Doi: https://doi.org/10.61841/cxc8f761 **Url:** https://nnpub.org/index.php/AS/article/view/2814

UTILIZING AN EXPERIMENTAL DESIGN AND SCALE UP OF A WET FLUIDIZED BED AGGLOMERATION PROCESS, TO PRODUCE NOVEL CARBON AGGLOMERATES AND TABLETS

Peter Langguth[1], Martin Oelofse[1,2], Marcelle Hilden[2], Sascha Kreutz[2],

[1]Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg University, Mainz, Germany

[2]Carbon Advanced Solutions GmbH, Heuchelheim, Germany

Corresponding author: Martin Oelofse, Department of Pharmaceutical Technology and Biopharmaceutics, Staudingerweg 5, 55128 Mainz, Germany
Email: martin.oelofse@web.de

How to cite this article:

ABSTRACT

Wet granulation and agglomeration processes are widely used in the pharmaceutical industry. This study was performed, aimed at developing a systematic approach to scale up a carbon agglomeration process from 10 kg to 100 kg. The goal was to achieve similar granule sizes with different granulators during production. The formulation of the powder bed at the start of the agglomeration process was based on carboxymethyl cellulose as a binder, carbon and peroxide powder. In the first production step this composition was used to produce agglomerates. Agglomerates were evaluated for particle flow and particle size. Finally, compressive strength of cylindrical carbon tablets was measured, following compression with a five cavity mechanical press. It was found that the agglomeration liquid quantity, the inlet air flowrate and the droplet size distribution play a fundamental role in the upscaling process. Therefore, these mentioned parameters had to be systematically scaled up for different batch sizes in order to achieve similar particle growth in the different fluidized bed sizes. A previous study, through a design of experiments has shown that a target geometric mean granule size of around 575 µm is desirable in terms of the granules flowability and granules properties. For example: The compressive strength of the carbon tablets. Furthermore, a DoE for the spraying parameters was applied to compare the final tablet properties. The scale up process from a laboratory to a production size granulator, was successfully performed. This was based on the granule's properties and the mechanical stability of the carbon tablets.

KEY WORDS: Scale up; Wet agglomeration; Fluidized bed; Design of Experiments; Carbon agglomerates and tablets

1. INTRODUCTION

Agglomeration processes can be complex and influenced by several process parameters [1]. During particle agglomeration in a fluidized bed, interactions between the process variables take place. Therefore, scaling up processes from small to larger scales are performed systematically and empirically in the pharmaceutical industry [2]. These variables include the batch sizes, the atomized air pressure, the feed rate, the inlet air flowrate, the inlet air temperature and the equipment type [3]. In terms of inlet air flow rate it was indicated that scale ups can be conducted by increasing the inlet air flowrate proportionally with the spray rate [4]. However, this approach may not always lead to acceptable results, because the droplet size and therefore the agglomeration kinetics and the fluidized bed moisture content play a fundamental role in creating round shaped agglomerates [5, 6]. Previous studies have taken place, to study carbon agglomerates in a fluidized bed, in a laboratory scale using several DoEs to develop optimal process conditions that lead to high quality granules and tablets. For example, a previous DoE for the formulation described in this study has shown that the spraying parameters are statistically significant with respect to the mechanical stability of the resulting tablets, following compression of the granules. This is an indication that the droplet size being defined by the atomized air pressure and the feed rate of the liquid have a significant effect on the agglomeration kinetics. The results of the previous study were the basis for this investigation to further scale up the fluidized bed process to a scale of 100 kg. Prior to the scale up, spraying tests with both nozzle types (model 940 and model 937) of the laboratory and production granulator were conducted at the Schlick test center. During these spraying tests the droplet size distribution at different atomized air pressure and feed rate levels were determined. This was done in order to ensure that similar droplet size distributions, during spraying for the scale up process, with the production granulator was achieved. An additional DoE was performed with the scaled parameters for atomized air pressure and the feed rate. For this matter, the agglomeration liquid quantity were scaled up and the spraying time were kept constant between the laboratory and production process. The desirable target for the scale up was a d_{50} value of the particle size distribution of approx. 575 µm based on previous investigations. The particle size distribution was monitored in-line with the agglomeration process. Carbon agglomerates were compressed in a 5 cavity mould with 60 strokes per minute. High quality agglomerates were targeted to achieve a fast, and constant mould filling with a tablet compressive strength above 8.0 MPa.

2. MATERIALS AND METHODS

2.1 EQUIPMENT

Two different fluidized bed granulators were used:

- Laboratory granulator (ProCell, Glatt, Weimar/Germany)
- Production granulator (Ghibli 100, IMA, Bologna/Italy).

In Table 1 the geometric dimensions and characteristics of the granulators are reported. The batch size was 10 kg for each agglomeration batch produced with the laboratory granulator and a 100 kg with the production granulator. The laboratory granulator was equipped with a GF3 vessel. Both granulators are fitted with a bottom spray technology with a two components nozzle (Schlick, Untersiemau/Germany). In the laboratory granulator the nozzle model 940 (Schlick, Untersiemau/Germany) was used and for the production granulator the model 937 (Schlick, Untersiemau/Germany). The nozzle diameter for the laboratory as well as the production granulator was 1.8 mm. The Ghibli granulator was equipped with a three-nozzle head and the Glatt granulator with a single-part nozzle head. The nozzle orifice of both fluidized bed granulators is the same. The cleaning of the filter bags took place continuously during the process within certain intervals. The spraying and fluidization of the particles did not stop

during filter cleaning. The inlet air was dehumidified, in both cases to approx. 5 g/kg before agglomeration, to achieve stable and comparable input conditions. It is clear, the granulator types do not have the same geometry.

Table 1: Dimensions of the fluidized bed granulators

Parameter	Unit	Fluidized bed granulators	
		Glatt ProCell	IMA Ghibli 100
Batch size	kg	10	100
Area distributor	m²	0.322	1.28
Product volume max	l	38	256
Fluidized air flowrate max	m³/h	250	1800
Nozzle orifice	mm	1.8	3 x 1.8

A Parsum Unit (Parsum, Chemnitz/Germany) was used to determine the particle size distribution during agglomeration. The measurement principle of the Parsum Unit is based on laser techniques, in which an extended spatial filter converts light obscuration signals from individual particles into size information [13, 14]. The Parsum Unit is made from stainless steel with a sapphire window in front. The particle size, is within the range of 50 µm and 6.000 µm with velocity measurements between 0.01 m/sec and 50 m/sec. The advantage of using the unit is that it can be directly inserted into the fluidized bed, to determine the in-line particle size distribution (PSD). Furthermore, a real time analysis of the agglomeration process is visible over the entire process by using the Parsum-View software [14].

2.2 MATERIALS

In Table 2, the raw materials used for the composition are shown. The carbon powder shows the highest particle size distribution (d_{90} of 251.0 µm), and a density of 1.40 g/cm³ at a moisture content of 1.6 %. The peroxide powder is the finest powder with a d_{90} of 26.0 µm, but the highest density of 2.91 g/cm³. The moisture content was determined with 1.0 % in the formulation. The binder in the formulation was the carboxymethyl cellulose (CMC) powder. Due to its hygroscopicity it showed the highest moisture content of around 7.0 %. The density of the binder was 1.59 g/cm³ at a d_{90} of 114.0 µm [21].

Table 2: Quality of raw materials used for preparation of the formulation (PSD determined with laser diffraction analyzer “Malvern Mastersizer 2000”) [21]

Solid state characteristics of raw materials						
ID	Quality	Mean particle size distribution			Raw material densities [g/cm³]	Moisture content [%]
		d_{10} [µm]	d_{50} [µm]	d_{90} [µm]		
Carbon powder	Q018	5.1	56.1	251.0	1.40	1.6
Peroxide powder	Ixper 75C	1.2	6.8	26.0	2.91	1.0
Carboxymethyl cellulose powder	Walocel CRT 2.00 PPA	17.0	47.0	114.0	1.59	7.0

The material composition of the powder bed consisted of [21]:

- 47.5 % peroxide powder produced by Solvay SA.
- 47.5 % fine carbon powder produced by ProFagus GmbH and grinded at Schunk Kohlenstofftechnik GmbH.
- 5.0 % carboxymethyl cellulose (CMC) powder produced by Dupont.

In the fluidized bed agglomeration process the CMC powder was used as a binder. 70 kg of tap water was sprayed onto the fluidized bed to partially dissolve the CMC particles, which then form bridges of solidified binder in the agglomeration of the primary particles [21].

2.3 AGGLOMERATION PROCESS

The droplet size distribution of the agglomeration fluid depends on the spraying parameters, the nozzle design and type of nozzle. Every nozzle type determines specific curves that describe the relationship between the atomization air consumption, at a certain atomization air pressure [7, 8]. The moisture content of the fluidized bed, again, depends on the agglomeration liquid supply and the liquid evaporation. Therefore, in a wet fluidized bed agglomeration process, it is necessary to maintain the overall moisture content of the fluidized bed, and the droplet size distribution on different scales [1]. Several investigations into critical process parameters, for fluidized bed granulation and agglomeration processes, have been performed to find optimum process conditions [9, 10, 11, 12]. The granules were produced in two fluidized bed scales (laboratory, 10 kg and production, 100 kg). The formulation of the powder bed consisted of carbon powder, peroxide powder and carboxymethyl cellulose (CMC) powder. The CMC powder was used as a binder in the fluidized bed agglomeration process. Tap water was sprayed onto the fluidized bed to dissolve the surface area of the CMC particles, which then form bridges of solidified binder material to agglomerate the primary particles.

2.4 ANALYTICAL METHODS

A KERN moisture analyser DBS was used to determine the moisture content of the agglomerates (KERN & SOHN, Balingen/Germany). The Loss of drying of the agglomerates was determined at 120 °C. As abort criterion, a constant mass for 30 seconds within ≤ 5 % mass variation was set [21]. According to DIN ISO 697 the bulk density was determined [15]. A Parsum Unit was used to determine the particle size distribution during agglomeration in-line [21]. The bulk density tester ERWEKA SMG 697 determined the bulk density of the agglomerates (ERWEKA, Langen/Germany). The flowability tester BEP2 with funnel and timer attachments determined the agglomerates flowability (Copley Scientific Limited, Nottingham/United Kingdom). Flow time of the agglomerates was carried out in accordance with DIN 53211 [16]. The compressive strength of the carbon tablets was analyzed using an automatic compressive strength tester (Instron, Norwood/USA, testing system 5944L6553) [21]. The behavior of the cylindrical carbon tablets under applied crushing loads on a stainless-steel plate was tested [21]. A cylindrical upper punch applied a compressive pressure and testing speed at 2mm/min to the carbon tablets [21]. The compressive strength as the final parameter was calculated by dividing the maximum load to the cross section of the carbon tablets [21]. An automatic density tester HST measured the tablet density (Borgwaldt, Hamburg/Germany) [21]. The laser-based HST analyzed the outer diameter, the length and weight to determine the tablet density through the equation: Density is equal to the mass divided by the volume [21]. The statistical software Minitab™ was used to conduct all statistical analysis [17]. To find the statistically significant process parameters for the given formulation on the tabled compressive strength a multilevel factorial design was conducted, which included central points as well as lower and upper limits for the spraying parameters [21]. To consider the statistical scattering three replication batches were produced [21].

2.5 **DESIGN OF EXPERIMENTS**

The following multilevel factorial design has been created for the scale-up with the production granulator:

- Two factors.
- One center point for each factor.
- Three replicates.
- Fifteen runs.

The two factors used in the multilevel factorial design were:

- Atomized air pressure.
- Water feed rate.

A pre-development fractional factorial design and multilevel factorial design were created and analyzed with the laboratory granulator, before carrying out this multilevel factorial design to find the statistically significant parameters. As statistically significant parameters for the investigated composition atomized air pressure and water feed rate were identified [21]. Previous development trials showed that a good central point for the water feed rate is 3.6 g/s and 1.4 bar for the atomized air pressure [21]. These mentioned development trials included the examination of spraying process limits for the current composition and showed good flowable agglomerates [21]. Based on the development trials the atomized air pressures for the scaled multilevel factorial design were decreased by 0.6 points and increased by 0.5 points in each direction around the central point with 3.9 bar. The central point of the water feed rate was set to 2160 g/min and increased and decreased by 180 g/min. In Table 3 the DoE levels are described as well as the agglomeration process parameters.

Table 3: Agglomeration process parameters

Parameter	**Unit**	**Lower level**	**Upper level**
Atomized air pressure	bar	3.3	4.4
Water feed rate	g/min	1980	2340
Process temperature	°C	Constant at 45	
Inlet fluidization air flowrate during spraying	m^3/h	Constant at 900	
Inlet fluidization air flowrate during drying	m^3/h	Constant at 900	

The atomized air pressure levels for the scaled multilevel factorial design were chosen according to the atomization air flowrate levels of the spraying nozzles. The water feed rate was also scaled up due to the development trials. This was done to keep the droplet size distribution constant and investigate the impact of the spraying parameters on the agglomerate characteristics. In Table 4 the experimental design for the scaled up multilevel factorial design is described.

Table 4: Experimental design for fluidized bed agglomeration process

StdOrder	RunOrder	CenterPt	Blocks	Atomized air pressure [bar]	Water feed rate [g/min]
2	1	1	1	4.4	1980
3	2	1	1	3.3	2340
4	3	1	1	4.4	2340
5	4	0	1	3.9	2160
1	5	1	1	3.3	1980
11	6	1	3	3.3	1980
13	7	1	3	3.3	2340
12	8	1	3	4.4	1980
15	9	0	3	3.9	2160
14	10	1	3	4.4	2340
8	11	1	2	3.3	2340
10	12	0	2	3.9	2160
6	13	1	2	3.3	1980
7	14	1	2	4.4	1980
9	15	1	2	4.4	2340

2.6 PROCESS PARAMETERS AND PERFORMANCE

The inlet air temperature was set to 45 °C for each run. For all runs produced both granulators were run in fully automated mode without any influence of the operators. This includes inlet air temperature, atomized air pressure, fluidization air flowrate and filter cleaning intervals. A DoE test plan was created and the spraying parameters were set. Based on a pre-development DoE the central points for the spraying parameters were chosen [21]. In Table 4 the variation of the spraying parameters of the DoE is listed. Before agglomeration the inlet air temperature was preheated to 45 °C. The raw materials were then loaded into the vessel of the granulator after reaching the inlet air temperature of 45 °C. Based on the results of the previous DoE studies, the agglomeration temperature including agglomeration and drying was kept constant at 45 °C. In a further step the raw materials were blended in the granulator for 10 sec. Immediately after blending the spraying of water onto the granules began. A target moisture content of approximately 30.0 % of the granules was achieved by a drying time of around 30 minutes. During agglomeration and drying the inlet fluidization air flowrate was kept constant [21]. The granules moisture content, particle size distribution, bulk density and flow time were considered as in-process control parameters. When the agglomeration and drying process was finished the mentioned in-process control parameters were checked. The flow time, bulk density and moisture content were determined according to the DIN methods described under analytical methods with a sample of approximately one kg. The granules particle size distribution throughout the whole process was determined in-line with a Parsum Unit. An operator recorded the particle size distribution values manually just before process was stopped. In able to reach a moisture content of approximately 30.0 % it was necessary to spray 5000 g of water onto the fluidized particles that were produced with the laboratory granulator and 50000 g of water onto the fluidized particles that were produced with the production granulator. The target moisture content of the granules between 29.0 – 31.0 % after drying had been precisely defined during the pre-development trials. Approximately a 5.0 g sample was taken out of the granulator vessel every 5 minutes through a sampler to determine the moisture content [21]. The laboratory granulator produced granules to mold 23000 tablets for each run. The production granulator produces granules to mold 230000 tablets. The granules were molded with a mechanical press (Press: MPA6 from Atlas, molding pressure at 22 kN to reach a tablet density of approx. 0,940

g/cm³). After molding the carbon tablets were immediately dried in a belt dryer (type TT-3A from Ring Maschinenbau GmbH) at 105 °C/25 minutes. During this process step every 10 minutes, 10 carbon tablets were taken as samples for in-process controls and final inspection, from the belt throughout the whole molding process. In terms of the compressive strength determination according to DIN ISO 2859-1 69 tablets were randomly taken and analyzed for each run with the laboratory granulator and 315 with the production granulator, respectively [18, 21].

2.7 **SCALING UP PRINCIPLES**

In a scale-up process there are factors and parameters that need to be consistent to produce high quality granules. The velocity of air that goes through the air distribution plate needs to remain constant for different scale-up levels. This ensures a similar fluidization behavior at different scales. The inlet air temperature and the dew point should be held constant. Another important parameter is the spray rate that describes the ratio between the atomization flow rate, and the feed rate. It is important to keep the droplet size distribution similar during scale ups. Unfortunately, in most cases the relationship between the atomized air pressure and atomizing air flowrate through the nozzle is not linear. Therefore, understanding of the atomizing air flowrate should be a known parameter and can be supplied by the nozzle vendor. To keep the moisture content similar during scale ups the quantity of the agglomeration fluid must also be constant [19]. Furthermore, characteristics like the batch size, particle size distribution, moisture content and density can be subject to change during the process.

Based on a previous study including a DoE, it was determined that a batch size of 10 kg led to a good mechanical stability of the carbon tablets and good flowability of the granules. These results were used as the basis for the scale-up. In Table 5 the scaled parameters for the production process with the Ghibli 100 granulator are shown.

Table 5: Scale-up parameters for IMA Ghibli 100

Parameter	**Unit**	**Fluidized bed granulators**	
		Glatt ProCell	IMA Ghibli 100
Batch size	kg	10	100
Agglomeration liquid quantity	l	5000	50000
DoE Center Point: Atomized air pressure	bar	1.4	3.9
DoE Center Point: Water feed rate	g/min	216	2160
DoE Center Point: Ratio value between the nozzle air flowrate and the feed rate	Nm³/kg	0.68	0.68
Fluidization air flowrate	m³/h	225	900

The following equation was used to determine a proper batch size for the scale up with the Ghibli 100 granulator:

$$X2 = \frac{X1 \cdot V2}{V1} \quad [20]$$

Where:
X2 = Batch size of unit 2 (kg)
V2 = Bowl volume of unit 2 (L)
X1 = Batch size of unit 1 (kg)

V1 = Bowl volume of unit 1 (L)

Another important parameter is the maintenance of the fluidization velocity at the air distribution plate. The following equations were used to determine the cross-sectional area of the air distribution plate:

$A = \pi \cdot r^2$ [20]

Where:
A = Air distribution plate area (m^2)
r = Radius of bottom screen (m)

Then,

$AV2 = \frac{AV1 \cdot A1}{A2}$ [20]

Where:
A1 = Air distribution plate area of unit 1 (m^2)
A2 = Air distribution plate area of unit 2 (m^2)
AV1 = Air fluidization flowrate of unit 1 (m^3/h)
AV2 = Air fluidization flowrate of unit 2 (m^3/h)

In order to maintain the droplet size distribution during scale-up the following equation was used to calculate the ratio between the fluidization air flowrate and the feed rate:

$R = \frac{NAF}{FR}$ [20]

Where:
R = Ratio value (Nm^3/kg)
NAF = Nozzle air flowrate (Nm^3/h)
FR = Feed rate (kg/h)

2.8 **OUTPUT PARAMETERS**

In Table 6 the output parameters and variables are shown. From a technical point of view the process can be run well within the lower and upper levels of the DoE.

Table 6: Granules and tablet target values

Parameter	**Unit**	**Target value**	**Lower limit**	**Upper limit**
Granules bulk density	g/cm^3	0.575	0.540	0.610
Granules moisture content	%	30.0	29.0	31.0
Tablet density	g/cm^3	0.940	0.920	0.960
Tablet compressive strength	MPa	8.0	7.0	9.0

3. RESULTS AND DISCUSSION

3.1 THE EFFECT OF THE LIQUID QUANTITY, INLET AIR FLOWRATE AND SPRAYING PARAMETERS

There are different variables and parameters that must be considered before scaling up the agglomeration processes. Firstly, the agglomeration liquid quantity and the spraying time must

be scaled up. Secondly, the inlet air velocity through the air distributor plate must be similar for the scale up process. Thirdly, the atomized air pressure and water feed rate defined the droplet size distribution. Therefore, the droplet size of the agglomeration fluid is responsible for the particle growth and needed to be adapted for scale ups.
The Parsum Unit to determine the particle size distribution in-line was fixed in a flange on the upper right part of the granulator vessel. The distance between the vessel wall and measuring unit was 50 mm. The Parsum Unit determined the particle size distribution during agglomeration and drying, e.g. $d_{10}/d_{50}/d_{90}$ [21]. In Figure 1 the particle size distribution throughout the process of a laboratory batch is shown in comparison to a production batch. The blue curves for the $d_{10}/d_{50}/d_{90}$ show the reference batch that was produced with the Glatt laboratory granulator with an atomized air pressure of 1.4 bar and a feed rate of 3,6 g/s. These settings were chosen as the center points of the previous DoE. The granules have shown the best flowability for these spraying parameters. The comparable batch with the production Ghibli granulator was produced with an atomized air pressure of 3.9 bar and a feed rate of 2160 g/min. These spraying parameters were defined for the scale up DoE as the center points to reach a similar particle growth during the process. In the diagram it is visible that the particle agglomeration over time is similar between the reference Glatt batch and the scaled Ghibli batch. It leads to the conclusion that the scaled parameters for the liquid quantity, inlet air flowrate and the spraying parameters define a comparable particle growth behavior in the fluidized bed for the same formulation.

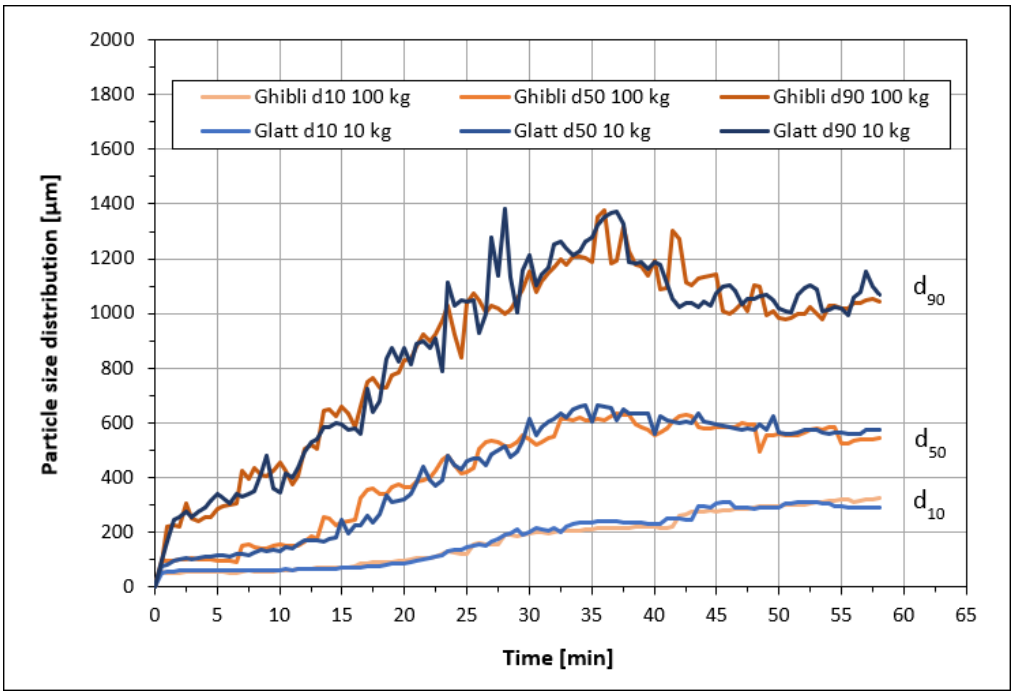

Fig. 1: Example of particle size distribution during agglomeration process

In Figure 2 the moisture content of two differently produced agglomeration batches are shown. Samples of 5 g were taken out during the process and analyzed with a moisture analyzer. The blue curve shows the produced batch with the laboratory Glatt granulator with an atomized air pressure of 1.4 bar and a feed rate of 3,6 g/s. The comparable batch with the production Ghibli granulator was produced with an atomized air pressure of 3.9 bar, and a feed rate of 2160 g/min. Both curves look comparable, which indicates that the behavior is similar between the droplet size distribution and the wetting of the particles during the agglomeration process.

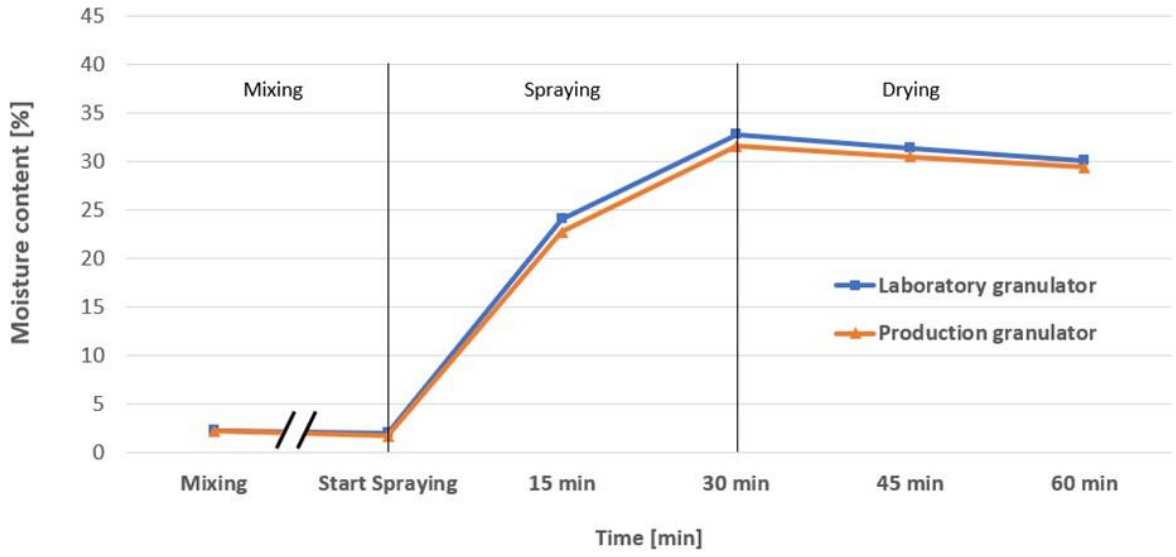

Fig. 2: Measurement of moisture content during agglomeration

3.2 STATISTICAL ANALYSIS

In Table 7 the output result of each batch is listed. Pareto charts have been created to visualize significant effects. These charts are used to compare the relative magnitudes and the statistical significance of main effects and interactions. Length's method is used to draw the reference line for statistical significance. The effects are plotted in decreasing order of their absolute values. The red vertical reference line on the chart indicates the statistically significant effects [17].

Table 7: Mean output results of DoE

No.	Atomized air pressure [bar]	Feed rate [g/sec.]	Tablet density [g/cm³]	Tablet compressive strength [MPa]	Bulk density [g/cm³]	Moisture content [%]	Flow time [s]	PSD d_{50} [µm]
1	4.4	1980	0.938	8,1	0.570	29.7	11.0	600
2	3.3	2340	0.939	8.3	0.572	30.5	8.3	552
3	4.4	2340	0.938	7.8	0.579	29.6	11.7	624
4	3.9	2160	0.942	8.2	0.55	29.8	7.9	586
5	3.3	1980	0.945	8.5	0.592	30.1	9.1	606
6	3.3	1980	0.939	8.5	0.591	30.2	9.3	612
7	3.3	2340	0.940	8.3	0.577	30.2	8.6	684
8	4.4	1980	0.939	8.2	0.570	30.3	11.3	624
9	3.9	2160	0.941	8.2	0.560	30.4	7.2	577
10	4.4	2340	0.935	7.7	0.572	30.8	11.4	597
11	3.3	2340	0.940	8.3	0.580	30.6	8.8	607
12	3.9	2160	0.941	8.2	0.580	30.3	7.3	566
13	3.3	1980	0.941	8.6	0.594	31.0	9.4	627
14	4.4	1980	0.937	8.4	0.571	30.5	11.0	619
15	4.4	2340	0.937	7.9	0.572	30.1	11.2	650

In Figure 3 shown for the present DoE there are two significant effects (a = 0.05): The granules bulk density and flow time. The two significant effects are atomized air pressure and feed rate. In the diagram it is clearly shown that in both cases the atomized air pressure (A) has the largest effect. This indicates that both spraying parameters directly influence the liquid droplet size distribution and the behavior of the particles during agglomeration. The droplet size distribution

created by the atomized air pressure and feed rate in the fluidized bed also affects the tablet density and its pore and volume structure. For the tablet compressive strength it is visible that atomized air pressure and feed rate show significant effects. Since the atomized air pressure defines the pore and volume structure during agglomeration, a moisture content of the agglomerates between 29.0 – 31.0 % was reached for each production run. After molding and drying of the tablets, the evaporation of water, (because of the heat treatment process) gave the tablets their defined pore and volume structure [21].

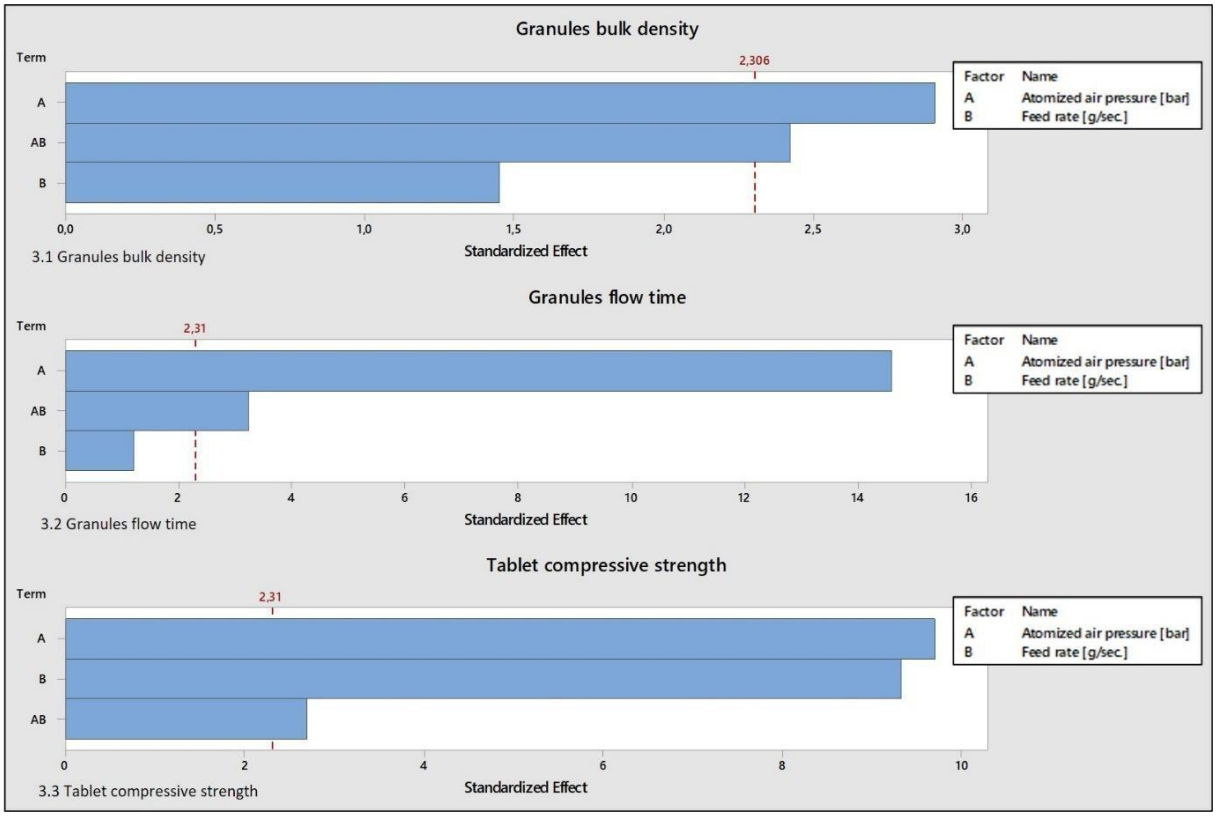

Fig. 3: Pareto Charts of standardized effects of atomized air pressure and feed rate on response variables of granules and compressed cylinders (i.e., 3.1 Granules bulk density, 3.2 Granules flow time, 3.3 Tablet density)

The calculation of S, R^2 and adjusted R^2 (R^2 adj) is an indication of how well the model fits the data. S is measured in the units of the response variable and represents the standard distance that the data values fall from the regression line. The R^2 value is another important parameter that describes the amount of variation in the observed response values that is explained by the predictors. R^2 is a useful parameter when comparing models of the same size. These mentioned values help to select the model with the best fit [17, 21]. In Table 8 the S and R^2 values are listed. It is shown that the model explains 98.2 % for the granules flow time and 78.7 % for the granules bulk density. Furthermore, the model explains 55.7 % for the granules moisture content and 39.1 % for the granules PSD d_{50} value of the variation in the data for the R^2 values. Additionally, the R^2 value for the tablet density is 96.1 % and 49.7 % for the compressive strength [21].

Table 8: Summary model of the DoE

Parameter	S	R^2
Granules bulk density [g/cm³]	0.0071	78.7 %
Granules moisture content [%]	0.3388	55.7 %
Granules flow time [sec.]	0.2758	98.2 %
Granules PSD d_{50} [µm]	33.8610	39.1 %
Tablet Density [g/cm³]	0.0638	96.1 %
Tablet compressive strength [MPa]	1.1381	49.7 %

The fitted means for each value of a variable in the model is plotted in the main effects plot. The lines in the diagram give an information as to whether a main effect is present for a variable. A main effect is great the greater the angle of the vertical position [17]. In Figure 4 it is visible that the flow time of the granules is mainly affected by the atomized air pressure. Furthermore, low flow times in the range between 7.0 – 9.0 s can be achieved with atomized air pressures ranging between 3.3 – 3.9 bar. Additionally, it seems that the granules show a good flowability, when the d_{50} of the particle size distribution is below 600 µm. The lowest flow time of approximately 7.5 s was archieved with an atomized air pressure of 3.9 bar. This finding correlates with the results of pre-development studies [21]. It appears that inadequate re-wetting of the agglomerates causes the granule growth rate to decrease during agglomeration. This also shows that this parameter was significant at the 0.05 a-level in the earlier analysis of the granules flow time Pareto Chart [21]. Another intriguing finding is that the compressive strength of the carbon tablets is positively impacted by an atomized air pressure of 3.3 bar and a water feed rate of 1980 g/min. The tablet compressive strength main effect plot displays this outcome. According to Figure 4, tablets with a density of approximately 0.941 g/cm³ will have a compressive strength of approximately 8.4 MPa. An atomized air pressure of 3.3 bar and a water feed rate of 1980 g/min are sufficient to achieve this outcome. At this stage, it appears that a higher tablet density caused the tablets' porosity to decrease, which in turn caused the predetermined breaking point to decrease. As a result, the tablet's compressive strength values are positively impacted [21].

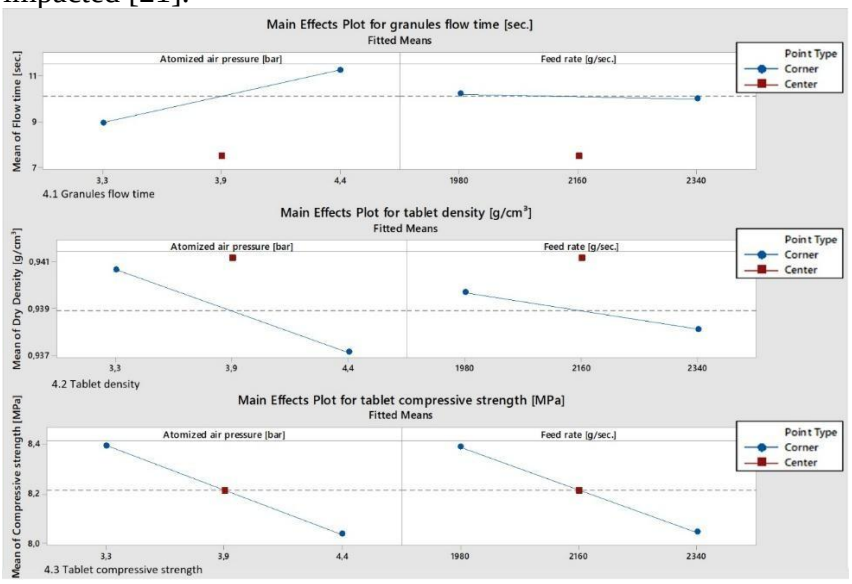

Fig. 4: Main effects plots (i.e., 4.1 Granules flow time, 4.2 Tablet density, 4.3 Tablet compressive strength)

Two-way interactions are evaluated using the interaction plots [17]. The strength of the interaction increases as the lines' angle increases. No interaction is indicated by parallel lines [17]. The interaction plots are displayed in Figure 5. It is evident that the atomized air pressure and the water feed rate interact in the case of the granules bulk density [21]. Lower water feed rates combined with an atomized air pressure of 3.3 bar resulted in somewhat higher bulk densities [21]. Another intriguing result shows that the relationship between feed rates and lower atomized air pressure influences the granules' flow time [21]. This suggests that the agglomerates have a more compact structure when the droplet sizes are smaller. This results in a lower porosity, which improves the flowability of the agglomerates [21].

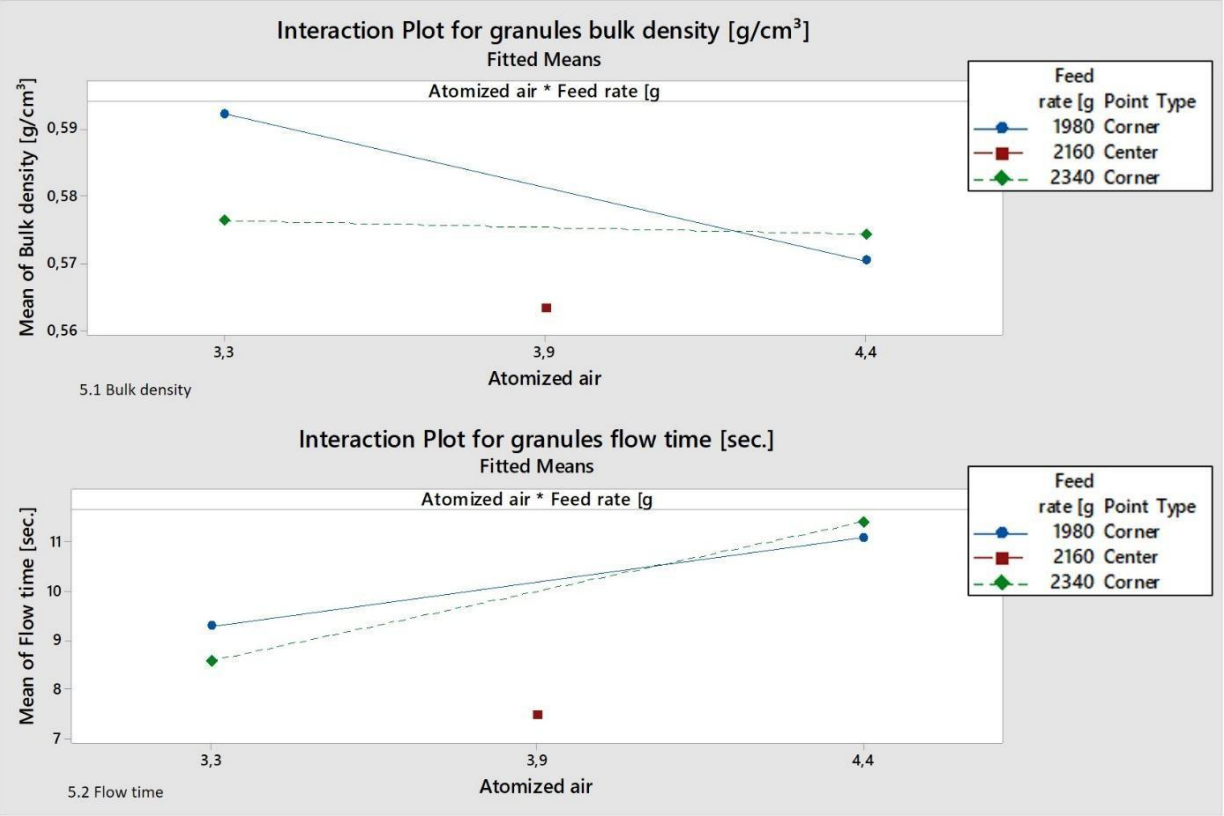

Fig. 5: Interaction plots (i.e., 5.1 Granules bulk density, 5.2 Granules flow time)

To investigate the relationship between three variables on a single plot, contour plots are utilized [17]. Figure 6's first contour plot illustrates the connection between the granules' bulk density, feed rate, and atomized air pressure. It is demonstrated that higher bulk densities resulted from lower feed rates at about 2000 g/min and lower atomized air pressures of about 3.4 bar. When the contour plot of the flow time is analysed, it is evident that the centre points of the feed rate and atomized air pressure show the lowest flow times, which are less than 8.0 seconds [21]. This clearly shows that the agglomerates' optimal flowability occurs at about 3.9 bar and 2160 g/s. The tablet compressive strength exhibits the highest values above 8.5 MPa at atomized air pressures below 3.6 bar and water feed rates below 2080 g/min, which is another intriguing finding. Larger droplets are produced during spraying when atomized air pressures and water feed rates are reduced [21]. Higher compressive strength values result from more compact agglomerates, which are influenced by larger droplet sizes [21].

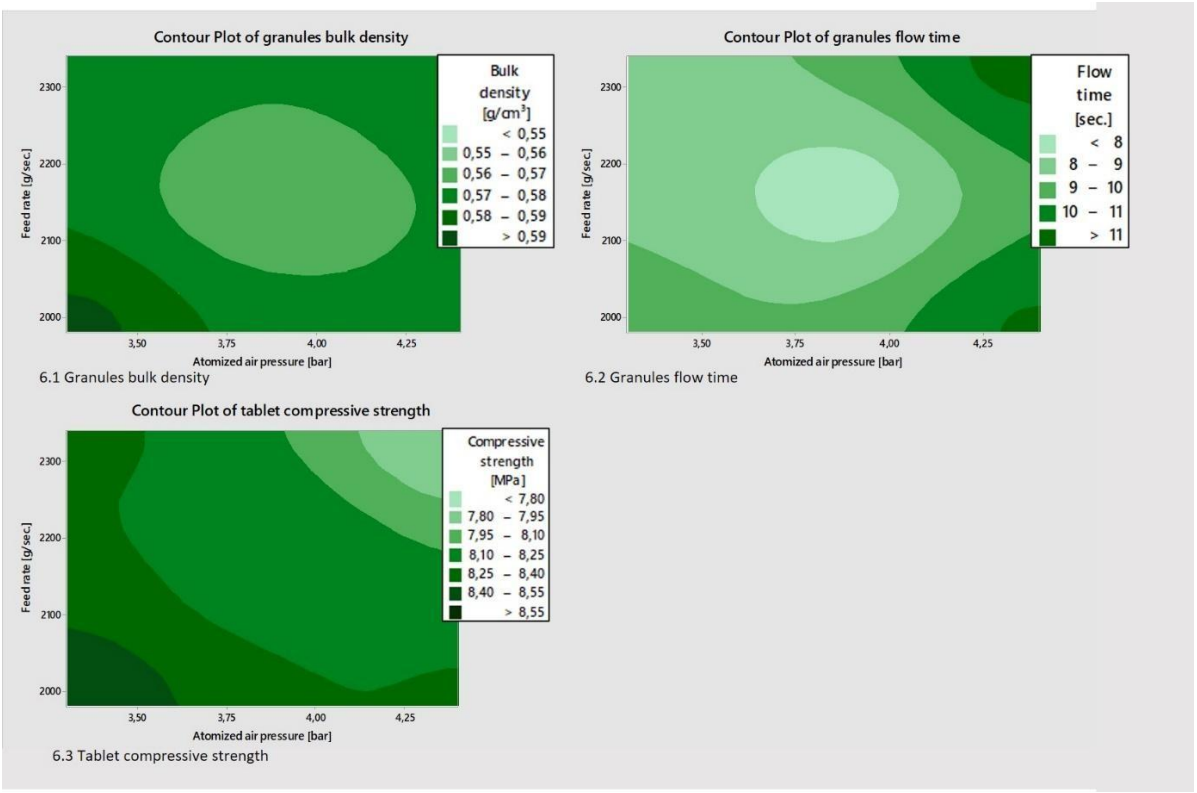

Fig. 6: Contour plots (i.e., 6.1 Granules bulk density, 6.2 Granules flow time, 6.3 Tablet compressive strength)

The two most crucial quality parameters were determined to be the tablet's compressive strength and the agglomerates flowability. An atomized air pressure and a water feed rate around the centre points of the DoE produced the best granule flowability below 8.0 seconds. An atomized air pressure and a water feed rate around the DoE centre points were used to target even the tablet compressive strength of greater than 8.0 MPa [21]. Three batches of IMA Ghibli 100 (a production granulator) and three batches of Glatt ProCell (a laboratory granulator) were compared for tablet compressive strength using a further analysis of variance (ANOVA) test. This was carried out in order to compare the primary quality of tablets [21]. The boxplots of the Glatt ProCell batches and the condensed IMA Ghibli 100 batches are displayed in Figure 7. The descriptive statistics for the Glatt ProCell and IMA Ghibli 100 batches are displayed in Table 9 below.

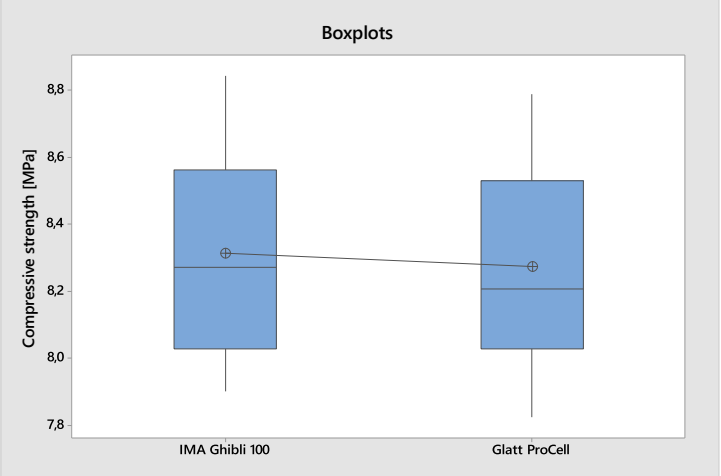

Fig. 7: Boxplot of compressive strength values

Table 9: Compressive strength of Glatt ProCell and IMA Ghibli 100 batches

Variable	Mean compressive strength [MPa]	StaDev compressive strength [MPa]	Minimum compressive strength [MPa]	Maximum compressive strength [MPa]
IMA Ghibli 100	8.31	0.296	7.90	8.84
Glatt ProCell	8.27	0.287	7.82	8.79

In conclusion, three batches were produced using the IMA Ghibli 100 granulator and the Glatt ProCell granulator. The compressive strength of the carbon tablets (exceeding 8.0 MPa), can be achieved by setting the feed rate at 2160 g/min and the atomized air pressure at 3.9 bar. ANOVA results with a P-Value of 0.604 at a significance level of 0.05 are displayed in Table 10 ($F(1,58) = 0.604$, $p > 0.05$). It was shown that the production and laboratory granulators' tablet compressive strengths did not differ statistically.

Table 10: One-way ANOVA of compressive strength data

Method Analysis of Variance Significance level: $\alpha = 0.05$	**F-Value**	**P-Value**
IMA Ghibli 100 vs. Glatt ProCell	0.27	0.604

4. CONCLUSION

Scaling up a fluidized bed agglomeration process from a laboratory to a production setting was the goal of this study. Ensuring that the integrity of the final carbon tablets compressed from these granules fulfill given requirements such as good flowability of granules to achieve a fast and constant mould filling and a compressive strength of 8 MPa. A consistent procedure and a superior product were additional objectives. Investigations into the influence of spraying parameters on the agglomerates as intermediates, and the compressive strength of carbon tablets. Different scale-up routines were evaluated, including a proper batch size, the fluidization velocity at the air distribution plate, the agglomeration liquid quantity and the droplet size. Even though interactions between process parameters took place, defined end product qualities were achieved. Agglomerate particle characteristics are obviously influenced by atomized air pressure and feed rate. Finding out about the growth of particle sizes during fluidized bed agglomeration was another goal of this study. The Parsum unit was used to measure the particle size in real-time during the entire process. It was observed that the spraying parameters affect the flowability of the agglomerates. A very good flowability has been reached around the center points of the DoE. This on the one hand, is important to optimize the flowability of the agglomerates, and on the other hand to achieve a consistent cavity filling before molding. Lower atomized air pressures lead to higher bulk densities. In that case larger droplet sizes lead to compact agglomerates and therefore higher bulk densities. Another outcome of the main effects plot was that lower atomized air pressures lead to higher compressive strength values. Through a comparison of the tablet compressive strengths between the production and laboratory granulator it was demonstrated that there is no statistical difference. This indicates that the scale-up was executed effectively.

REFERENCES

[1] Matsen, J. M., Scale-up of fluidized bed processes: Principle and practice, Powder Technology, Vol. 88, Issue 3, Pages 237-244, 1996

[2] Faure, A., York, P., Rowe, R.C., Process control and scale-up of pharmaceutical wet granulation processes: a review, Review article, European Journal of Pharmaceutics and Biopharmaceutics 52, 2001, Pages 269–277

[3] Godek, E.J., Bring Fluid Bed Granulation Up to Scale, Scaling up commercial manufacturing with the same quality and results, Pharmaceutical Manufacturing magazine, 2013

[4] Mehta, A.M., Scale-up considerations in the fluid-bed process for controlled-release products, 1988, Pharm. Tech. 12, 46–52

[5] Schaefer, T., Worts, O., Control of fluidized bed granulation, IV Effects of binder solution and atomization on granule size and size distribution, Arch. Pharm. Chemi. Sci. Ed. 6, 1978, Pages 14–25

[6] Watano, S., Fukushima, T., Miyanami, K., Heat transfer and granule growth rate in fluidized bed granulation, 1996, Chem. Pharm. Bull. 44, 572–576

[7] Waldie, B., Growth mechanism and the dependence of granule size on drop size in fluidized-bed granulation, 1991, Chemical Engineering Science, Vol. 46, No. II, pp. 2X-2785

[8] Schick, R.J., Spray Technology Guide: Understanding Drop Size, Spray Analysis and Research Services, Wheaton, IL 2008

[9] Hartung, A., Johansson, E., Knoell, M., Valthorsson, H., Langguth, P., "Design Space" Determination of a Paracetamol Fluid Bed Granulation Using Design of Experiments, Cantor Verlag, Aulendorf (Germany), 2012, Pharm. Ind. 74, Nr. 4,644-650

[10] Diez, E., Meyer, K., Bück, A., Tsotsas, E., Heinrich, S., Influence of process conditions on the product properties in a continuous fluidized bed spray granulation process, Chemical Engineering Research and Design, Volume 139, November 2018, Pages 104-115

[11] Terrazas-Velarde, K., Peglow, M., Tsotsas, E., Kinetics of fluidized bed spray agglomeration for compact and porous particles, Chemical Engineering Science, Volume 66, Issue 9, 1 May 2011, Pages 1866-1878

[12] Rambali, B. et al., Using experimental design to optimize the process parameters in fluidized bed granulation, Drug Dev Ind Pharm, 2001, 27:47-55

[13] Schmidt-Lehr, S., Moritz, H-U., Jürgens, K.C., Online Control of Particle Size during Fluidised Bed Granulation, Pharm. Ind. 69, Nr. 4, 478−484, 2007

[14] Dietrich, S., Petrak, D., In-Line Particle Size Characterization of Multiparticulate Systems, Springer-Verlag, Chapter 12, Pages 301-332, 2017

[15] DIN ISO 697: 1984-01, Determination of apparent density; Method by measuring the mass of a given volume, 1984

[16] DIN 53211 :1987-06, Determination of flow time by DIN cup, 1987

[17] Minitab 17 Statistical Software, Minitab StatGuide, Analyze Factorial Design, 2014

[18] DIN ISO 2859-1:2014-08, Sampling procedure for inspection by attributes, Part 1 : Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection (ISO 2859-1:1999 + COR. 1:2001 + AMD. 1:2011), 2004

[19] Godek, E. J., Bring Fluid Bed Agglomeration Up to Scale, Scaling up commercial manufacturing with the same quality and results, Pharmaceutical Manufacturing magazine, 2013

[20] Gerstner, S., Wirbelschicht, Schlick Atomizing Technologies, Internal Presentation, 2017

[21] Oelofse, M., Rack, R., Hilden, M., Langguth, P., Optimization of product characteristics of porous carbon agglomerates using a design of experiments in a fluidized bed agglomeration, Pariticulogy, Pages 258-269, 2024

[22] Godek, E. J., Bring Fluid Bed Agglomeration Up to Scale, Scaling up commercial manufacturing with the same quality and results, Pharmaceutical Manufacturing magazine, 2013