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Original Article

OPTIMIZATION OF PANTOPRAZOLE ENTERIC PELLETS COATING PROCESS BY QBD: EFFECT OF COATING PROCESS VARIABLES ON THE INTERMEDIATE QUALITY OF THE PRODUCT AND SCALE UP

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ABSTRACT

Objective: The aim of this study was to optimize pantoprazole enteric coating process based on Quality by Design (QbD) principle and successful scale up.

Methods: The critical process parameters (CPP) were identified based on Failure Mode and Effect Analysis (FMEA) tool. A full factorial design was applied to develop design space and determine control strategy for pantoprazole enteric coating process, have promising yield, assay and reduced process time. The coating process variables studied were air volume (X_1), spray rate (X_2) and atomization air pressure (X_3), versus percentage fines (Y_1), percentage agglomerates (Y_2) and assay (Y_3) as responses. The pellets were coated in Wurster and characterized for assay, dissolution, scanning electron microscopy and loss on drying.

Results: When X_2 at low level and X_3 at high level, spray drying increased hence fines increased while X_2 at a high level and X_3 at a low level, agglomeration increased. The optimization performed to decide level of X_2 and X_3 for fines and agglomerated free process. The operating ranges, for robust coating process of desired pellets yield and quality, X_1, X_2 and X_3 were 46-58 CFM, 6-9 g/min and 1.1-1.3 bar respectively. In scale up of pellets, physical and chemical parameters reproduced based on process ran as per scale up factor calculation.

Conclusion: It was concluded that a promising pellets coating process was successfully designed using QbD approach and successfully scale upscale up possible based on complete optimization of process variables, understanding of risk associated with variables and implementation of scale-up factor calculation provided by the vendor.

Keywords: Wurster, Risk assessment, Design space, Control strategy, FMEA, Scale up, QbD

INTRODUCTION

As the pharmaceutical industry tries to embrace the methodologies of quality by design (QbD) provided by the FDA's process validation (PV) guidance [1] and International Conference on Harmonization (ICH) Q8/Q9/Q10 [2-4], many companies are challenged by the evolving concept of criticality as applied to quality attributes and process parameters.

ICH Q8 (R2) explained the Critical Process Parameter (CPP)-A process parameter whose variability has an impact on a critical quality attribute (CQA) and therefore, should be monitored or controlled to ensure the process produces the desired quality [2]. The CPP states that a parameter is considered critical when its variability has an impact on a CQA. The amount of impact is not defined, which leads to the question, does even a small impact to a CQA mean that the parameter is critical? It is not difficult to imagine the example of an extreme shift of a process parameter having a minor impact on a CQA, whether measurable or not [1]. CPP selection has traditionally been difficult because of a lack of a systematic approach to the problem which due to a large number of unit operations and complexity. Failure to identify critical parameters can result in unexplainable variation during batch processing and lot acceptance [5].

The pellets coating in the bottom spray is considered very critical process than other pelletization techniques because it involved number of process variables which are directly or indirectly affecting the product quality. As per the literature, there are selected potential process parameters-product temperature [6-8], humidity [9], inlet air flow [10-11], atomization air pressure [12-14], spray rate [14,16], column height [11,17-18] responsible for the product quality however others like nozzle tip diameter, filter bags type and drying time are also important based on practical experience.

The FMEA is the best risk management tool can used for Wurster based pellet coating process to categories the risk of process variables. The risk of each failure is prioritized based on the risk priority number (RPN). RPN is a decision factor based on three ratings: Severity (S), Occurrence (O) and Detection (D). These ratings are scaled with numbers between 1 and 10 [19]. Risk Priority Number, which is the product of the severity, occurrence and detection ratings is calculated as RPN = S x O x D. The RPN must be calculated for each cause of failure. RPN shows the relative likelihood of a failure mode, in that the higher number, the higher the failure mode. From RPN, a critical summary can be drawn up to highlight the areas where the action is mostly needed [20]. Risk priority numbers (RPNs) were calculated as the product of occurrence, severity and detectability scores. Failure mode scores could range from 1 to 1000 [21]. We ranked S, O and D of 1-3 as best-case value, 4-7 as moderate-case value and 8-10 as worst-case value, and then a maximum RPN of 1000 and a minimum RPN of 1 are possible.

In this study pantoprazole enteric coated pellets used to prepare oro dispersible multiunit particulate system (MUPS) tablet of pantoprazole where enteric coating was a functional coating which decided the acid resistance capacity of pellets. Not only optimization of formulation variables (performed in previous work) required in this case but optimization of coating processes also the potential impact on pellets quality.

Successful pellet coating process optimization at lab level using small scale Wurster is half work done. Successful scale-up of Wurster based coating process at commercial scale is a challenging task. Nowadays USFDA also demanding for a scientific approach for scale activity based on development batches. In one of the USFDA's guide to inspections report pre/post approval issues explained the expectations of regulatory authority on scale up activity said-it is important that the development and scale-up of the process be well

documented so that a link between the bio/clinical batches and the commercial process can be established [22].

Scale up/pilot batches perform in single Wurster. The development of the product is normally done in 6" Wurster with the batch size 0.5 to 1.5 kg where Wurster column and spray nozzle is small hence overall coating zone is small. The recommended pilot model is 18" Wurster where the Wurster column and base plate are much larger. From the lab to pilot although there is single spray nozzle, but the nozzle is much bigger and can permit higher spray rate. The batch depth and mass flow density increases. Overall, the coating zone increases from lab to pilot scale. The overall coating zone will remain same in the pilot and commercial scale except the height of the Wurster column. Therefore, the base area of Wurster column plays important role in efficient coating. All process parameters should be proportional to the base area of Wurster column compared with lab model column.

All the process variables again show their significance in scale up model also. Nevertheless, once the effect of variables are studied and understood in lab model, it will make the analysis much easier. Just like the variables remaining same in pilot scale also, the same process control will apply. Only the unknown factor will be the mass effect. As in the lab scale, one has to follow sequential approach to set the parameter for the scale up.

The aim of this study was to investigate the influence of process parameters on the pellets quality using an experimental design and risk mitigation performed based on QbD principles for quality product. Successful scale-up of pellets coating process performed based on process optimization conducted at lab scale equipment. Here attempt to help the industry to plan scale up activity in linear as the demand of regulatory authority to prove extrapolation of design space in commercial scale or in post-approval changes stage.

MATERIALS AND METHODS

Materials

Pantoprazole sodium sesquihydrate was gifted from Hetero drugs. Methacrylic Acid Copolymer Dispersion (Eudragit® L30D-55, Evonik) and PlasACRYL® HTP20 (Emerson) were gifted from Evonik, India.

Methods

Preparation of enteric coated pellets

Weighed quantity of PlasACRYL HTP20 was dispersed and shaken well in the container to get a homogenous dispersion. Separately Eudragit L30D-55 dispersion was made, to this PlasACRYL HTP20 dispersion was added under slow stirring followed by addition of purified water. The dispersion had stirred for 30 min using mechanical stirrer (Remi Elektrotechnik Ltd, India) and strained through 100 mesh screens. Accurately weighed 500 gm of seal coated pellets were loaded in Wurster (Pam GPCG 1.1) and preceded at suitable process parameters using this coating mixture.

Process variables involved in Wurster based pellets coating process

There are five sets of process variables involved in Wurster based pellets coating process equipment variables, solution/dispersion preparation variables, preheating variables, spraying variables and drying variables. The variables come under each set provided in fig. 1.

The process variables categorization and risk identification performed based on previous experience and literature before conducting the preliminary trials.

Preliminary trials

Initial trials were performed by varying the process parameters to understand the impact on product quality. Enteric coating is a functional coating which is one of the critical processes in the manufacturing of MUPS PTZ tablet. We varied the levels of all process parameters mentioned in table 1 and concluded the selected critical process parameters (CPPs) which needs systemic optimization plan to reduce the risk.

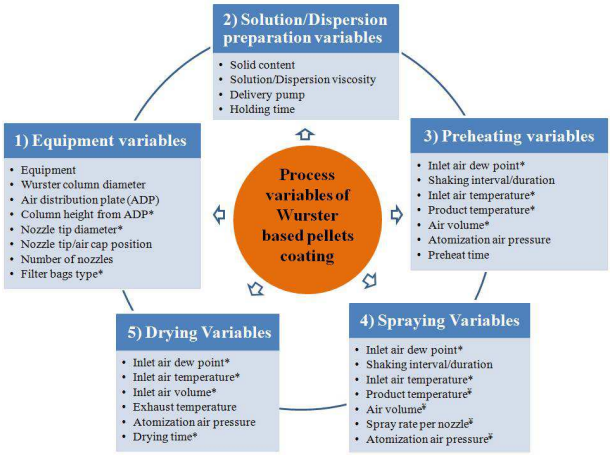

Fig. 1: Process variables involved in Wurster based pellets coating process

Table 1: Process parameters for enteric coating of preliminary trials

Process parameters	Values
Batch Size	600 gm
Air distribution plate	B
Wurster column height	12-18 mm
Nozzle tip diameter	1.0 mm
Filter porosity	100 µ
Product temperature	25-32 °C
Atomization air pressure	0.9-1.4 bar
Spray rate	4-10 g/min
Air volume	45-70 cfm
LOD	NMT 1.5 %

Characterization of pellets

Assay

Enteric coated pellets assay were performed as per Pantoprazole Sodium Delayed-Release Tablets USP monograph [23].

Dissolution studies

Dissolution studies were carried out in two stages. Dissolution in acidic condition, i.e., simulated stomach condition was performed in USP apparatus II, dissolution medium used was 1000 ml of 0.1 N hydrochloric acid at a speed 75 rpm and temperature 37±0.5 °C for 120 min followed by dissolution in simulated intestinal condition using USP apparatus II, dissolution medium used was 1000 ml of phosphate buffer pH 6.8 at a speed 75 rpm and temperature 37±0.5 °C for 30 min.

Scanning electron microscopy

Enteric coated pellets were placed onto a double-sided carbon tape mounted on studs and sputter-coated (JFC-1100, Jeol, Tokyo, Japan) with gold. Photomicrographs of gold coated enteric coated pellets were obtained using a scanning electron microscope (SEM; Phenom, Netherlands).

Loss on drying (LOD)

Accurately weighed pellets (1.5 to 2 gm) were placed on tare aluminium plate of moisture balance (Mettler Toledo HR83P). The test was performed at a temperature 105 °C till a constant weight was achieved. The reading displayed on the screen was noted as the LOD of the sample.

Initial risk assessment of coating process

Initial risk assessment performed using FMEA tool. The pareto chart was plotted of process variables vs RPN. The initial risk assessment of the enteric coating process presented in fig. 2

identified the risk of the enteric coating step to impact yield and drug release from the drug product as high. Process variables that could potentially impacted enteric coating process were identified and their associated risk was evaluated based on preliminary trials. Conducting design of experiments (DoE) to evaluate all the variables involved in a Wurster coating process is not feasible.

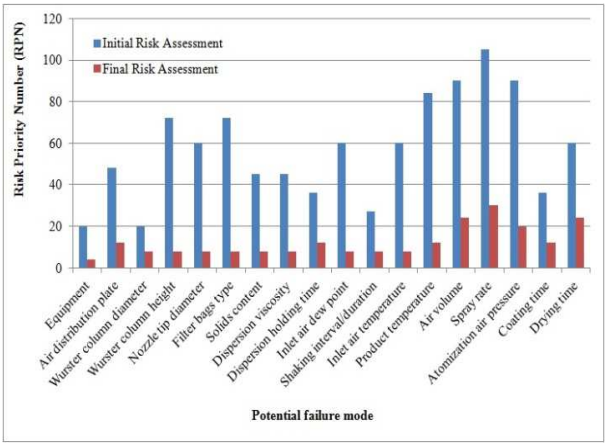

Fig. 2: Pareto chart showing RPN scores for the coating process parameters for pantoprazole enteric coated pellets before and after risk mitigation

Therefore, variables ranked based on RPN value. The RPN threshold below 60 ranked low risk, 60-80 ranked medium risk and above 80 ranked high-risk process variables.

The variables ranked as high risk i.e. Air volume, spray rate and atomization air pressure, and were evaluated by conducting DoE studies to gain process understanding and remaining kept constant.

Identification of CQAs

The aim of this work was to decide the ranges of CPPs involved in enteric coating process. Yield is an important quality attributes. In pellet formulation, yield is reduced either due to fine generation or agglomerates formed. In this study, % fines (<355µm) and % agglomerate (>600µm) selected as intermediated CQAs which directly related to yield. For chemical characterization, assay is the best test to conclude quality of coating, which is another CQA. Impact of process variables on dissolution in acidic condition already studies in preliminary trial and concluded variation in process parameters no affect on dissolution.

Screening of design of experiments

Prior to optimization, historical data were analyzed and several screening DoE analyses were done. A 2^3 full factorial design with two center points was performed to screen the effect of process parameters on yield and assay to explore the quadratic response surfaces and for constructing a second-order polynomial models using Design Expert (Version 8.1.6; Stat-Ease Inc., Minneapolis, Minnesota). A design matrix comprising 10 experimental runs including 2 centre points was constructed.

The response (Y_i) in each trial was measured by carrying out a multiple factorial regression analysis using the quadratic model:

$$Y_i = b_0+b_1X_1+b_2X_2+b_3X_3+b_4X_1X_2+b_5X_1X_3+b_6X_2X_3+b_7X_1^2+b_8X_2^2+b_9X_3^2$$

Where Y_i is the dependent variable; b_0 is the arithmetic mean response of all trials; and b_i is the estimated coefficient for factor X_i. The main effects, X_1, X_2, and X_3, represent the average value of changing factor one at a time; X_1X_2, X_1X_3, and X_2X_3 represent the interaction terms and the polynomial terms (X_1^2, X_2^2 and X_3^2) are used to assess nonlinearity [24].

Table 2: 2^3 Full factorial design-Factors, levels and successful operating range

Independent variables (Process variables)	Unit	Levels		
		-1	0	1
X_1: Air volume	cfm	46	58	70
X_2: Spray rate	g/min	3	6	9
X_3: Atomization Air Pressure	bar	0.8	1.1	1.4
Dependent variables (CQAs)	**Unit**	**Successful operating range**		
Y_1: Fines (<250 µm)	%	<2		
Y_2: Agglomerate (>425 µm)	%	<2		
Y_3: Assay	%	$95<Y_3<105$		

The independent variables selected were air volume (X_1), spray rate (X_2) and atomization air pressure (X_3). The dependent variables were release % fines (Y_1), % agglomerates (Y_2) and assay (Y_3). The range of independent variables under study is shown in table 2 along with their low, medium, and high levels, which were selected based on the results from preliminary experimentation.

Development of design space and control strategy

The relationship between the process variables and CQAs were described in the design space (DS). DS was determined from the common region of successful operating ranges for multiple CQAs discussed in table 2. It is expected that operation within the DS space will result in a product possessing the desired CQAs. Optimized process variables s*et al.* so get from this DS. A control strategy (CS) is designed to ensure that a product of required quality will be produced consistently [2]. The acceptable range of material attributes was determined based on DS. LOD of enteric coated pellets was targeted less than 1.5% w/w.

Scale up of pantoprazole enteric coated pellets

After successful optimization trials, values of CPPs were finalized and covered in lab scale CS. In scale up of pellets, CPP needs to frame based on linearity function of both i.e. lab scale and pilot/commercial scale equipment. Bottom spray fluidized bed processor (Wurster technology) supplier always designs all capacity equipment in linear scale which help to make scale up activity easy. There are some scientific theoretical factors involved in scale up activity. We performed to scale up trial in Pam FBE 125C which is linear with Pam GPCG 1.1 equipment and comparative pellets coating process parameters presented in table 3.

In Wurster column, 100 % coating process and 70-80% drying process completed. So out off whole coating assembly, Wurster column is a functional area for quality coating. Wurster column base area considered for theoretical factor calculation in scaling up activity. In table 3, values of CPPs during lab scale and pilot scale are given.

RESULTS AND DISCUSSION

Preliminary trials

Trials were performed to understand behavior of process parameters on pellets quality. Product temperature kept 26-29 °C as optimum temperature range to form a film and to run process smooth. Above 32 °C, film formation starts in gun and frequently gun

choked and below 25 °C, agglomerates formation started due to less drying of sprayed dispersion.

During the preliminary trials for the process, the dew point was maintained 8-11°C to reduce static charge generated initially due to preheating of seal coated pellets. The spray rate was initially 4 g/min and was incrementally ramped up during the course of the preliminary batch. At 10 g/min, agglomeration was observed, suggesting that the spray rate should not exceed 10 g/min. smooth spraying was observed at atomization air pressure of 0.9-1.2 bar but above 1.4 bars more spray drying occurred. Air volume below 45 cfm, pellets didn't fluidize properly and above 70 cfm pellets impacting on the filter wall and less time spend in Wurster column. Spray rate, atomization air pressure, and air volume were the key coating process parameters. These parameters were considered as process variables for DoE study.

Table 3: Comparative pellets coating process parameters of Pam GPCG 1.1 and pam FBE based on scale up factor

Parameters	Units	Pam GPCG 1.1	Scale up factor	Pam FBE 125 C
Equipment parameters				
Wurster column diameter	m	0.072	-	0.219
Wurster column height	m	0.20	-	0.36
Base plate area	m^2	0.0145	-	0.1918
Suitable air distribution plate	-	B	-	B-I
Working volume	L	2.4	35	84
Batch size (preferred)	kg	0.6	35	21.0
Wurster column base area	m^2	0.0041	9	0.0377
Process parameters				
Inlet air temperature	° C	26-35	-	26-35
Product temperature	° C	26-28	-	26-28
Wurster column height from base plate	mm	15-20	-	40-45
Inlet air volume	CFM	9	9	81
Spray rate	g/min	10-20	9	90-180
Spray gun model	-	970/0		940-943/7-1 S91
Atomization air pressure	bar	1.0 (1.2)	9	2.5 (10.8)
	(CFM)*	1.5 (1.4)	9	3.0 (12.6)
		2.0 (1.7)	9	4.0 (15.3)

*bar to CFM calculation performed based on the type of spray gun. CFM value was scaled up.

Experimental design

The aim of this work was to optimize process variables for enteric coated pellets processing. The ideal coating parameters should reduced the generation of fines, and agglomerates and maintain the uniform enteric coat quality from batch to batch.

The full factorial design (FFD) is one the most widely used type of experimental designs. The results (table 4) showed that the percentage fines generation varied from 0.2 to 5.4%, the agglomerates generation varied from 0.2 to 7.1% and assay varied from 96.8 to 100.1%.

The wide variation in the percentage fines and agglomerates for different formulations and the high degree of reproducibility suggested that these responses are strongly dependent on the selected independent factors. In case of the assay, although small variations were noticed between different formulations, the results seemed to be systematic and repeatable, which may suggest dependency on the studied factors.

Table 4: Experimental matrix and results

Trial	Process variable (Factors)			Responses (CQAs)		
	X_1	X_2	X_3	Y_1	Y_2	Y_3
F11	-1	-1	-1	0.2	0.5	100.1
F12	1	-1	-1	0.8	0.7	9.7
F13	-1	1	-1	0.2	7.1	97.8
F14	1	1	-1	0.4	6.2	97.5
F15	-1	-1	1	1.2	0.4	96.8
F16	1	-1	1	5.4	0.4	98.9
F17	-1	1	1	0.5	0.6	99.6
F18	1	1	1	0.2	0.4	99.8
F19	0	0	0	0.2	0.3	99.5
F20	0	0	0	0.2	0.2	99.8

Trial F15 and F16 showed highest fines generation however, it has no effect on pellet surface. In trial F13 and F14, high spray level and low atomization air pressure leads to the formation of more agglomerates. Comparatively in other trials percentage of agglomerates formation was considerably less. The SEM images of enteric coated pellets presented in fig. 3.

Response surface plots interpretation

The results indicated that the fines (Y_1) generation was significantly influenced by the linear models of spray rate (X_2), atomization air pressure (X_3) and in small percentage of air volume (X_1), in addition to the interactive model of the quantity of spray rate-atomization air pressure (X_2X_3). Fig. 4a portray the three-dimensional surface plot indicated that when X_3 increased from-1 level to+1 level, Y_1 was found to increased linearly due droplet size reduced which increased spray drying while X_3 level has least on Y_1. The large positive coefficient (+1.02) of X_3, negative coefficient (-0.90) of X_2 and negative coefficient of (-1.08) of X_2X_3 suggested that atomization air pressure, spray rate and spray rate-atomization pressure combination respectively had significant effect on Y_1 comparative X_1 (+0.40) as per Eq. (1). This study indicated that atomization air pressure governed the fines generations, as pressure increased, fines generation increased proportionately.

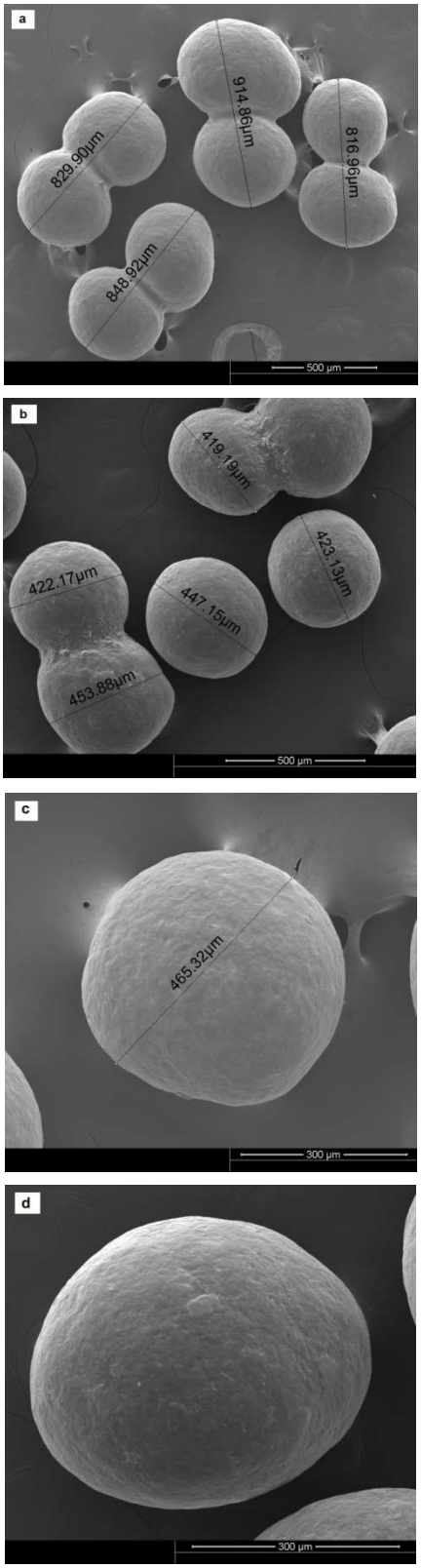

Fig. 3: SEM images of enteric coated pellets of-a) F13, b) F14, c) F17 and d) F19

The agglomerates (Y_2) formation was equally influenced by the linear models of spray rate (X_2), atomization air pressure (X_3) and spray rate-atomization air pressure (X_2X_3). Three-dimensional surface plot (fig. 4b) indicated that when X_3 increased from-1 level to+1 level, Y_2 was found to decreased linearly due to lesser droplet size those avoid the pellets to pellets sticking while X_2 increased from-1 level to+1 level, Y_2 was found increased due to over wetting of pellets. The positive coefficient (+1.54) of X_2 had major effected followed by negative coefficient (-1.59) of X_2 and (-1.49) of X_2X_3 on Y_2 as per Eq. (2) indicated X_2 and X_3 has equal effect of Y_2. Spray rate above optimum over wet the pellets while atomization air pressure increased at same spray rate reduced droplet size and reduced agglomerates generation.

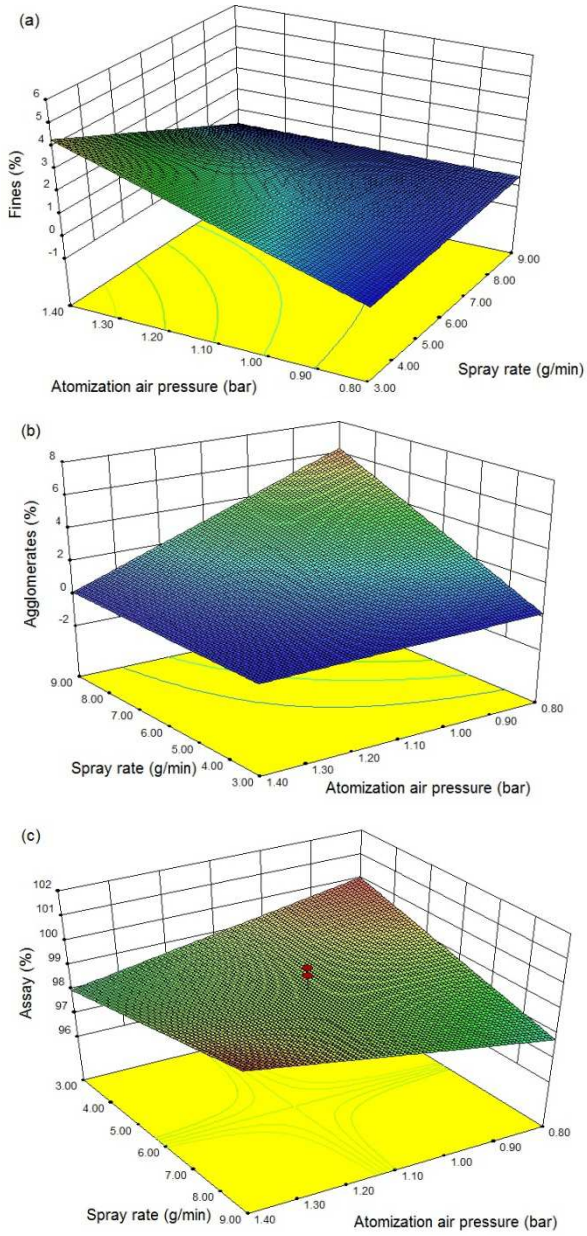

Fig. 4: Response surface plot showing the influence of process variables on-a) fines, b) agglomerates, and c) assay

Assay was significantly influenced by the linear models of spray rate (X_2). Fig. 4c portray the three-dimensional surface plot indicated that when X_2 increased from-1 level to+1 level, Y_3 were found to increased linearly could be due decreased loss of coating solution due to spray drying.

The negative coefficient (-0.10) of X_2 had major impact followed by positive coefficient (+1.02) of X_2X_3 on Y_3 as per Eq. (3). The X_3 had very less impact of Y_3 which is not covered in equation. X_2 and X_3 were the most critical process parameters found affecting on yielded and assay of pellets while X_3 has less impact.

The resulting equation for all three responses Y_1 (fines), Y_2 (agglomerates) and Y_3 (assay) are presented below:

$$Y_1 = +1.33+0.40X_1-0.90X_2+1.02X_3-1.08X_2X_3 \quad \text{..... (1)}$$

$$Y_2 = +1.68+1.54X_2-1.59X_3-1.49\ X_2X_3 \quad \text{..... (2)}$$

$$Y_3 = +98.95-0.10X_2+1.02\ X_2X_3 \quad \text{..... (3)}$$

Analysis of variance

Analysis of variance (ANOVA) was performed to evaluate the significance of the quadratic models (linear, interactive and polynomial) on the responses and to estimate their quantitative effects. table 5 summarizes the effects of the model terms and associated p-values for all three responses. At a 95% confidence level, a model was considered significant if the p-value<0.05. The sign and value of the quantitative effect indicate trend and magnitude of the term's influence on the response, respectively. Positive signs indicate an increase in the response value while negative signs demonstrate a decrease in the response value.

The correlation coefficients (R^2) for all three responses indicated good fits to the raw data. However, lower correlation coefficients were obtained for fines (0.883) and assay (0.780). This might be due to some spray dried coating material wet through filter bag and not considered in the calculation of percentage fines. For assay, results were observed in the range of 96.8-100.1% which very narrow range. Small change in decimal results made big error. Hence, value of correlation coefficients found less than 0.9.

Table 5: Summary of results for testing validity of the models

	DF	SS	MS (Variance)	F	*P*	R^2
Fines						
Model	4	25.41	6.35	55.65	<0.0009	0.8829
Lack of Fit	3	0.45	0.15	30.00		
Agglomerates						
Model	3	56.77	18.92	210.27	<0.0001	0.9108
Lack of Fit	4	0.44	0.11	22.25		
Assay						
Model	3	8.48	2.83	5.90	0.0425	0.7799
Lack of Fit	4	2.35	0.59	13.06		

Statistical analysis for testing the validity of the models in summarized in table 5. The p-values for all the simulated responses were well below the significant level *(<0.05), suggesting that all the models were significantly in predicting their response values.

Experimental validation of design space

The multidimensional combination and interaction of independent variables and process parameters that have been demonstrated to provide assurance of quality is termed as the design space [25]. DS could be determined from the common region of successful operating ranges for the two responses. Experimental validation of DoE trials was undertaken by fabrication of optimized process variables. For optimized process variables, levels of factors which provided fines (Y_1) in 0-2% range, agglomerates (Y_2) in 0-2% range and assay in 95-105% range were screened. Fig. 5a, b and c shows the overlay plot for air volume 46 CFM, 58 CFM and 70 CFM respectively kept constant. Fig. 5d showed the overlay plot showing the optimized parameters suggested by DoE software to obtain the desired responses for process variables.

The DS was established which was delineated in the green region in fig. 5d, the range of the process variable was the air volume of 46-58 CFM, spray rate of 6-9 g/min and atomization air pressure of 1.1-1.3 bar of the point inside the green region.

The model predicts that process variables (represented by flag in fig. 5d) with fines of 0 %, agglomerates of 1.14% and assay of 99.54% will have 58 CFM, 9 g/min and 1.30 bar of air volume, spray rate, and atomization air pressure respectively. After prediction by software, the trial was taken with set of process variables suggested by model and characterized. As shown in table 6 predicted and experimentally determined values for Y_1, Y_2 and Y_3 were comparable. These values were in very close agreement and established the reliability of the optimization procedure.

Table 6: Comparison between predicted and experimentally observed values for process variables

Responses	Predicted	Observed
Fines (Y_1)	0.0	0.1
Agglomerates (Y_2)	1.14	1.17
Assay (Y_3)	99.54	99.45

To make QbD a reality, a DS must be defined within which final product quality as defined by all CQAs is ensured. That space defines the arranges of each CPP, taking into account multivariate interactions. Then, the mathematical model between the CPPs and the CQAs provides the right combinations of CPPs that realize the desired quality.

Working within the DS space is not considered as a change; however the movement out of the DS is considered a change and would normally initiate a regulatory post approval change process. DS is proposed by the applicant and is subject to the regulatory assessment and approval" [2]. The quadratic response surface of CQAs as a function of selected variables was given in fig. 4. A vital step of optimization is to achieve appropriate response functions for both dependencies and independences. In Design Expert, the desirability response values were set Y_1<2%, Y_2<2% and Y_3 was 95-105%. The optimized process parameters set was successfully extrapolated for pilot batches and it worked 100%. In future, due to any reason process parameters need to change for commercial batches then based on DS it is possible without taking the prior approval supplement.

Updated risk assessment

Following completion of process development studies, a greater understanding of the risks to product yield and assay associated with coating process been developed in DS which covered all validated range of process variables. Risk associated with process variables and mitigated discussed in fig. 2 (Pareto chart) based on validated design model and optimization study results. Using FMEA, the modes of failure can be prioritized for risk management purposes according to the seriousness of their consequences (effects), it can also be used to predict how frequently they occur and how easily they can be detected [26].

Control strategy for enteric coating process variables

For ensuring a product of required quality of robustness and consistency during producing, ICH Q10 defines the control strategy as "a planned set of controls, derived from the understanding of current product and process that assures process performance and product quality [4].

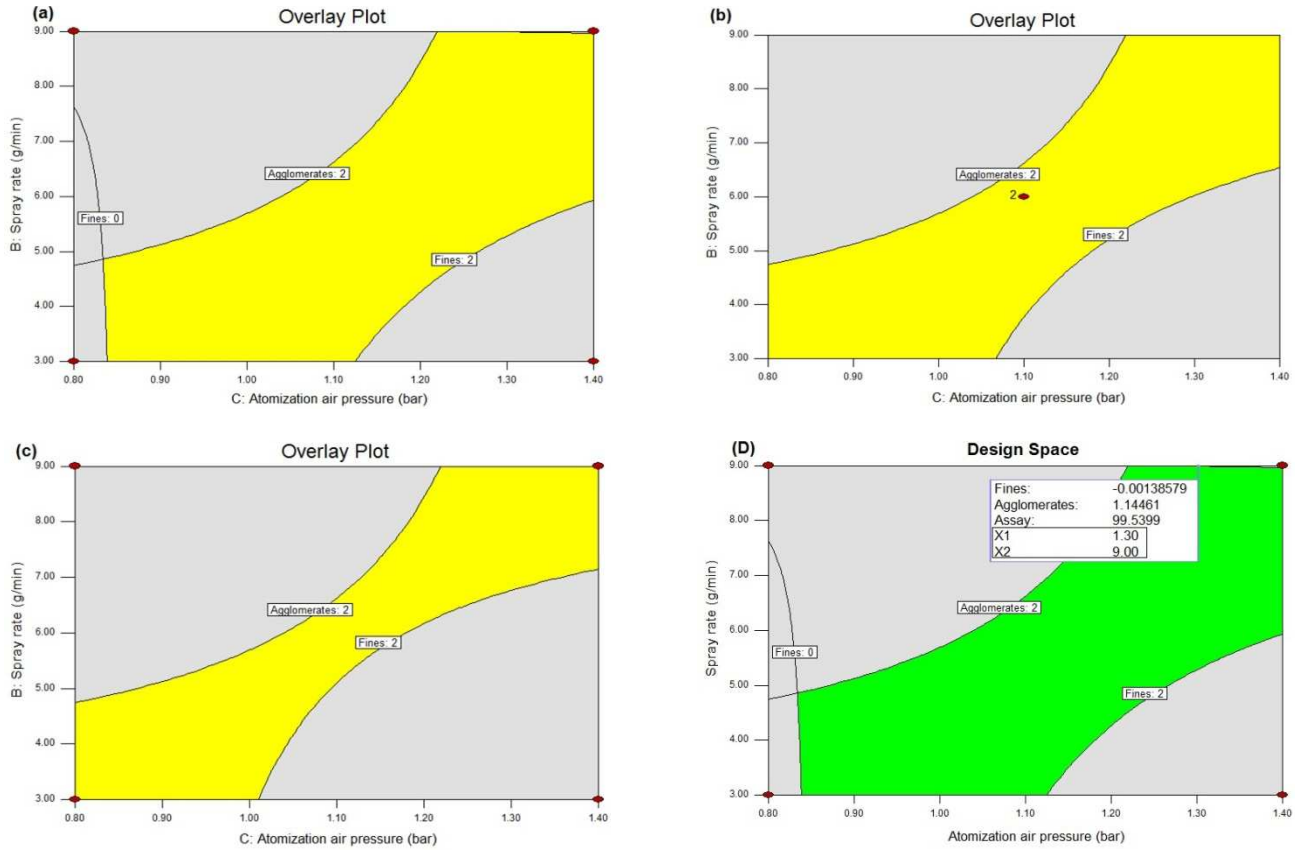

Fig. 5: Overlay plot to EC process comprised of the overlap region of ranges for the three CQAs-a) 46 cfm of air volume, b) 58 cfm of air volume, c) 70 cfm of air volume and d) design space

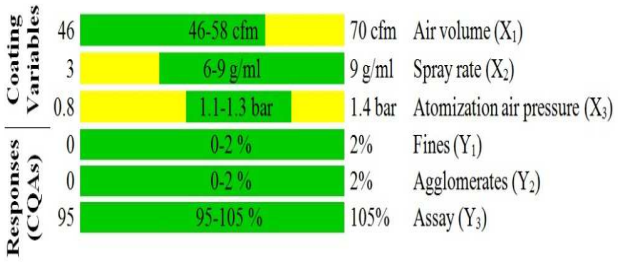

Fig. 6: The control strategy for pantoprazole enteric coating process

The normal operating ranges is CS which is defined as the upper and/or lower limits for the critical material attributes. In the CS, the parameters were routinely controlled during production in order to assure the reproducibility [25]. The acceptable range of material attributes was determined basing on the knowledge space from screening design and DS, the detail information was explained in fig. 6.

Evaluation of industrial batches

Scale up was performed in Pam FBE 125C (18'' Wurster) based on the optimized process parameters of coating process in Pam GPCG 1.1. The results were reproduced during scale up and found 0.05% of fines, 0.08% of agglomerates and 99.74% of assay. The desired spray rate was achieved in 1 h after start coating by slowly ramp up the pump rpm and after wards ran the process on constant spray rate. The comparative SEM images of enteric coated pellets of optimized process parameters run at lab and scale up presented in fig. 7 and found same pellet surface.

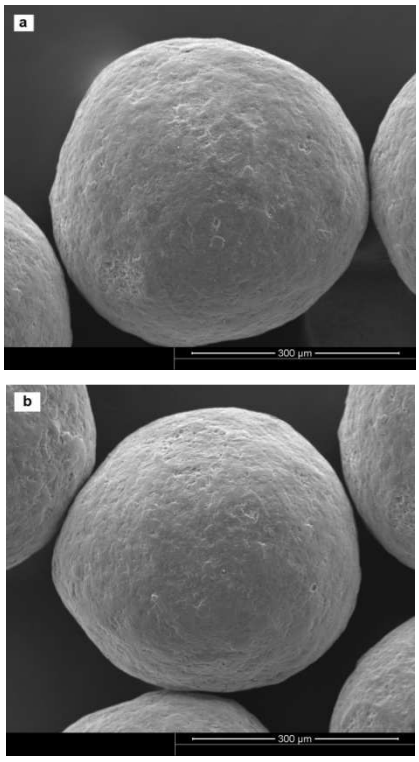

Fig. 7: SEM images of enteric coated pellets of-a) optimized process parameters of trial V1 b) scale up batch (PTZ40-001).

Successful scale-up batches

Linear scale-up from lab scale to pilot scale assumed that the occupancy was the same and the distribution plate in each piece of equipment is geometrically similar. Additionally, ratios of air volume to plate area and spray rate to air volume maintained. The scale-up factor from Pam GPCG 1.1 to Pam FBE 125C is approximately 9-fold based on vendor recommendation used for successful scale up.

CONCLUSION

The QbD based enteric coating process development given promising output which used in scale up activity. Scale up of pellets can be possible based on complete optimization of process variables, understanding of risk associated with variables and implementation of scale-up factor calculation provided by vendor.

CONFLICT OF INTERESTS

Declared None

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