"Design Space" Determination of a Paracetamol Fluid Bed Granulation Using Design of Experiments

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ABSTRACT

This study was performed to increase understanding of a paracetamol fluid bed granulation process and to identify the critical process parameters in a laboratory scale granulation process. The screening of the process parameters and their influence on final granules quality attributes were investigated using a factorial design. For this purpose the process parameters were first screened and depicted by the Ishikawa diagram. The experimental runs performed, given by the design model, identified spray rate followed by inlet air flow and atomizing spray pressure as the critical process parameters. Trials with high spray rates lead to granules with excellent flow properties. Furthermore, by increasing the inlet air volume granules with tight particle size distribution were obtained.

ZUSAMMENFASSUNG

Bestimmung eines "Design Space" für die Wirbelschichtgranulation einer Paracetamol-Formulierung mittels experimentellem Design

Ziel der vorliegenden Arbeit ist es, einen Beitrag zum besseren Verständnis des Wirbelschicht-Granulationsprozesses zu leisten. Die Herausforderung lag darin, unter Verwendung einer Paracetamol-Formulierung Einflüsse und Wechselwirkungen von ausgewählten Prozessparametern im Labormaßstab zu untersuchen. Das Screening der Prozessparameter und ihr Einfluss auf die Qualität des erhaltenen Endprodukts, des Granulates, wurden mit Hilfe eines faktoriellen Versuchsplans bearbeitet. Zu diesem Zweck wurden die Prozessparameter zunächst unter Anwendung der Ishikawa-Methode ausgewählt. Die Experimente wurden dann entsprechend des Versuchsplans durchgeführt. Experimente mit hoher Sprührate führten zu einem Granulat mit hervorragenden Fließeigenschaften. Durch die Erhöhung der Zuluftmenge wurden Granulate mit einer engen Teilchengrößenverteilung erhalten

KEY WORDS

- Design of experiments
- Design space
- Fluid bed granulation
- Paracetamol
- Quality by design

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1. Introduction

"Quality by design" means designing and developing formulations and manufacturing processes to ensure predefined quality by understanding how formulation and manufacturing process variables influence the quality of a drug product [1, 2]. There is a need for developing deeper scientific understanding of critical process and product attributes. As a result the "design space" should be established, i. e., a range of process parameter settings that have been demonstrated to provide predefined end product quality. Mathematically, it is a multidimensional combination and interaction of input variables and process parameters which can be varied within the design space but still provide assurance of quality [1].

Considerable effort has been invested in order to investigate the effect of process parameters on granule properties as well as to find optimum conditions in preparing solid dosage forms from them [2–10]. The critical process parameters for fluid bed granulation have been studied extensively by several other authors [2, 11, 12]. However, there has been no approach, yet, that takes this all the way to establish a design space as suggested by ICH Q8 R2 [1].

For this purpose, knowledge about the process itself is mandatory. The granulation step is a process step of size enlargement of fine particles into larger particles for improving flowability and compressibility [13]. Many parameters may affect the fluidized bed granulation and hence

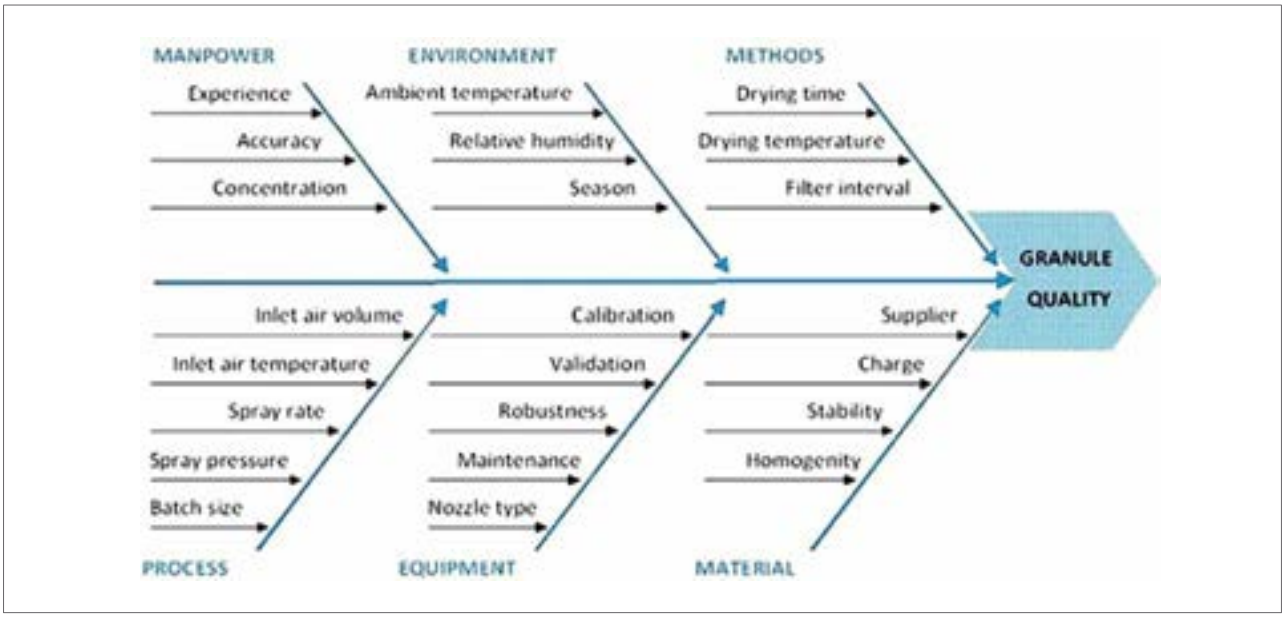

Fig. 1: The Iskikawa diagram helps pointing out potential critical process parameters.

the resulting outcome – therefore this is a complex process [14]. Knowing the effect of these parameters including their interactions is an essential condition for controlling it. Optimization of processes depends on finding the best set of controlled variables leading to the best results with consistent product quality.

The basic principle of a fluidized bed process is an upward directed air stream passing through a heated powder bulk and shifting the powder bulk into a liquid-like state. Equilibrium between liquid supply and the evaporation of liquid plays a fundamental role in fluidized bed granulation. The fluid bed moisture content is a central parameter to control the growth of granules. If the liquid supply by the spray rate is too high or the evaporation of the liquid is not in balance with the wetting, an increase of the moisture of the powder bed is observed. Above a certain moisture level the powder bed becomes overwetted and defluidized [14], which can result in caking.

1.1 Risk analysis by use of the Ishikawa diagram

By use of an Ishikawa diagram (Fig. 1) a risk analysis of the fluid bed granulation process parameters with impact on granule properties such as particle size distribution, flowability and residual moisture was performed [2, 7, 9]. The major process influencing parameters as depicted by the Ishikawa diagram are inlet air volume, inlet air temperature, spray rate and atomizing spray pressure.

1.2 Experimental design

Design of Experiments (DoE), a structured method to determine the relationship between process parameters and the output, was used to obtain maximum information from a minimum of process experiments. A modified 2^3 full factorial design with two center points was used. This type of design supports the development of mathematical models comprised of linear and interaction terms. The full factorial design was modified so that the center points had a higher "atomizing spray pressure" of 0.8 bar (= $0{,}8 \cdot 10^5$ Pa) instead of 0.65 bar (= $0{,}65 \cdot 10^5$ Pa) compared to the standard design. The underlying reason for this was that experimental points had been tested in earlier experiments and were found to yield good results. Experiments 3 and 7 were modified as a high "spray rate" with a low "inlet air volume" resulted in very wet conditions with a high risk for caking of the powder bed. The condition number for the experimental design plan is 1.52 for a model with all linear and interaction terms. The condition number for a perfect design is 1.12. Based on this small difference in condition number it was concluded that the design was acceptable.

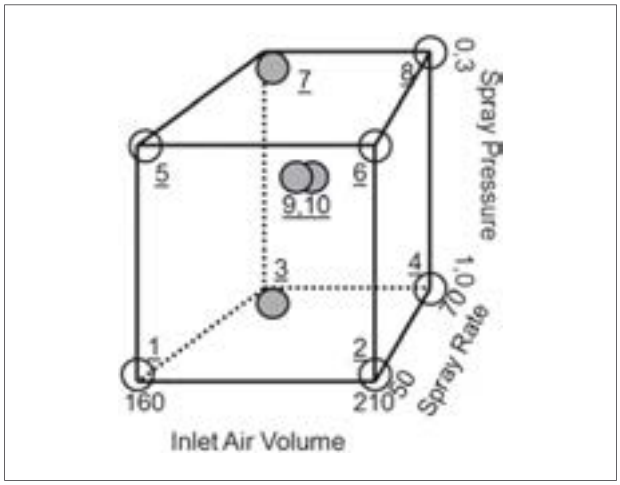

Fig. 2: Design region for the reduced/factorial design. Experiments modified from the standard setting are shown in grey circles.

Table 1

Experimental design plan for paracetamol fluid bed granulation mixture (10 runs).

Factor Name	Inlet Air Volume	Spray Rate	Spray Rate
Abbreviation	InAir	Spray	Press
	[m^3/h]	[g/min]	[bar]
1	160	50	0.3
2	210	50	0.3
3	166	67	0.3
4	210	70	0.3
5	160	50	1
6	210	50	1
7	166	67	1
8	210	70	1
9	185	60	0.8
10	185	60	0.8

1.3 Experimental design plan

The design is depicted in Fig. 2. The factorial design was carried out according to the experimental design plan given in Table 1.

2. Materials and methods

2.1 Equipment

All studies were performed using a Unilab (Hüttlin GmbH, Schopfheim, Germany) laboratory scale fluid bed granulator [8] with a batch size of 3 kg. The Unilab is equipped with bottom spray technology implemented in an efficient air distribution plate "Diskjet". Two 3-component nozzles were used for spraying the binder solution. The liquid nozzle used had a diameter of 1.2 mm.

2.2 Materials

The formulation of the powder bed consists of 3 kg paracetamol; a 8 % solution of PVP K90 in water was used as a liquid binder. The binder solution was prepared by mixing 80 g of solid phase PVP K90 and 920 g of purified water until all of the PVP was dissolved. Paracetamol was incorporated as raw powder mass and sucked into the Unilab fluid bed granulator after its preheating.

2.3 Analytical methods

The particle distribution measurements were performed using a QicPic® apparatus (Sympatec GmbH, Pulverhaus, Germany). The moisture analysis were determined by loss on drying (LOD) method (105 °C, 10 min) using a halogen balance (Sartorius GmbH, Göttingen, Germany). The flowability characteristics, e. g., the flow time analysis, were carried out by using a flow tester (Erweka GmbH, Heusenstamm, Germany). The granules tapped density was measured using a tap volumeter (Erweka).

The statistical design plan has been developed by using the software MODDE 9 (Umetrics AB, Umea, Sweden) [15]. The statistical analysis was also carried out by use of MODDE 9. For the optimization of the granulation process a modified factorial design was used.

2.4 Process variables and performance

The granulation process variables were first evaluated by means of the Ishikawa method within the screening design study. The limits for the process variables were chosen based on pilot experiments carried out previously. They are listed in Table 2.

The starting material was sucked into the fluid bed granulator after the product container was preheated to 35 °C. Mixing took place until the desired product temperature of 43 °C was reached. This took about 10 min after which the spraying of binder solution commenced. The process parameters such as inlet air volume, spray rate and atomizing air pressure were adjusted according to the factorial design plan. The final drying time of the granules was kept constant at 3 min in all trials before they were discharged and passed to in-process control (IPC) testing. Residual moisture, particle size distribution, tapped density and flow time were considered as relevant response variables for the final granules.

Table 2

Process variables for paracetamol fluid bed granulation.

Process variable	Abbreviation	Unit	Lower limit	Upper limit
Inlet Air Volume	InAir	m^3/h	160	210
Temperature	Temp	°C	constant at 70	constant at 70
Spray Rate	Spray	g/min	50	70
Spray Pressure	Press	bar	0.3	1.0

Table 3

Output parameters from paracetamol fluid bed granulation.

Output parameter	Abbreviation	Unit	Lower limit	Upper limit	Target
Residual Moisture	Moist	[%]	1.2	2.5	1.8
Particle Distribution	d50	[µm]	150	300	200
Tap Density	Dens	[g/ml]	0.3	0.45	0.4
Flow Time	Flow	[s]	5	15	10

2.5. Output parameters

The process performance output parameters or response variables are shown in Table 3. These are performance parameters related to how well the process can be run from a technical point of view.

3. Results

The values for the output parameters (response variables) obtained are listed in Table 4.

3.1 Statistical evaluation of output parameters

The quality of the models is represented by the R^2, Q^2 and the standard deviation (SD) of replicates. A very good model will have R^2 and Q^2 close to 1.0 and a very small standard deviation (SD) of replicates. Good models show low noise and low prediction error and, therefore, yield a sharper definition of the design space. Weak models such as models for tap density will introduce more noise and will result in a definable design space when almost all of the experiments are conducted within the given limits. The low Q^2 value for the flow time is an effect of the missing data, as the Q^2 is a warning signal if a statistical model has sufficient degrees of freedom. The model diagnostics for the output parameters are given in Table 5.

In Fig. 3 the process data from Table 4 is plotted. The experiment number is shown on the x-axis while the value for this experiment is depicted on the y-axis.

Experiments 9 and 10 are on the same pole in all four plots as these are the duplicates from the centre point. The red line in the plots simulates the lower and upper limit of the process variable, respectively. The blue line simulates the target value of the process variable as already defined in Table 3.

From Table 5 and Fig. 3 it can be concluded that only the experiments 4, 8, 9 and 10 fulfill the criteria for all four output parameters. That means that only for these experiments the output parameters are within their predefined range of lower and upper limits. Given the number of process conditions which failed to hit the target region, this demonstrates the complexity of the fluid bed granulation process for the investigated paracetamol formulation.

The coefficient plots for all four output parameters in Fig. 4 show that the spray rate (Spray) is the most important factor for the fluid bed granulation process of a paracetamol formulation followed by inlet air volume (InAir). By increasing the spray rate an increase of residual moisture and an increase of particle distribution will be achieved. By increasing the spray rate granules tap density

Table 4

Output parameter values.

Output Parameter	Residual Moisture	Particle size Distribution	Tap Density	Flow Time
Abbreviation	Moist	d50	Dens	Flow
	%	µm	g/ml	s
1	1.04	157	0.427	13.2
2	0.41	129	0.439	20.2
3	6.61	285	0.347	n.a.
4	1.68	236	0.364	10.9
5	1.01	199	0.365	7.5
6	0.39	121	0.497	12.8
7	4.95	214	0.348	n.a.
8	1.84	189	0.363	10.6
9	1.77	170	0.339	11
10	1.85	182	0.331	11

Table 5

Model diagnostics for the output parameters.

Output	Lower limit	Upper limit	Runs outside specification	R^2	Q^2	SD of replicates
Residual Moisture [%]	1.2	2.5	1, 2, 3, 5, 6, 7	0.99	0.96	0.01
Particle Distribution [µm]	150	300	2, 6	0.93	0.67	8.5
Tap Density [g/ml]	0.3	0.45	6	0.74	0.16	0.006
Flow Time [s]	5	15	2, 3, 7	0.97	0.00	0.00

and flow time will decrease. The effect of inlet air volume is countercurrent with the effect of the spray rate. By increasing inlet air volume more thermodynamic energy is applied in the fluid bed, therefore the residual moisture and the particle size of the granules will decrease.

These coefficients should be seen as a process overview plot together with the more detailed information in the contour plots shown in Fig. 5.

The International Conference on Harmonisation (ICH) has outlined quality by design (QbD) principles for pharmaceutical development which introduced the concept of design space (DS). ICH Q8 defines DS as "the multidimensional combination and interaction of input variables that have been demonstrated to provide assurance of quality" [2].

The example in the ICH guideline uses overlapping contour plot similar to the graphs below to define the design space. Fig. 5 shows the two factors spray rate and inlet air volume which have been identified as most influencing parameters. They are plotted in a contour plot to understand their impact on the final granule properties. The models from Fig. 5 are then used to find a Set Point and Process Window by using a Monte Carlo method described below.

The definition of a design space region is done with Monte Carlo simulations on the factor setting. For each given set point the largest possible range for each input parameter is demonstrated that still meets all response requirements taking the uncertainty of the prediction at that set point into account. The Monte Carlo simulation requires a definition of the distribution around the set point for each input parameter as well as the risk for failure defined as "defects per million operations (DPMO)". In this study a normal distribution was used and it was decided to set the risk at 10000 DPMO which is equivalent to a 1 % risk.

In Fig. 6 the "lower limit design" and "upper limit design" define the range of the design, sometimes des-

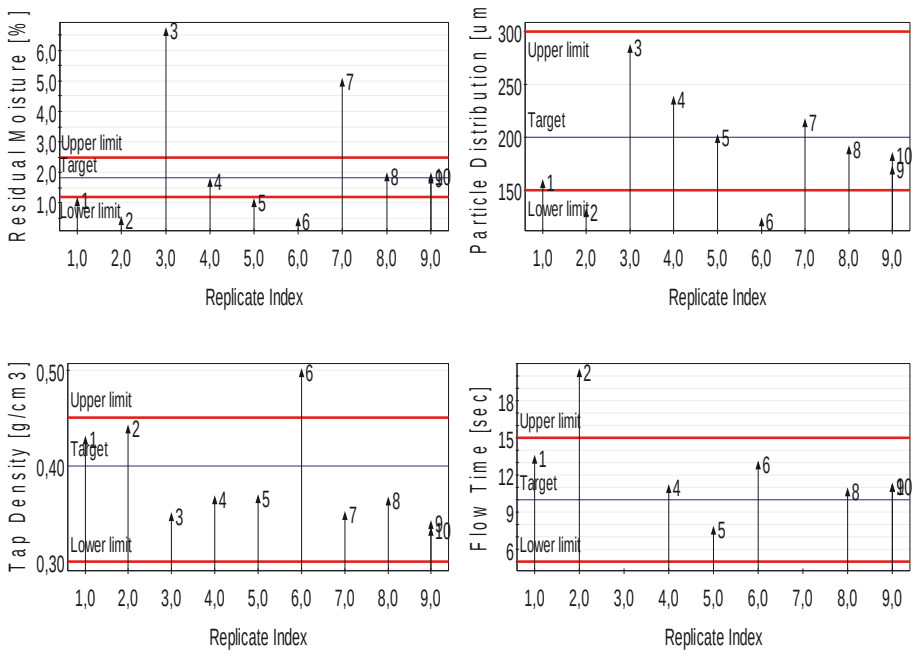

Fig. 3: Data plots for the individual responses as well as their replicates of the output parameters from the experimental design.

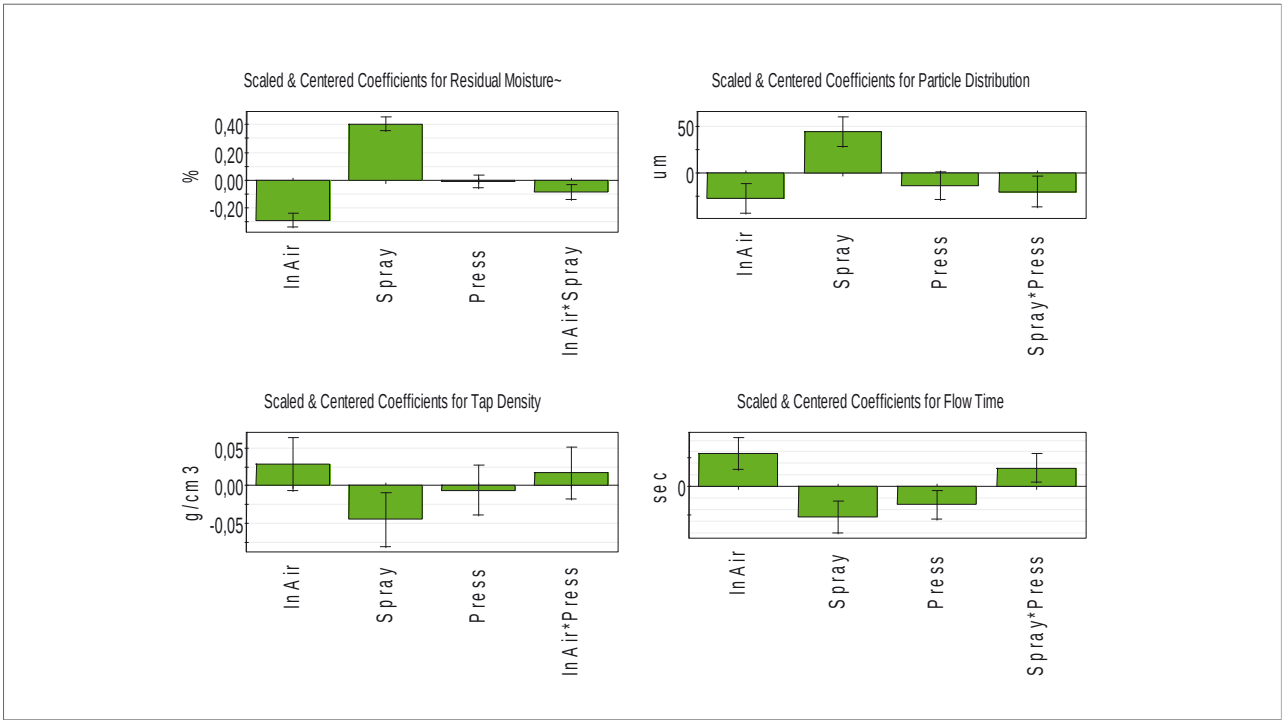

Fig. 4: Coefficient plots showing the impact of the input parameters on the individual responses.

ignated as the knowledge space. The set point is the point where the process is set to run with allowed variations of the input parameters given by the so called process window (95 %). The y-axis demonstrates that the distribution seen is from a number of individual simulations "count" and the important parameter to find is a value for the 95 % confidence interval.

4. Conclusion

The main purpose of this study was the definition of an optimal process point with a corresponding process window that ensures quality for a pharmaceutical granulation process using a paracetamol formulation. A range of process parameter settings has been demonstrated to provide predefined end product quality. The present study confirms that the parameters spray rate and inlet air volume clearly affects the granule particle attributes. Increasing the spray rate leads to granules with excellent flow properties. By increasing spray rate the liquid supply increases; powder particles agglomerate by building liquid bridges, as at the same time more liquid is present in the process. The liquid bridges between powder particles

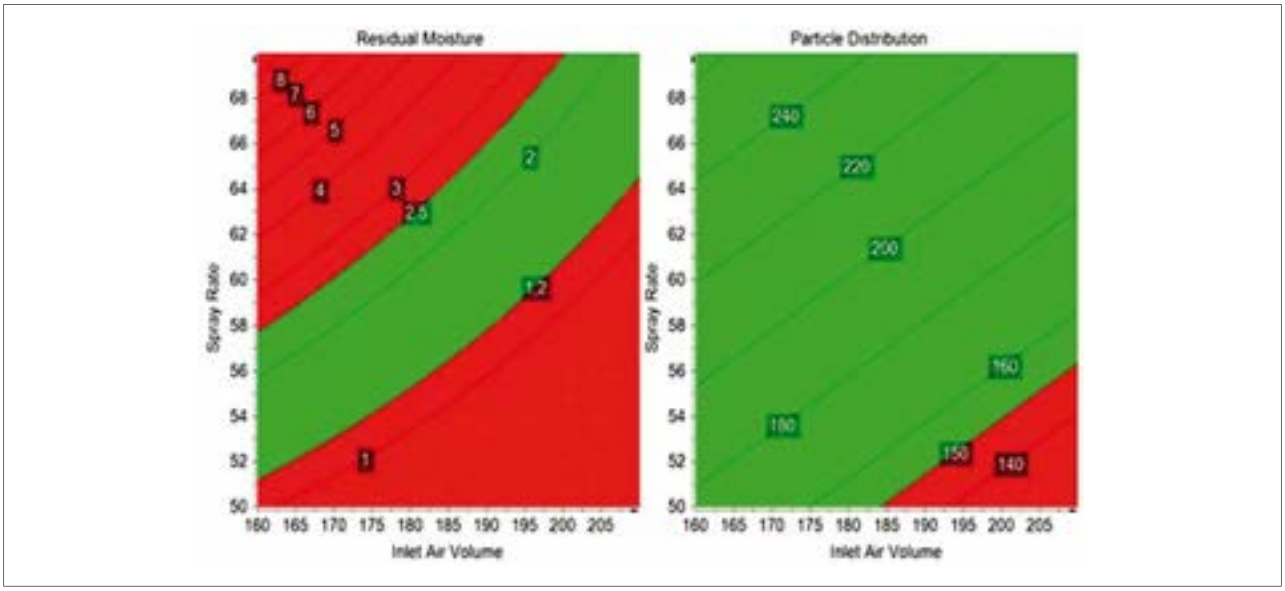

Fig. 5: Impact of Spray Rate and Inlet Air Volume on Residual Moisture and Particle Distribution shown as contour plots.

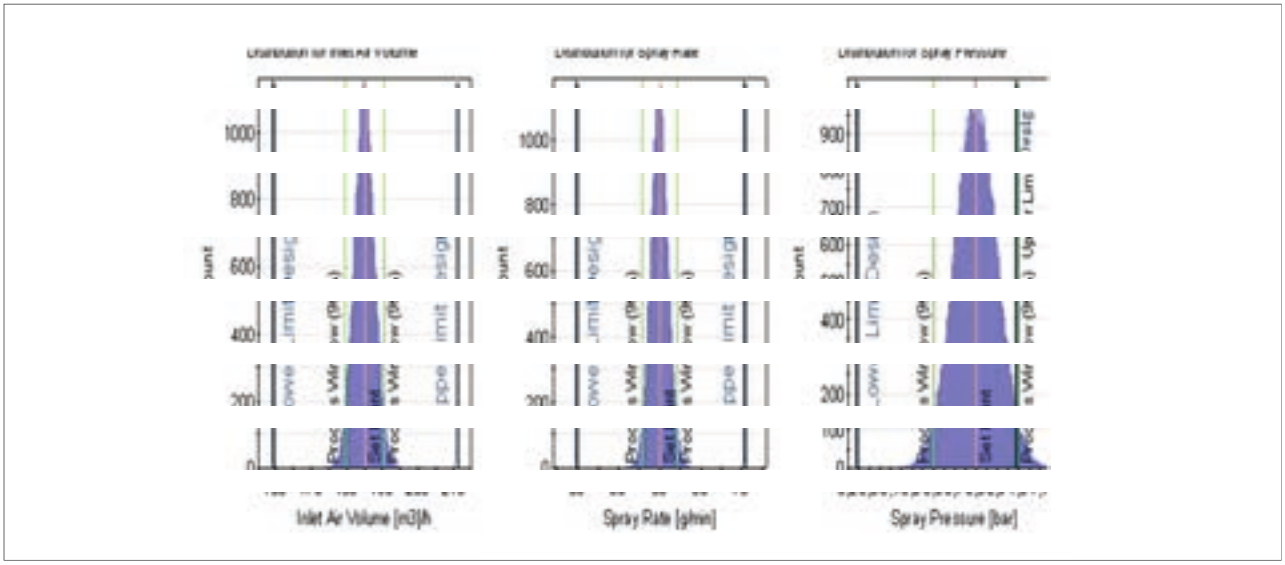

Fig. 6: Confidence Interval: (95 %) for the input parameters. Process window demontrating the input parameter range resulting in consistent response complying with the product qualityspecifications.

are transferred into solid bridges during drying by the evaporation of liquid. The described mechanism of bridging is most important for granule growth. Therefore, the particle size of the resulting granules is larger when increasing spray rate and the corresponding flow properties will improve as well. By increasing the inlet air volume granules with tight particle size distribution were obtained. An increase of inlet air volume leads to a higher evaporation rate of liquid. With increasing the inlet air volume an increase of thermodynamic energy in the process is achieved. The powder bed becomes drier as the product temperature is increasing. The total drying time decreases, therefore the particles are presented to mechanical stress during drying for shorter periods of time. Granules produced with higher inlet air volume will result in tight particle size distributions with less fines compared to granules produced with lower inlet air volume.

The multi-dimensional combination and interaction of both parameters spray rate and inlet air volume will provide assurance of quality. This means that the way of combination of parameters is of central importance in achieving a design space for the paracetamol fluid bed granulation process. The optimum processing conditions and conclusions from the experimental design analysis performed in this study suggest that design of experiments can be a valid tool for scaling up fluid bed granulation processes when processing a paracetamol formulation.

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