also possibly caused the coating solution to spray on the area outside of the tablet bed, resulting in the loss of active. Inlet temperature had a moderate effect on % recovery ($P < 0.05$). Increase in temperature caused a mean relative decrease of 3.23% in recovery. Increased temperature was responsible for spray drying during process. None of the other variables were critical with respect to recovery ($P > 0.05$). There was an excellent correlation between observed and fitted values ($r^2 = 0.95$). Fig. 3 shows the response surface plot for % recovery. It is clear from this plot that at least 80% recovery is possible to achieve in this process even when the parameters responsible for content uniformity are controlled to achieve % RSD below 6%.

This observation was confirmed theoretically by using the combined response feature in Echip. A combined response is a weighted sum of scaled individual responses. It is a strategy for simultaneous optimization of individual responses. The optimum value of this combined response is the trade-off between individual optima to get the best compromise. The two individual responses, RSD and recovery have very different scales. Therefore, they needed to be mapped to a uniform scale so that they could be fairly combined. We created a combined response using Echip in such a way, that % RSD was minimized and % recovery was maximized. In this procedure, response surface of % RSD was inverted and then mapped to a uniform scale whereas response surface of % recovery was simply mapped to uniform scale before combining. This procedure resulted in an average optimum value of 4.87% for % RSD while maintaining recovery at 80.72%. The average value of the combined response was 2.65. The simultaneous optimization procedure resulted in the best case scenario with % RSD of 1.37%, % recovery of 87.78% and a combined response of

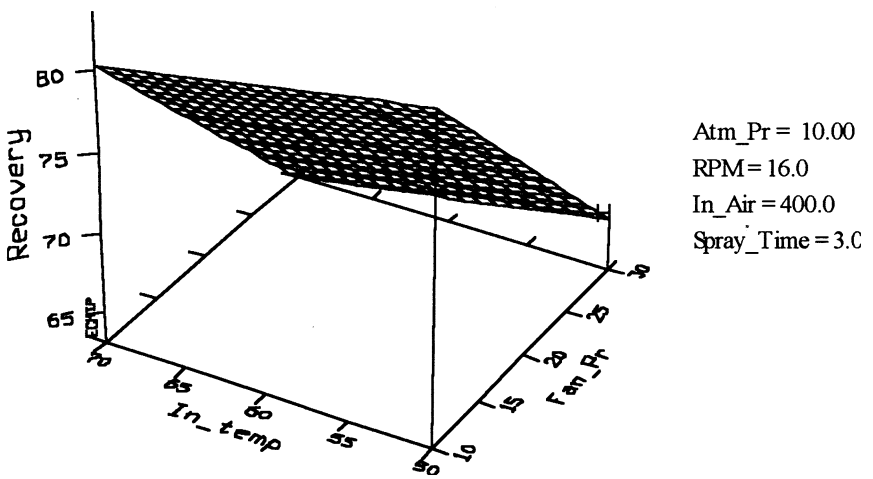

Fig. 3. Response surface plot showing effect of fan pressure and inlet air temperature on dye recovery in % (coating efficiency). Atm_Pr, atomization pressure in psi; Fan_Pr, fan pressure in psi; In_Air, inlet airflow in cfm; Spary_Time, coating time in hours; In_Temp, inlet air temperature in °C; and RPM, pan speed in rotations per minute.

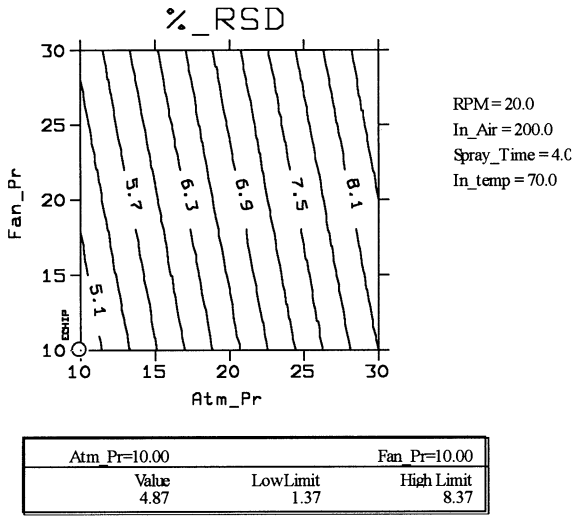

Fig. 4. Contour plot showing optimized conditions for % RSD (content uniformity). Atm_Pr, atomization pressure in psi; Fan_Pr, fan pressure in psi; In_Air, inlet airflow in cfm; Spary_Time, coating time in hours; In_Temp, inlet air temperature in °C; and RPM, pan speed in rotations per minute.

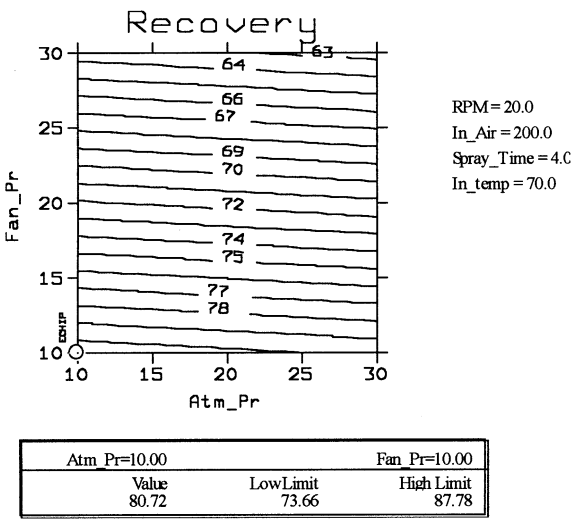

Fig. 5. Contour plot showing optimized conditions for dye recovery in % (coating efficiency). Atm_Pr, atomization pressure in psi; Fan_Pr, fan pressure in psi; In_Air, inlet airflow in cfm; Spary_Time, coating time in hours; In_Temp, inlet air temperature in °C; and RPM, pan speed in rotations per minute.

3.43. It also predicted the worst case scenario with % RSD of 8.37%, % recovery of 73.66% and a combined response of 1.87. Figs. 4–6 show the contour plots of optimized conditions for % RSD, % recovery and the combined response as well as theoretically optimized values of the independent variables.

This report focuses on screening critical process variables by employing a simple linear model. We have successfully identified the critical process variables via statistical analysis. We have also shown that it is possible to achieve an acceptable content uniformity, % RSD $< 6\%$, while maintaining a high recovery, $> 80\%$. To further optimize the model to one with predictive power, a higher polynomial such as a quadratic model may be necessary. This usually requires augmenting the current design with additional experimentation. It is also noted that, in the present study, a simple solution coating formulation comprising of a soluble dye has been used in order to focus on the processing variables. In practice, many insoluble drugs would require the use of suspension. In that case, formulation factors along with process variables will require optimization in order to achieve

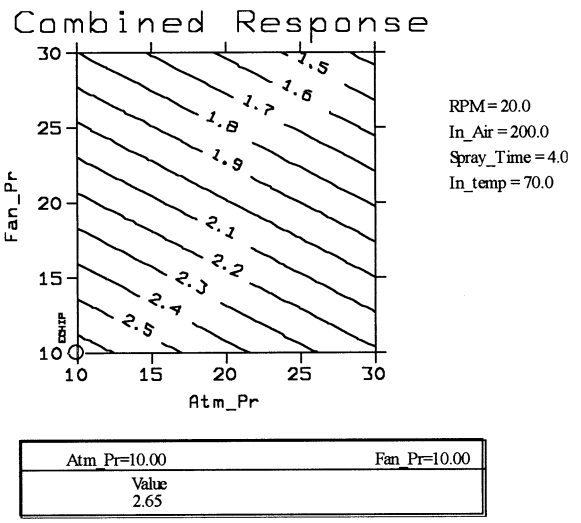

Fig. 6. Contour plot showing optimized conditions for the combined response (see text). Atm_Pr, atomization pressure in psi; Fan_Pr, fan pressure in psi; In_Air, inlet airflow in cfm; Spary_Time, coating time in hours; In_Temp, inlet air temperature in °C; and RPM, pan speed in rotations per minute.

acceptable content uniformity and optimum recovery. This will be the subject of a future investigation.

4. Conclusions

Atomization pressure, pan speed and duration of coating were found to be critical process variables in order to achieve acceptable content uniformity of the tablets coated using 24″ Accela-Cota. Lower atomization pressure, higher pan speed and longer duration of coating seem to favor good content uniformity. Fan pressure and inlet air temperature, were important with respect to coating efficiency, i.e. recovery of the dye. Lower fan pressure and temperature favor good recovery. It is possible to achieve % RSD less than 6% while maintaining the recovery at 80%. Hence it is feasible to use, a perforated coating pan such as 24″ Accela-Cota to develop a coated tablet drug product containing an active agent in the film coat.

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