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https://doi.org/10.31925/farmacia.2023.1.4 **ORIGINAL ARTICLE**

OPTIMIZATION STUDY OF AQUEOUS FILM-COATING PROCESS IN THE INDUSTRIAL SCALE USING DESIGN OF EXPERIMENTS

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Abstract

Experimental design approach has been used for optimization of film-coating phase of the immediate release tablets manufacturing process in order to evaluate the effects of the potential critical process parameters (CPPs) and define the optimal operating conditions. Optimization was performed during the transfer of the process on a film-coating machine for pilot and industrial scale production. Immediate release ready-to-use coating system Opadry® White was used as the coating. Central Composite Orthogonal design with 17 coating runs of size of 103000 pcs was used for the study. The ranges of film-coating process parameters: inlet air flow, inlet air temperature and spray rate for the spraying stage of the coating process were optimized and the effects on: hardness, disintegration time, coating defects, coating efficiency and coating time were evaluated. The results showed that among the process parameters, the spray rate had the highest significant effect on all responses. The inlet air temperature showed a significant effect on the disintegration time. Interaction effects of the spray rate with the inlet air flow were found to be significant for the coating efficiency and disintegration time. Target values and sweet spot area were set for the parameters of the process in order to gain results with fastest disintegration time, highest coating efficiency, lowest number of coating defects, fastest coating time and hardness within the predetermined acceptance criteria.

Rezumat

Abordarea prin design experimental a fost utilizată pentru optimizarea fazei de acoperire în procesul de fabricație a comprimatelor cu eliberare imediată, pentru evaluarea efectelor potențialilor parametri critici ai procesului (CPP) și definirea condițiilor optime de funcționare. Optimizarea a fost efectuată în timpul transferului procesului folosind un echipament de acoperire pentru producție pilot și industrială. Sistemul de acoperire cu eliberare imediată a fost Opadry® White. Pentru studiu a fost utilizat un design ortogonal central compozit cu 17 serii de acoperire cu dimensiunea de 103000 buc. Au fost optimizați parametrii procesului de acoperire cu film: debitul de aer de admisie, temperatura aerului de intrare și rata de pulverizare pentru etapa de pulverizare a procesului de acoperire și au fost evaluate efectele asupra: durității, timpului de dezintegrare, defectelor de acoperire, eficienței acoperirii și timpului de acoperire. Rezultatele au arătat că dintre parametrii procesului, rata de pulverizare a avut cel mai semnificativ efect asupra tuturor răspunsurilor. Temperatura aerului de intrare a arătat un efect important asupra timpului de dezintegrare. Efectele de interacțiune ale vitezei de pulverizare cu fluxul de aer de intrare s-au dovedit a fi semnificative pentru eficiența acoperirii și timpul de dezintegrare. Valorile țintă și aria punctului favorabil au fost stabilite pentru parametrii procesului, pentru a obține rezultate cu cel mai rapid timp de dezintegrare, cea mai mare eficiență de acoperire, cel mai mic număr de defecte de acoperire, cel mai rapid timp de acoperire și duritate, în cadrul criteriilor de acceptare predeterminate.

Keywords: optimization; film-coating; experimental design; process parameters

Introduction

The aqueous film-coating process in a perforated coating pan is a widely used method in the pharmaceutical industry and is a critical step in the manufacturing of oral solid dosage forms – tablets. During the coating process, a polymer-based coating suspension is dispersed as droplets on the moving tablet bed in a rotating coating pen forming a thin layer on the surface of the tablets as the coating is dried. Depending on its use, the film-coating could be functional or non-functional. In order to ensure a process that is both efficient and results with a satisfactory quality attributes of the tablets with minimum coating defects, multiple process parameters need to be controlled [15, 21]. The process parameters of the aqueous coating process may also have a potential effect on critical quality attribute (CQAs) of film-coated tablets such as disintegration time, hardness and dissolution [12].

Potential critical process parameters (CPPs) of the film-coating process include: spray rate, atomization and pattern air, inlet air flow, inlet and outlet air temperature and pan speed. The inlet air flow [2] and temperature are important process parameters which contribute to the drying conditions inside the coating pan. High inlet air temperature increases the drying efficiency of the aqueous film-coating process [12], but this could also result in a loss of coating efficiency [14]. The parameters of the spraying of the coating solution through the spray nozzle, atomization and pattern air and their ratio, and also the ratio of the atomization air and pattern air are important for the size of the droplet and the width of the tablet bed area affected by the droplets of the coating solution [1]. The spray rate may also affect the droplet characteristics [6] and speed and the quality of the coating. Coating defects such as twinning, picking, sticking and logo-bridging may arise from high spray rates. A significant correlation has been established between the relative humidity of the tablet bed and the number of coating defects of logo-bridging [10, 11]. Low spray rate, on the other hand, may result with lower coating efficiency and spray drying. Spray rate along with inlet air temperature may significantly affect appearance of tablets through surface roughness measurement [20]. The speed of the pan is also important for ensuring proper distribution of the coating solution on the tablet bed and therefore coating uniformity. Tablet shape along with speed of pan may also affect coating uniformity [19]. The solids content and viscosity of the coating suspension and the formulation of the tablet core are other factors which can also have an effect on the critical quality attributes (CQAs) of the coating process.

With the inclusion of QbD principles and tools in formulation and process development extensive knowledge is gathered for the product which helps improve and maintain its quality throughout the life-cycle of the product. Experimental design has been widely used as a statistical quality-by design (QbD) tool for optimization of the process and increasing product and process knowledge. A limited number of studies [3-5, 9, 13, 16, 17] are described in literature for the optimization of the film-coating process with experimental design.

In our study, an optimization of the film-coating process using experimental design was performed in order to ensure a robust coating process after acquiring a new coating equipment O’Hara Labcoat 100 for industrial scale production of cefixime 400 mg film-coated tablets. The scalability of the coating process is difficult and further optimization in the industrial scale is necessary in order to gain a robust process. Preliminary coating trials, equipment manufacturer recommendations and parameters on previous coating pan in the facility were used for establishing the starting set of potential CPPs of the coating phase and their ranges. The ranges for the parameters inlet air flow, inlet air temperature and spray rate of the coating stage were optimized while parameters pan speed, atomization and pattern air pressure were kept constant. The effects on quality attributes of the film-coated tablets: hardness, disintegration time, coating defects, coating efficiency and coating time were evaluated, and optimal operating conditions were set.

Materials and Methods

The film-coating was performed on a generic product by Alkaloid AD - Cefixime® 400 mg film-coated tablets. The film-coated tablets are white to slightly cream oblong biconvex film-coated tablets with bisection line on one side, and have the following excipients: cellulose, microcrystalline as disintegrant, filler, starch pregelatinized as binder, disintegrant, calcium hydrogen phosphate, dihydrate as filler and magnesium stearate as lubricant. Cefixime trihydrate API was obtained from manufacturer Orchid Pharma, Alathur, India. The coating system Opadry® White is an aqueous hypromellose based non-functional coating for immediate release obtained from Colorcon, Dartford, UK. The coating is applied to achieve elegant appearance of tablets and to obtain taste masking.

Evaluation of raw data and model interpretation were performed using MODDE® 12 (Umetrics, Sweden) statistical software. Partial Least Squares technique (PLS) was used to obtain optimal fitting of the model.

The batch size for each coating trial corresponds to 77.250 kg tablet cores or 103000 pcs. Tablets were manufactured by wet granulation in a Diosna P300 mixer granulator (Diosna Dierks & Söhne, Osnabrűck, Germany) and compressed on a rotary tablet press (Fette 1200i, Schwarzenbek, Germany) using 20 x 8 mm oblong punches at a mean compression force of 22 kN. Tablets were then coated on a coating machine O’Hara Labcoat 100 (O'Hara Technologies, Toronto, Canada) equipped with a 36-inch side-vented fully perforated coating pan. The spraying system consists of 4 (1.2 mm) spray guns positioned at a distance of gun-tablet bed of 20 cm. The tablet cores were pre-heated at 65^0C, pre-sprayed and then coated with Opadry® White coating suspension containing 15% of solids, until a weight gain of 15 mg was achieved or max. 12 kg of coating suspension was sprayed. During the coating stage, the parameters pan speed (6 rpm), atomization (2.5 bar) and pattern air pressure (3 bar) were kept constant and the ranges of inlet air temperature, inlet air flow and spray rate were optimized.

The coating efficiency was calculated as the ratio of the weight gain and the theoretical weight gain. The weight gain was calculated as the % difference of the average mass of 20 film-coated tablets at the end of the coating process and the average mass of preheated tablet cores.

At the end of coating of each sub-batch appearance of the film-coated tablets was checked on a number of 200 tablets five times per trial for a presence of film-coating defects.

Disintegration time was tested on apparatus for disintegration Erweka ZT322 (Erweka, Germany) according to Ph. Eur. method 2.9.1 on 6 film-coated tablets using deionized water at 37°C. Hardness of coated tablets was tested on a hardness tester Erweka TBH 425TD (Erweka, Germany) on 10 film-coated tablets.

Results and Discussion

Design of experiment

CCO - Central Composite Orthogonal design with 17 coating runs including 3 central points, 8 factorial points and 6 orthogonally scaled star points was used for optimization of coating process parameters: inlet air flow, inlet air temperature and spray rate. The CCO design was chosen as it is a response surface design which can estimate interactions and quadratic terms.

The experimental design matrix for process parameters: inlet air flow, inlet air temperature and spray rate for each experimental trial is shown in Table I.

The acceptance criteria for film-coated tablets are presented in Table II.

The results from the responses for each coating run are displayed in Table III.

Table I

Experimental design matrix of CCO design for coating process parameters

Exp. No.	Run order	Inlet air temperature (^{0}C)	Inlet air flow (m^3/h)	Spray rate (g/min)
N1	2	58	1700	225
N2	13	62	1700	225
N3	6	58	1900	225
N4	11	62	1900	225
N5	12	58	1700	255
N6	8	62	1700	255
N7	9	58	1900	255
N8	17	62	1900	255
N9	7	57.3	1800	240
N10	16	62.7	1800	240
N11	15	60	1664.7	240
N12	14	60	1935.3	240
N13	1	60	1800	219.7
N14	10	60	1800	260.3
N15	3	60	1800	240
N16	5	60	1800	240
N17	4	60	1800	240

Table II

Acceptance criteria for film-coated tablets

- appearance	white to slightly cream oblong biconvex film-coated tablets with bisection line on one side
- coating defects	less than 1%
- coating efficiency	target 100%
- hardness	147.15 N - 294.3 N
- disintegration time	Max. 30 min (1800 s)

Table III

Results from responses for each experimental run

Exp. No.	Hardness (N)	Disintegration time (s)	Coating defects (%)	Coating time (min)	Coating efficiency (%)
N1	276.74	240	0.6	56	77
N2	284.59	311	0.5	52	88
N3	288.61	158	0.6	57	94
N4	284.88	166	0.5	56	93.5
N5	254.57	127	0.9	47	101
N6	261.54	161	0.7	49	109.5
N7	271.25	145	0.8	49	99.5
N8	265.56	141	0.7	48	97.5
N9	270.46	129	0.6	52	102
N10	264.58	225	0.7	50	89.5
N11	247.60	139	0.6	50	83
N12	261.34	117	0.5	50	94.5
N13	277.33	270	0.5	59	98
N14	268.21	172	0.7	51	112.5
N15	264.18	190	0.6	51	96
N16	272.62	180	0.5	50	101.5
N17	258.89	240	0.5	51	92.5

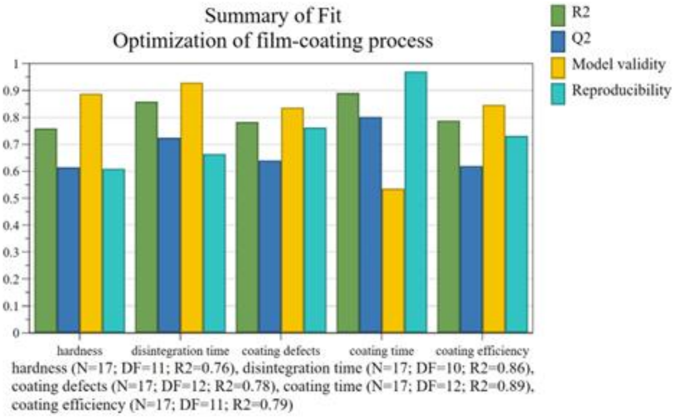


Figure 1.

Summary statistics for model fitting

The model was fitted and the summary of the basic model statistics in two parameters R^2 and Q^2 as well as model validity and reproducibility are presented in Figure 1.

The models show good fit R^2 of the data for all responses. The values for $Q^2 > 0.50$ and the difference between R^2 and $Q^2 < 0.30$ indicate good predictive ability for the models for all responses. The validity of all models is very high > 0.25 which shows that there is no lack of fit. The reproducibility is > 0.50 which indicates a low pure error and good control of the experimental procedure. The insignificant terms with coefficients with p-value > 0.05 were removed which increased the predictive ability. Transformation of the models was not necessary.

Significant effects of the process parameters

Upon evaluation of the coefficients of the factors on the responses, as presented in Figure 2, it can be concluded that all tested factors spray rate, inlet air flow and inlet air temperature as independent variables have significant effects on at least one of the responses. Positive effects of the factors result with an increase of the response, while negative effects result with a decrease.

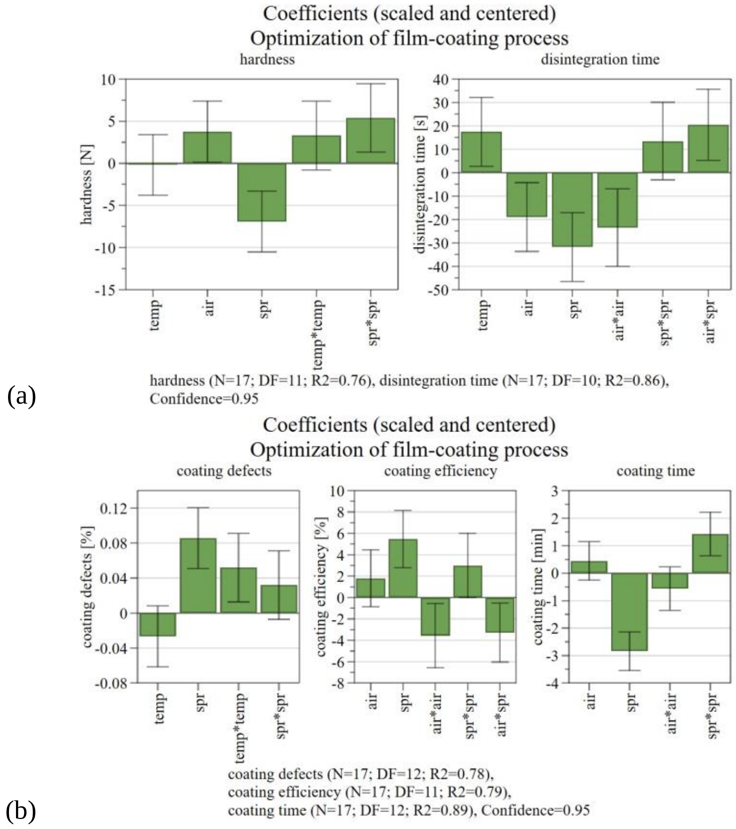


Figure 2.

Coefficient plot for effect of factors on responses (a) hardness, disintegration time (b) coating defects, coating efficiency, coating time. The significant coefficients have a confidence interval that doesn't cross zero.

The spray rate as an independent factor was shown to be significant for all responses: hardness, disintegration time, coating defects, coating efficiency and coating time. The spray rate showed a significant positive effect on coating efficiency and coating defects and a significant negative effect on hardness, disintegration time and coating time.

Along with increasing the spray rate, the size of the droplet which is in contact with the tablet surface is increased which results with a faster coating time and a higher weight gain. This improves the coating efficiency of the process as the weight gain is correlated with the coating efficiency. This coincides with findings in previous studies [9, 18].

The coating time and the number of coating defects were shown to be mostly dependent on the spray rate. The results for coating defects showed satisfactory appearance on all coating runs with a small number of less than 1% coating defects. The small number of coating defects were presented as picking and twinning of the tablets. Minimum coating defects were obtained with lower spray rates while faster coating time was obtained with the highest spray rates. Maki *et al*. [8] also reported that increase in spray rate resulted in a shorter coating process duration. As coating time is decreased with the increase in spray rate, the tablets are less affected by the inlet air temperature, additional hardening is not observed, and the disintegration time is faster. This explains the negative effect of the spray rate on the disintegration time. The negative effect of the spray rate on hardness has also been established in other studies [7, 17].

The inlet air temperature showed a significant positive effect on the disintegration time. The observed positive effect of the inlet air temperature on the disintegration time can be explained as the increase in temperature is affecting the amount of moisture removed during the process. In the study by Teżyk *et al*. [17] it was revealed that inlet air temperature is a significant factor for the hardness of film-coated tablets [17]. In the mentioned study, and also, in the study by Teckoe *et al*. [16] the tested coating parameters didn't show a significant effect on the disintegration time.

The inlet air flow showed a positive effect on the hardness and a negative effect on disintegration time, and this may be explained with the same mechanism as the effect of the temperature on the disintegration time. As the inlet air flow is increased, the drying on the tablet surfaces is accelerated.

Significant quadratic effects were also observed for the inlet air flow on the coating efficiency and disintegration time, for the spray rate on the hardness and coating time and for the temperature on the number of coating defects. As multiple quadratic effects were found to be significant, this confirms that the response surface design contains curvature.

Significant interaction can be observed for the spray rate and the inlet air flow on the coating efficiency and disintegration time (Figure 3). The interaction of the spray rate and the inlet air flow showed a negative effect on the coating efficiency and a positive effect on the disintegration time.

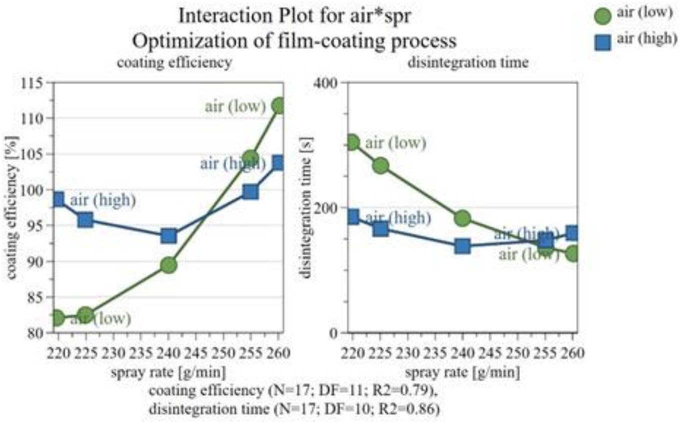
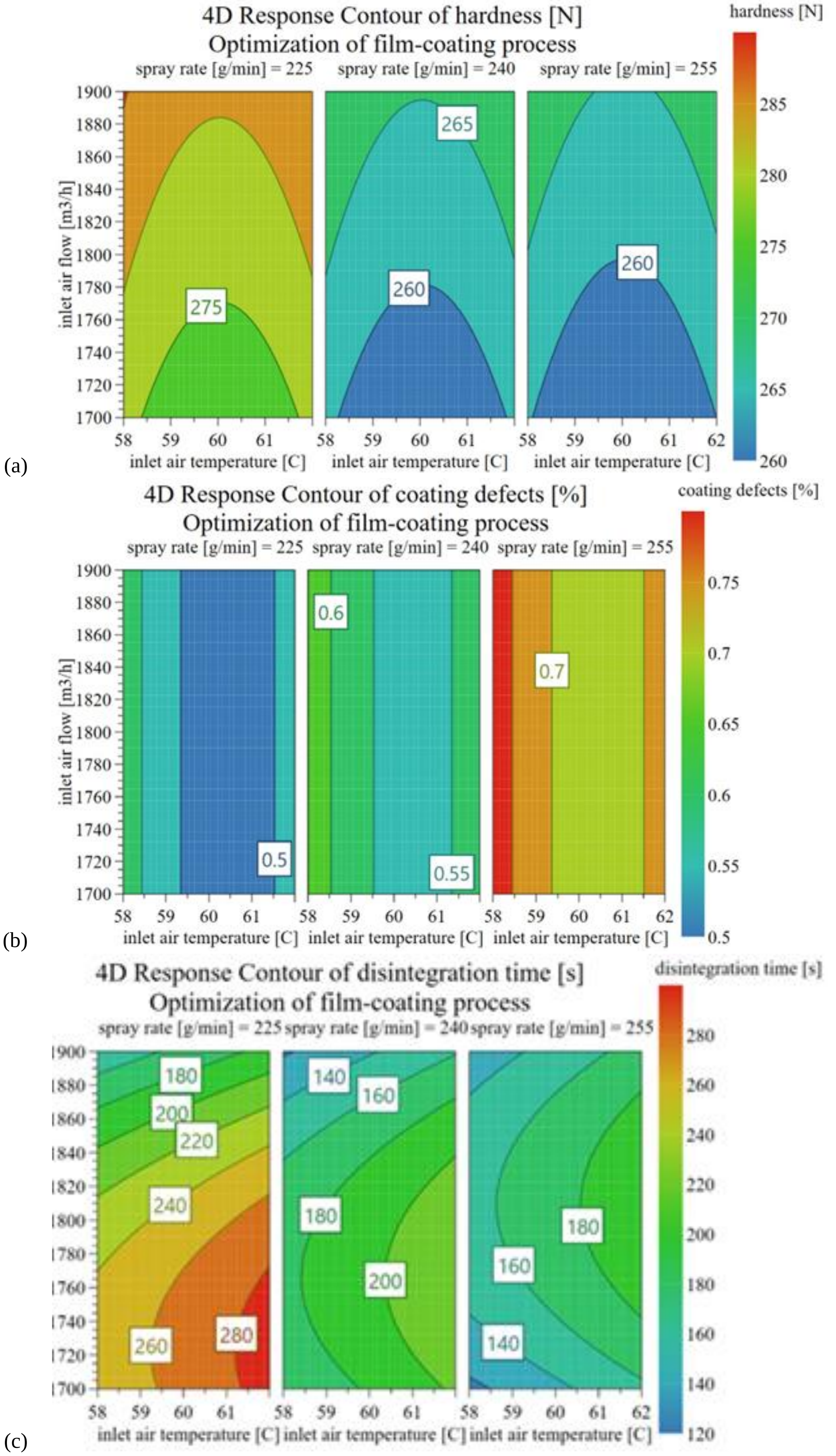


Figure 3.

Interaction plot of factors spray rate and inlet air flow on responses coating efficiency and disintegration time

The effect of the spray rate on the coating efficiency depends of the inlet air flow as when the inlet air flow is set at the low level 1700 m^3/h and the spray rate varies from 220 - 260 g/min the rise in the coating efficiency is sharp, whereas when the inlet air flow is set at the high level 1900 m^3/h the coating efficiency follows a different curve and isn't affected as much by the change in the spray rate. Similarly, but in a negative manner, the effect of the spray rate on the disintegration time depends of the inlet air flow and a sharper decrease in disintegration time can be seen when the inlet air flow is at the low level 1700 m^3/h and the spray rate varies from 220 - 260 g/min.

The 4D response contour plots (Figure 4) display the predicted results of the effects of the process parameters on each of the responses.


4D Response Contour of hardness [N]
Optimization of film-coating process
spray rate [g/min] = 225
spray rate [g/min] = 240
spray rate [g/min] = 255
hardness [N]
inlet air flow [m3/h]
1900
1880
1860
1840
1820
1800
1780
1760
1740
1720
1700
275
265
260
260
inlet air temperature [C]
58
59
60
61
62
285
280
275
270
265
260
(a)
4D Response Contour of coating defects [%]
Optimization of film-coating process
spray rate [g/min] = 225
spray rate [g/min] = 240
spray rate [g/min] = 255
coating defects [%]
inlet air flow [m3/h]
0.5
0.6
0.55
0.7
inlet air temperature [C]
0.75
0.7
0.65
0.6
0.55
0.5
(b)
4D Response Contour of disintegration time [s]
Optimization of film-coating process
spray rate [g/min] = 225
spray rate [g/min] = 240
spray rate [g/min] = 255
disintegration time [s]
180
200
220
240
260
280
140
160
180
200
160
140
180
inlet air temperature [C]
280
260
240
220
200
180
160
140
120
(c)

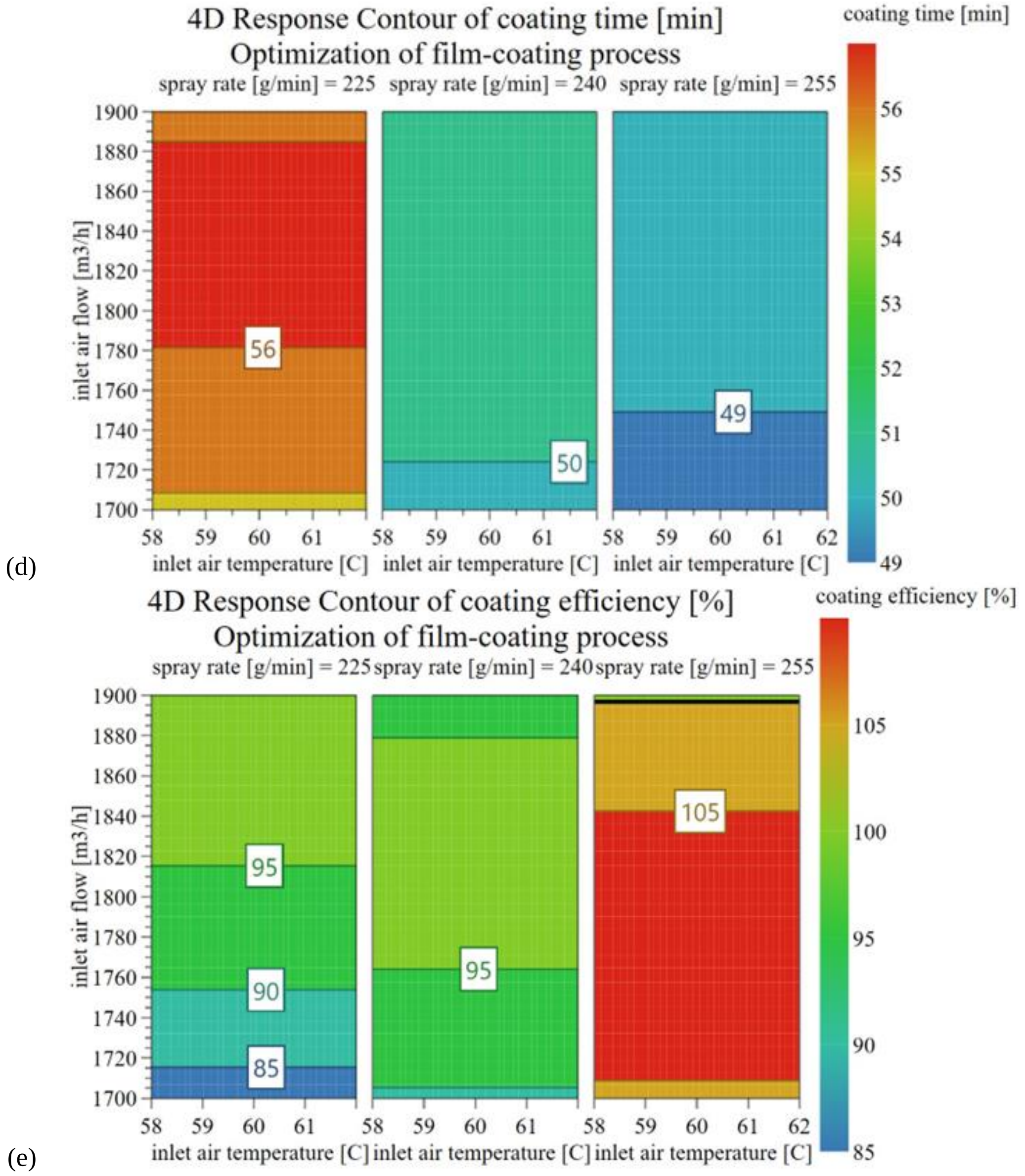


Figure 4.

4D Response Contour plots for hardness (a), coating defects (b), disintegration time (c) coating time (d) and coating efficiency (e), as a function of the factors: inlet air temperature, inlet air flow and spray rate

Optimization of the process

Upon evaluation of the main, interaction and quadratic effects of the factors on the responses, optimization was performed and criteria for optimization were set for the responses as shown in Table IV.

Table IV

Criteria for optimization of the responses

Response	Criteria
Coating efficiency	Target
Coating time	Minimize
Coating defects	Minimize
Hardness	Predicted
Disintegration time	Minimize

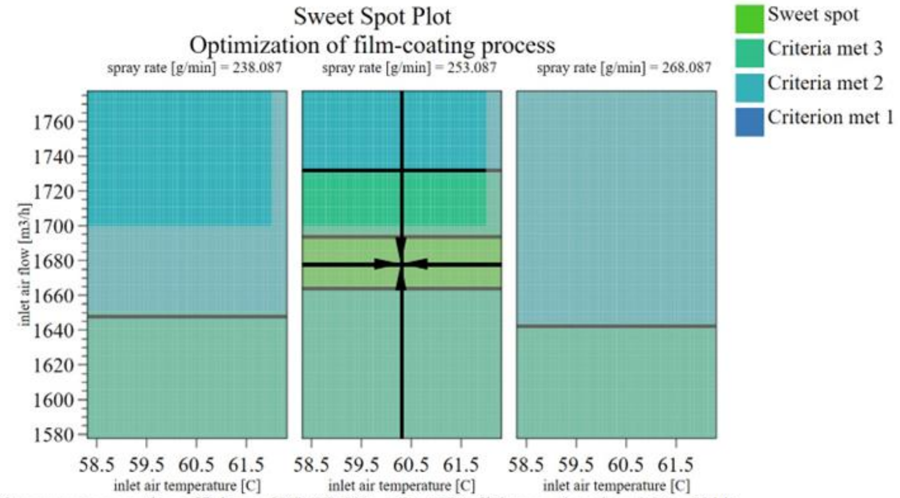
For optimal results of the responses, the run with the lowest distance to the target - log (D) was chosen and the best factor setpoints were selected by the software. The optimized parameters, ranges and predicted results of the responses are presented in Table V.

As all responses are within the acceptance criteria for the responses, the acceptable range for the parameters concedes with the design constraints in the study. The optimal point as a function of the inlet air temperature, inlet air flow and spray rate, is presented on the Sweet Spot Plot for optimization of the process. The sweet spot for the optimization study (Figure 5) is presenting the area around the target optimal point of the parameters, meeting the optimization and acceptance criteria of the responses.

Table V

Optimized values of parameters and predicted results of responses

Parameter	Optimized value	Optimized range	
Inlet air temperature (^{0}C)	60.3	57.3	62.7
Inlet air flow (m^3/h)	1677.6	1665	1935
Spray rate (g/min)	253.1	220	260
Response	**Prediction**	**Prediction interval**	
Coating efficiency (%)	100.00	92.49	107.51
Coating time (min)	47.63	45.97	49.29
Coating defects (%)	0.66	0.60	0.72
Hardness (N)	254.1	245.9	262.3
Disintegration time (s)	126.1	84.6	167.5



Sweet spot = coating efficiency [%] (98.501 - 101.499), disintegration time [s] (- 1800), coating defects [%] (- 1), coating time [h] (- 48.7105)

Figure 5.

Sweet Spot Plot for optimization of the process

Conclusions

The aqueous film-coating process is a complex process with a large number of process parameters involved and the effects of the individual process parameters and their possible interactions on the attributes of the coated tablets are still not very well understood and require further optimization in the industrial scale in order to gain a robust process. An optimization study of film-coating process in the industrial scale production using experimental design approach was performed. The results showed that the spray rate had the highest influence on all responses: hardness, disintegration time, coating defects, coating efficiency and coating time. The inlet air temperature showed a significant positive effect on the disintegration time. Interaction effects of the spray rate with the inlet air flow were shown to be significant for the coating efficiency and disintegration time. Upon optimization of the process, optimal operating conditions were set for the parameters of the film-coating process. This highlights the benefits of the experimental design in increasing product quality and process knowledge through optimization of the process of film-coating. Thus, our study will contribute to elucidate the relationship between the process parameters in the coating stage and the design approach could be beneficial for optimization/robustness during transfer of the film-coating process in the industrial scale.

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Conflict of interest

The authors declare no conflict of interest.

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