Stability and repeatability of a continuous twin screw granulation and drying system

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Abstract

The aim of this study was to investigate the process transfer of a commercially available product from the current batch fluid bed granulation and drying production method to an innovative continuously operating 'from powder to tablet' production line using twin screw granulation as an intermediate granulation step. By monitoring process outcomes (torque, water temperature at the granulator jacket inlet, differential pressure over the dryer filters, temperature mill screen) and granule and tablet quality in function of process time, the stability and repeatability during long production runs were determined.

Three consecutive 5h 'from powder to tablet' production runs were performed using the ConsiGma™-25 system (GEA Pharma Systems, Collette™, Wommelgem, Belgium). A premix of two active ingredients, powdered cellulose, maize starch, pregelatinized starch and sodium starch glycolate was granulated with distilled water. After drying and milling (1000µm, 800rpm), granules were in-line blended with magnesium stearate and directly compressed using a Modul™ P tablet press (tablet weight: 430 mg, main compression force: 12 kN). Granule (loss on drying, particle size distribution, friability, flow) and tablet (weight uniformity, hardness, thickness, friability, content uniformity, disintegration time and dissolution) quality was evaluated in function of process time.

For each of the logged process outcomes, a stabilization period was needed to reach steady-state conditions. Slightly deviating particle size distribution and friability results for milled granules were observed during start-up due to initial layering of the mill screen. However, no deviating tablet quality was detected in function of process time.

For multiple hours, granule and tablet quality was constant in function of process time. Furthermore, process data trends were highly repeatable. Consequently, the

ConsiGma™-25 system can be considered as a stable and repeatable system for the continuous production of tablets via wet granulation.

KEYWORDS: Continuous twin screw granulation and drying, Process transfer, Stability, Repeatability, Granule and tablet quality

1. Introduction

Whereas most pharmaceutical manufacturing processes are currently run via a series of batch-wise unit-operations, continuous processing offers several advantages to improve the manufacturing efficiency of solid dosage forms. Continuous production leads to reduced costs through faster development and less scale-up, smaller equipment footprint and elimination of intermediate storage. Furthermore, online monitoring and real-time testing results in improved product quality.

However, despite several advantages related to continuous production, the pharmaceutical industry has been slow to adopt the principle of continuous processing. On the one hand, high investment costs are required for the installation of new manufacturing equipment allowing continuous production. On the other hand, limited material volumes typical for the pharmaceutical industry would lead to frequent product changeovers on the continuous line. Additionally, pharmaceutical companies fear delay of product approval by the regulatory authorities. Due to high profit margins on their products, until recently, the economical need to change the manufacturing concept of pharmaceuticals was low. Currently, however, also the pharmaceutical industry is forced to improve the cost efficiency of their production due to the competition with the generics [1-4].

Although specific types of continuous wet granulators have been on the market for years (e.g., horizontal fluid bed granulators, multistage fluid bed, spray drier with integrated fluid bed, instant granulators, plough-shear mixers), none of these have made a significant impact within the pharmaceutical industry. On the one hand, this could be explained by the reluctance to move towards continuous processing (e.g., high profit margins, regulatory hurdles,…). On the other hand,

equipment-related deficiencies were encountered as these techniques were only suitable for high material throughputs which are seldom required for pharmaceutical processing [3, 4]. However, equipment manufacturers have identified the specific needs for continuous wet granulation within the pharmaceutical industry and as a result a new generation of small and versatile continuous granulators has emerged, also suitable for manufacturing pharmaceuticals at a low production rate (10-50 kg/h).

To fully benefit from the advantages offered by continuous wet granulation, the new techniques should be applicable to new products but also to existing products. Hence, it should be possible to continuously process formulations currently agglomerated using conventional batch-wise fluid bed or high-shear granulation into an end product having similar physico-chemical characteristics (hardness, friability, disintegration, dissolution,…). This would allow transferring existing production processes from a batch process using low or high shear granulators to the novel continuous wet granulator. Furthermore, appropriate continuous manufacturing techniques for solid dosage forms should allow conversion of powder into tablets in development, pilot, clinical and production volumes in a single compact unit and batch sizes should only be determined by the length of the run. Therefore, it is essential that the process continuously operates under steady state conditions to manufacture granules and tablets of a specific quality for any length of time.

During the last decade, twin screw granulation as a continuous particle size enlargement technique has already been described by several research groups [5-10]. Keleb et al. evaluated the continuity of the technique over a period of 8h [5]. Recently, Dhenge et al. published a study on the progression of granules in different compartments along the length of the screws in a twin screw granulator, helping to provide an understanding of the twin screw granulation process [9].

The aim of the current study was to investigate the process transfer of a commercially available product from the actual batch fluid bed granulation and drying production method to an innovative continuously operating tablet manufacturing line, the ConsiGma™-system (GEA Pharma Systems, Collette™, Wommelgem, Belgium). The wet granulation module of this system consists of a high-shear twin screw granulator. After initial optimization work, three consecutive 5h 'from powder to tablet' production runs were performed in order to investigate the stability and repeatability of this system. Therefore, granule and tablet quality attributes were determined in function of process time. Besides, quality attributes of granules and tablets produced by the actual batch process and the continuous system were compared.

2. Materials and methods

2.1. Materials

The formulation consisted of two active ingredients, powdered cellulose, maize starch, pregelatinized starch and sodium starch glycolate. A high-dosed slightly soluble API was combined with a low dosed freely soluble API. Both d50 values of the APIs were lower than 100 µm. Distilled water was used as granulation liquid. Magnesium stearate was applied as lubricant during tableting. All materials were delivered by Johnson&Johnson, Janssen-Cilag, Italy.

2.2. Preparation of granules and tablets

Granulation and drying experiments were performed using the ConsiGma™-25 unit (GEA Pharma Systems, Collette™, Wommelgem, Belgium) (Fig. 1). This system consists of three modules, as already described by Chablani et al. [11] and

Fonteyne et al. [12]: a high-shear wet granulation module, a six-segmented fluid bed dryer module and a granule conditioning module.

The granulation module consists of a high-shear co-rotating twin screw granulator without die plate. The length-to-diameter ratio of the granulation unit is 20:1. The barrel of the continuous granulator can be divided into two segments: a feed segment, where powder enters the barrel and consisting of conveying elements to transport the material through the barrel; and a work segment, where the powder is intensively mixed with the granulation liquid by kneading elements [12, 13]. At the work segment, the temperature of the barrel wall was controlled by a Pt100 temperature sensor. As the barrel jacket was not divided into different temperature zones, the full length of the barrel was preheated to equal temperature (25°C). To evaluate the stability of the granulation process, the torque on the screws and the temperature of the water at the granulator jacket inlet (1 s interval) were recorded. The latter was monitored as changes of the temperature of the barrel wall at the work segment caused by friction were controlled by adapting the temperature of the water inside the granulator jacket (feedback control system). Both torque and water temperature at the granulator jacket inlet give an indication of the shear and compaction forces experienced by the materials inside the barrel. The equipment had an in-built torque gauge. The screw speed was set at 900rpm. The screw configuration was composed of 2 kneading zones each consisting of 4 kneading elements (L=D/4 for each kneading element) at an angle of 60 degrees (Fig. 2). Both kneading zones were separated by a conveying element (L=1.5D). An extra conveying element (L=1.5D) was implemented after the second kneading block together with 2 narrow kneading elements (L=D/6 for each kneading element) in order to reduce the amount of oversized agglomerates, as reported by Van Melkebeke et al.. During processing, a powder premix of two active ingredients, powdered cellulose, maize starch, pregelatinized starch and sodium starch glycolate was gravimetrically

dosed at a feed rate of 20 kg/h by a twin screw feeder (KT20, K-Tron Soder, Niederlenz, Switserland). Distilled water as granulation liquid was gravimetrically pumped into the screw chamber using two peristaltic pumps (Watson Marlow, Comwall, UK) and silicon tubings (internal and external diameter of 1.6 and 6.4 mm, respectively) connected to 1.6 mm nozzles. Liquid was added in front of the first kneading element. The water concentration was equal to 13% (w/w), calculated on wet mass.

In the ConsiGma^{TM}-25 unit, the granulation unit is directly connected to a six-segmented fluid bed dryer, either horizontally or vertically. As the granulation and drying unit of the ConsiGma^{TM}-25 unit used in this study were lined up vertically, the wet granules were gravimetrically transported to the top of the six-segmented fluid bed dryer (six identical dryer cells) through a rotating inlet valve. The filling time per cell was 180 seconds, resulting in a cell load of 1 kg granules (based on dry mass) at 20 kg/h powder feed rate. The inlet air temperature, humidity and airflow rate were set at 45°C, 10% and 420 m^3/h, respectively. The drying time was fixed at 790 seconds. At the end of the drying cycle, a rotating discharge valve allowed the respective dryer cell to be vacuum discharged followed by one blow back in order to clear the corresponding filter. During production, the differential pressure over the dryer filters was monitored as an indication for the filter loading.

After drying, the dry granules were pneumatically transported to the granule conditioning unit. In this unit, each package of dry granules was milled through a Quadro comil U10 (Quadro Engineering, Ontario, Canada), equipped with a 1000µm grater screen rotating at 800rpm. The temperature of the mill screen was monitored by a Pt100 temperature sensor. After milling, materials were pneumatically transported to an in-line conical ribbon blender and blended with 0.58% (w/w) magnesium stearate (60rpm for 1 min). The final blend was gravimetrically

transported to the hopper of a MODUL^{TM} P tablet press (GEA Pharma Systems, Courtoy^{TM}, Halle, Belgium). The tablet press was equipped with oblong shaped concave Euro B punches (15.5 mm x 6.3 mm). Tablets (430 mg) were manufactured at a compression force of 12 kN per tablet.

For all runs, milled granules and tablets were sampled every 30 minutes. Furthermore, the first filling cycle of the dryer (6 cells) and the last filling cycle of the dryer (6 cells) were collected as milled granules and tablets for run 1 and run 2, respectively. Samples of milled granules were taken by disconnecting the vacuum transfer line between the granule conditioning unit and the in-line lubricant blender at predefined time points. Loss on drying (LOD), particle size distribution (PSD), friability, bulk and tapped density and Hausner ratio were determined for the milled granules. Weight uniformity, hardness, thickness, friability, content uniformity, disintegration time, and dissolution of the tablets were tested. Quality attributes of granules and tablets produced by the continuous system were compared with granule and tablet quality data derived from three batches of the actual batch process (Table 1).

For the continuous process, 100 kg of dry powder blend was processed into tablets during 5h production time (i.e. 20 kg/h). Although the actual process time for the batch process was similar (about 12h for 240kg), the total time to manufacture the tablets via the batch process was much longer compared to the fully continuous from-powder-to-tablet process due to the lag time and off-line testing between the different unit operations of the batch process. Flow diagrams of both production methods are shown in Fig. 3.

2.3. Evaluation of granules

2.3.1. Loss on Drying (LOD)

Immediately after collection, the residual moisture content of the milled granules was determined via loss on drying (LOD) using a Mettler LP16 moisture analyser, including an infrared dryer and a Mettler PM460 balance (Mettler-Toledo, Zaventem, Belgium). A sample of approximately 9 g was dried at 105°C until the rate of change was less than 0.1% LOD for 30 seconds and the % LOD was then recorded (n=1). For run 1, LOD measurements of samples taken from the first and last filling cycle of the dryer were performed in triplicate.

2.3.2. Particle size analysis

Sieve analysis was performed using a Retsch VE 1000 sieve shaker (Haan, Germany). Milled granules were placed on the shaker during 5 min at an amplitude of 2 mm using a series of sieves (75, 125, 250, 500 and 1000 µm). The amount of granules retained on each sieve was determined. All granule batches were measured in triplicate. The amount of fines and coarse agglomerates were defined as the fractions <75 and >500 µm, respectively.

2.3.3. Friability of granules

The granule friability was determined (n=3) using a friabilator (PTF E Pharma Test, Hainburg, Germany) at a speed of 25 rpm for 10 min, by subjecting 10 g (I_{wt}) of milled granules together with 200 glass beads (mean diameter: 4 mm) to falling shocks. Prior to determination, the granule fraction <250 µm was removed to assure the same starting conditions. Afterwards, the glass beads were removed and the weight retained on a 250 µm sieve (F_{wt}) was determined. The friability was calculated as $((I_{wt} – F_{wt}) / I_{wt})*100$.

2.3.4. Flowability

The bulk volume (V_0) of 30 g milled granules was recorded in a 100 ml measuring cylinder as well as the volume after 1250 taps (V_{1250}) in a tapping machine (J. Englesman, Ludwigshafen, Germany) (n=3). Bulk and tapped densities were calculated as 30 g / V_0 and 30 g / V_{1250}, respectively. The Hausner ratio (HR) was calculated from the bulk and tapped density using the following equation,

Hausner Ratio (HR) = ρ_f / ρ_i

where ρ_i is the bulk density and ρ_f is the tapped density [14]. Flow properties were described accordingly to the range of Hausner ratio described in USP Powder flow <1174> [15].

2.4. Tablet evaluation

2.4.1. Weight uniformity, hardness and thickness

Weight uniformity was determined after weighing 20 individual tablets of each sample taken. The average mass and the amount of tablets deviating by more than 5% and 10% from the average mass were calculated. The hardness and thickness of tablets (n=10) were determined (Sotax HT 10, Basel, Switserland) after a storage period of at least 24 h at 21 °C and 30% RH.

2.4.2. Friability

The tablet friability was determined (n=3) using a friabilator described in Eur. Ph. (PTF E Pharma Test, Hainburg, Germany), at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

2.4.3. Content uniformity, disintegration time and dissolution

To assess the content uniformity, the individual content of the two active substances of 10 tablets was determined via HPLC analysis (see section 2.4.4.). The disintegration time was determined (n=6) using the apparatus described in Eur. Ph. (PTZ-E Pharma Test, Hainburg, Germany). Tests were performed in distilled water at 37 ± 0.5 °C using disks. Dissolution tests were performed (n=3) in 900 ml 0.1N HCl (pH = 1) using the paddle method (VK 7010, Vankel, Cary, NC, USA). The temperature of the dissolution medium was maintained at 37 ± 0.5°C, while the rotation speed was set at 50 rpm. A 5 ml sample was withdrawn at 30 min after starting the dissolution. The content of both drug components was determined via HPLC analysis.

2.4.4. HPLC analysis

API concentrations were determined by a validated reversed phase high-performance liquid chromatography (HPLC)–UV method with gradient. For content uniformity analysis, 10 individual tablets per sample were accurately weighed and placed into a 50 ml volumetric flask. 30 ml of 20 mM potassium phosphate monobasic (PPM) solution was added and mixed for 10 to 15 minutes in order to disintegrate the tablets. After the tablets were completely disintegrated, 20 ml of acetonitrile:methanol (50/50, v/v) was added. Sample solutions were diluted above to volume with PPM solution and mixed. Before filling into the injection vials, the solutions were filtered through a 45 µm PFTE filter.

The HPLC equipment used for analysis was a Waters 2695 Separations Module Alliance system. The Separations Module is an integrated solvent and sample management platform (quaternary solvent, high-performance solvent delivery system). A PDA detector (λ = 215 nm) (Waters 2996 PDA Detector) was connected to the Alliance system and a Supelcosil LC-8-DB column (150 mm x 4.6 mm, 5 μm) was used as the silica gel carrier with reversed phase properties. This sorbent was packed into a LiChroCart® 125-4 HPLC cartridge (Merck KGaA, Darmstadt, Germany).

3. Results and discussion

3.1. Evaluation of granulation, drying and milling processes

During processing, the ConsiGma^{TM}-25 system continuously logged 55 different process parameters/outcomes (1 s interval), supplying a huge amount of data. Fig. 4 shows the evolution of four critical process outcomes during the 5h runs: the torque on the screws of the granulation unit, the temperature of the water at the granulator jacket inlet, the differential pressure over the dryer filters for the dryer module and the temperature of the mill screen for the granule conditioning module. From these graphs, it is clear that for each parameter a stabilization period was needed to reach steady-state conditions. During the initial 30 min of each run, the torque increased from 1.5 to 2.0 Nm (Fig. 4a) due to layering of the screws and the screw chamber wall with powder material. As the granulation process generates heat by friction, the initial layering of the screws and barrel wall with wet mass caused an increase of the barrel wall temperature at the work segment of the granulator (from 25.0°C to 26.0°C). The temperature of the barrel wall was again down regulated to the setpoint value (25.0°C) by a feedback control system which compensated by a

decrease of the water temperature at the granulator jacket inlet (from 26.5 to 21.5°C) (Fig. 4b).

During the 5h production runs, a gradual increase of the differential pressure over the dryer filters was observed due to increased filter loading with fine particles (Fig. 4c). However, the rate of the increase dropped in function of process time: from a 15 mbar increase over the 1st hour to 1 mbar during the last hour. By performing a 19h production run, it was confirmed that after 8h, a plateau phase for this parameter was reached (data not shown). A limited increase of the temperature of the mill screen was observed during the first part of the process, indicating initial layering of the mill screen (Fig. 4d). All process data trends were found to be highly comparable between the different runs, indicating the excellent repeatability of the system.

3.2. Evaluation of granule properties

Different from conventional batch fluid bed drying processes where the drying endpoint is mainly determined by temperature-based monitoring methods [16-20], a fixed drying time for each cell of the segmented dryer unit was applied in order to retain the continuity of the system. LOD values obtained after drying of granules produced by the actual batch process were 1.77%, 1.93% and 1.91% for batch 1, 2 and 3, respectively (Table 1). For the three consecutive continuous runs, the residual moisture content of the dried granules was determined in function of process time. All LOD values approximated the target LOD value (1.5%) and were in compliance with the specifications (1.0-2.0%) of the actual batch process, indicating a stable and reliable drying process (Fig. 5). Besides, the drying capacity was clearly not affected by the increase of the differential pressure over the dryer filters (Fig. 4c). Although the time between the first and the last portion of wet granules entering each cell was 180

seconds (as filling time per cell was equal to 180 seconds), the standard deviation between the different LOD measurements per cell was low (0.01 – 0.08%).

Particle size distributions (PSD) of milled granules were determined. Fig. 6 shows an overview of the evolution of the amount of material on the different sieves in function of process time for run 1. Particle size results were similar over the full length of the runs. However, it can be seen from the results of run 1 that slightly deviating PSD results were obtained during the first filling cycle of the dryer (Fig. 6). During the start-up phase, a lower amount of particles smaller than 250 µm and a higher amount of particles larger than 500 µm were produced. The fraction between 250 µm and 500 µm remained stable. It is suggested that the deviation of PSD observed at start-up was due to the initial layering of the grater type mill screen (as can be seen from Fig. 4d) as a result of which particles encountered more friction yielding a slightly higher amount of fines and smaller amount of particles larger than 500 µm. PSD results obtained for run 2 and run 3 were similar to the results for run 1 (data not shown).

Fig. 7 shows the PSD results obtained from milled granules produced by the continuous twin screw granulation/fluid bed drying process versus the actual batch fluid bed granulation/drying process (Table 1, PSD results for batch 1). The continuous process resulted in a wider and bimodal PSD, as the PSD consisted of a higher amount of fines (F<75 µm) combined with a higher amount of coarse particles (F>500 µm), in comparison with the unimodal PSD results for the batch fluid bed process. This is in agreement with findings of other researchers who described the appearance of bimodal PSD for granules produced by twin screw granulation [8, 10, 21, 22].

Results for friability and Hausner ratio of milled granules are shown in Fig. 8. For all granules, the friability, an estimate for granule strength, was low (12 to 20%)

(Fig. 8a). Due to the low friability, downstream processing problems were avoided. Again, slightly deviating results were obtained during the start-up phase, as shown by the results for run 1. The milled granules obtained during the first filling cycle of the dryer had a lower friability, suggesting that the oversized fraction is milled into smoother granules when the mill is not yet layered during the initial phase of the process. No friability values were recorded for granules produced by the actual batch process.

The results for the bulk densities of continuously produced granules ranged from 0.508 to 0.545 g/ml, and the tapped densities from 0.612 to 0.652 g/ml. Hausner ratio values were calculated from the bulk and tapped densities to describe the flowability of the granules. As the Hausner ratios ranged between 1.18 and 1.24, all granules could be classified as fair flowing (Fig. 8b). The slightly deviating PSD results obtained during the start-up phase of run 1, did not significantly influence the flowability of the granules. The bulk densities of the granules produced by the batch fluid bed granulation/drying process ranged from 0.420 to 0.523 g/ml, whereas the tapped densities ranged from 0.453 to 0.570 g/ml. For the batch process, lower Hausner ratios (1.04 to 1.09) were obtained in comparison to the continuous process. This can be explained by the higher amount of fine particles (<75 µm) produced by the continuous process which negatively influenced the flow properties (Fig. 7). Besides, several researchers already described the elongated shape of the granules produced by twin scew granulation, while the batch fluid bed process typically resulted in the formation of spherical granules [9, 10, 21, 22].

3.3. Evaluation of tablet properties

After milling, granules were transferred to an in-line lubricant blender followed by the production of tablets. Fig. 9 shows an overview of results for weight uniformity

and hardness of tablets. Although higher Hausner ratio values were obtained for granules produced by the continuous process in comparison with the batch process, the weight uniformity of these tablets was excellent (Fig. 9a). Mean weight values between 426.1 and 432.3 mg were obtained (maximal RSD-value of 1.12 %RSD for all samples) for the continuous process, whereas mean weight values for the batch process ranged between 428.0 and 431.8 mg (maximal RSD-value of 0.81 %RSD for all samples). Hardness values of tablets produced by the continuous system were stable in function of time (Fig. 9b). Mean hardness values ranged from 78.2 to 94.4 N and were in compliance with the specifications of the actual batch process (70-110 N). Mean thickness values (5.25-5.34 mm) were close to the lower acceptance limit of the batch process (5.30 mm) in order to obtain conforming hardness values. This could be explained by the higher density of the granules produced by twin screw granulation and therefore higher resistance to deformation during tableting. Thickness values for tablets from the conventional process were also low as mean thickness values ranged between 5.32 and 5.37 mm. Compared to the continuously produced tablets, mean hardness values of tablets from the batch process were higher (from 90.4 to 99.6 N). This could be explained by the usage of starch paste as binder during the batch fluid bed granulation process, whereas for the continuous process water was used as granulation liquid. In this way, continuous manufacturing of starch paste could be avoided which decreased the complexity of the continuous process from a practical point of view. No deviating results for weight uniformity, hardness and thickness were obtained for tablets produced during the start-up and shut down phase of the continuous runs (Fig. 9, run 2).

Friability was low for all tablets (0.09-0.20%), allowing subsequent coating. Compared to the continuous process, friability was lower for tablets produced by the batch process (0.02-0.03%). Again, this could be explained by the usage of starch paste as binder during the batch process (see above).

Content uniformity of tablets was determined (samples from beginning, middle and end of run 2). For the continuous as well as for the batch process, all assay results of tablets were within ± 2.5 % of the declared potency (data not shown). Mean disintegration times ranged between 123 and 200 seconds and between 176 and 285 seconds for the continuous and the batch process, respectively (Fig. 10 and Table 1). To meet the specifications for dissolution of the actual process not less than 80% of the labeled amount should be dissolved after 30 min. From Fig. 11 and Table 1, it is clear that the fast disintegration of the tablets produced by both processes resulted in a complete release for both APIs after 30 minutes. Similar results for dissolution were obtained for the three consecutive continuous runs (data of run 1 and run 3 not shown). No deviating results for friability, content uniformity, disintegration time, and dissolution were obtained for tablets produced during the start-up and shut down phase (Fig. 11). Hence, waste during start-up and shut down was avoided.

4. Conclusions

The results of this study showed a successful process transfer of a commercially available product from a batch fluid bed granulation and drying process to a continuous twin screw granulation and fluid bed drying process. During three consecutive 5h continuous production runs, granule and tablet quality was constant in function of time. Although PSD and Hausner ratio values of milled granules were found to be different for granules produced by the twin screw granulation process compared to the batch fluid bed granulation process, results for critical tablet quality attributes were in compliance with the specifications defined for the batch process.

For each of the investigated process outcomes (torque, water temperature at the granulator jacket inlet, differential pressure over the dryer filters, temperature mill

screen) a stabilization period was needed to reach steady-state conditions. However, the granules and tablets produced during start-up were in compliance with the specifications. No deviant granule and tablet properties were detected at the end of each run. Furthermore, process data trends were highly repeatable. Consequently, the ConsiGma^{TM}-25 system can be considered as a stable and repeatable system for the continuous production of tablets via wet granulation.

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Figures

Figure 1: Consigma™-25 continuous tablet manufacturing line: 1. Powder dispensing, 2. Screw-based wet granulation module, 3. Segmented fluid bed dryer, 4. Granule conditioning unit with 5. Quadro® comil® and 6. Blender (external phase), 7. Blender (lubricant), 8. Modul™ P tablet press.

Figure 2: Detail of last part of twin screws.

Figure 3: Process flow diagrams for the actual batch process (left) and the continuous process (right).

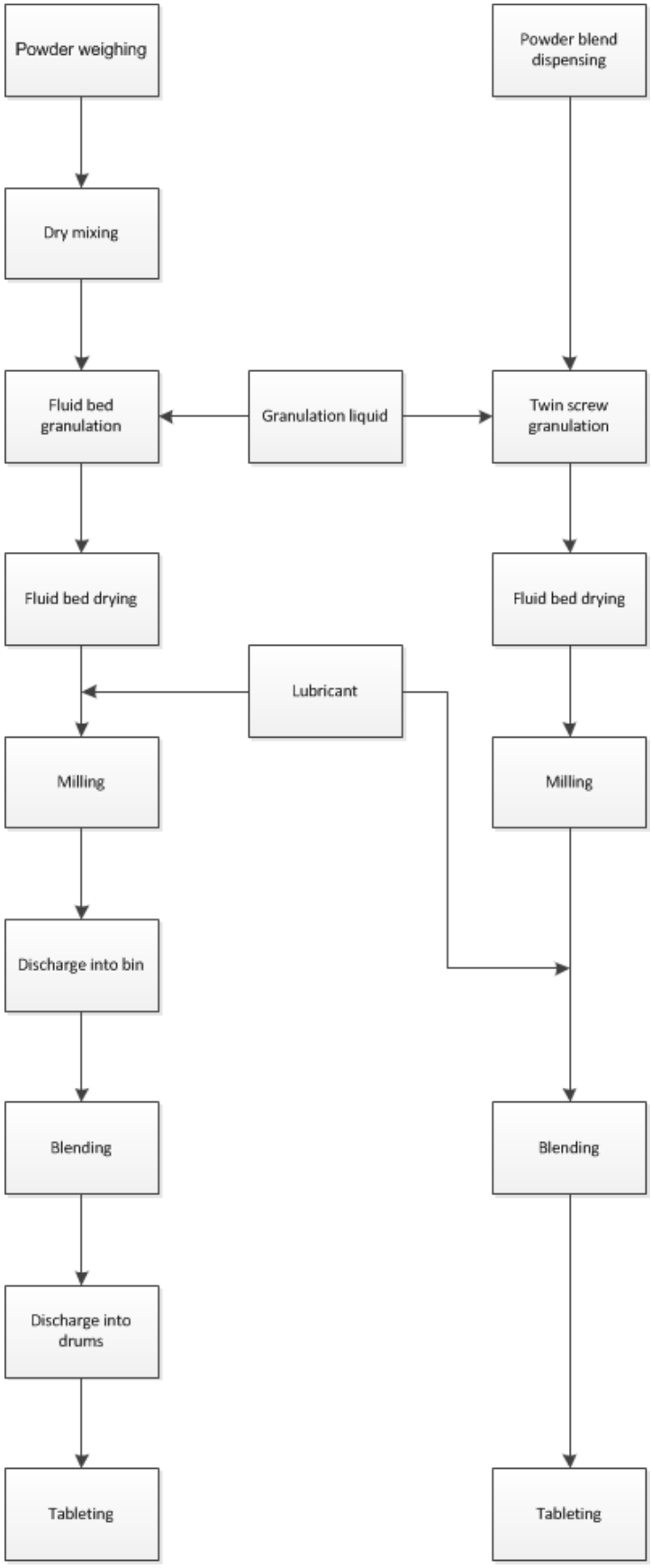
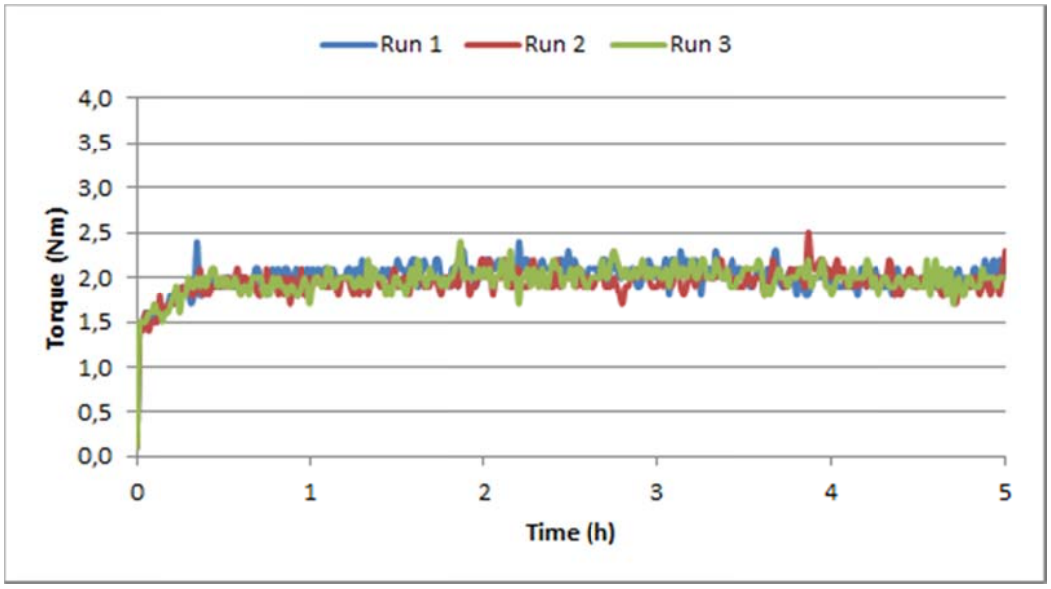
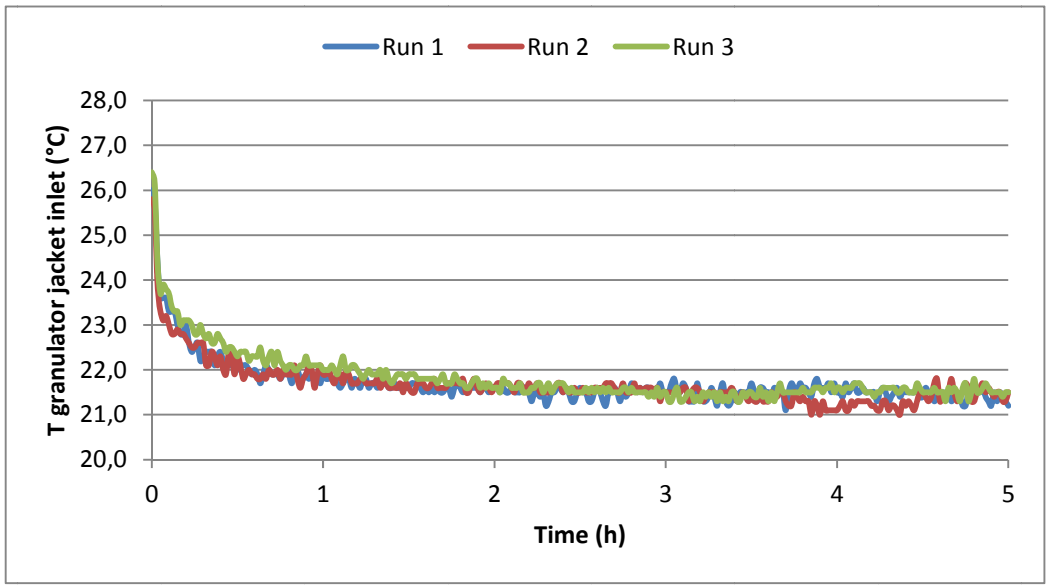


Figure 4: Evolution of critical process outcomes in function of process time: (a) torque, (b) water temperature at the granulator jacket inlet, (c) differential pressure over the dryer filters, (d) temperature of mill screen.

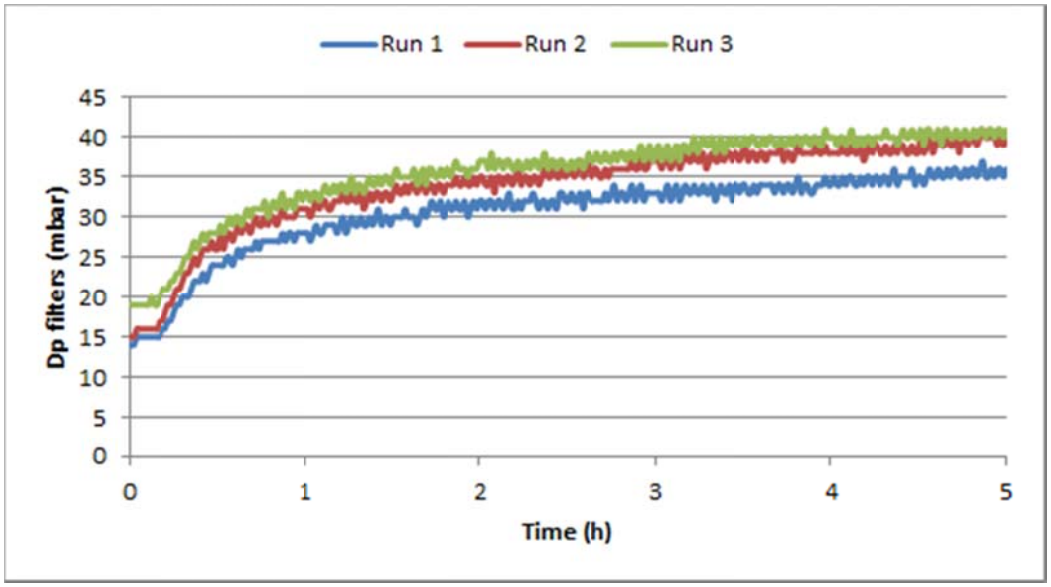
a



b



c


Run 1
Run 2
Run 3
Dp filters (mbar)
45
40
35
30
25
20
15
10
5
0
0
1
2
3
4
5
Time (h)

d

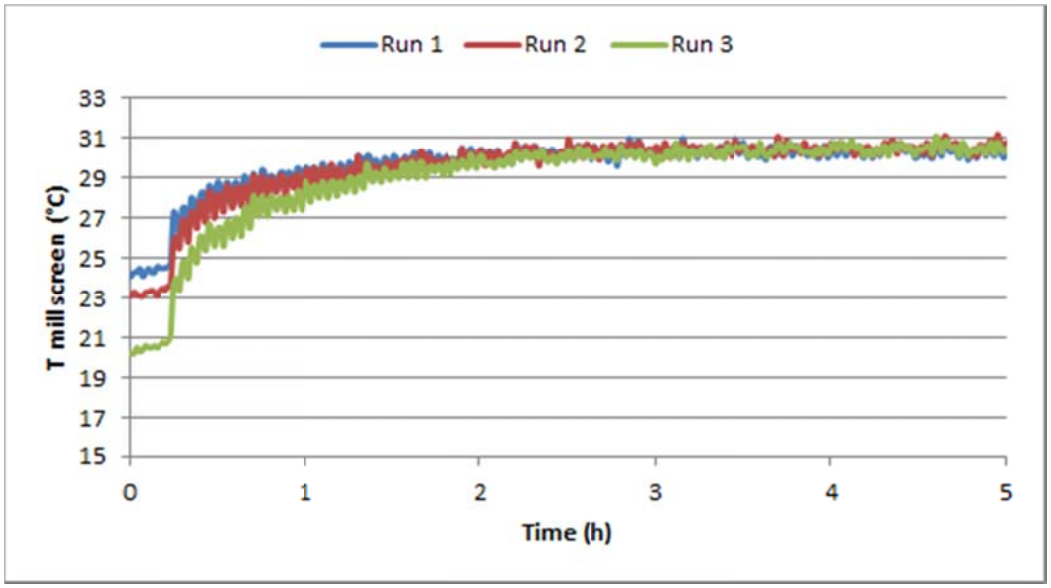

Run 1
Run 2
Run 3
T mill screen (°C)
33
31
29
27
25
23
21
19
17
15
0
1
2
3
4
5
Time (h)

Figure 5: LOD results of milled granules in function of process time.

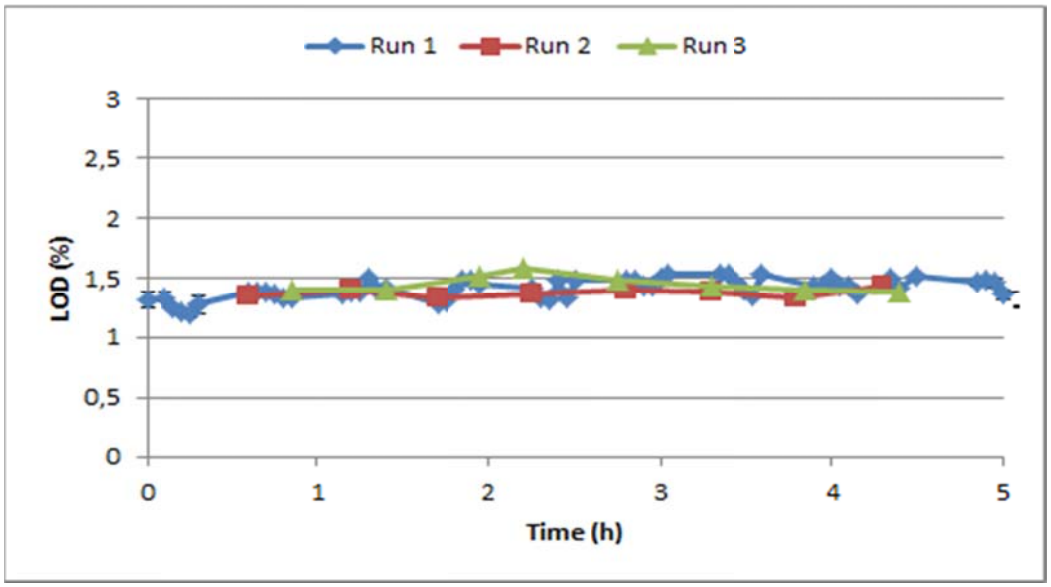


Figure 6: Evolution of particle size distribution of milled granules in function of process time for run 1.

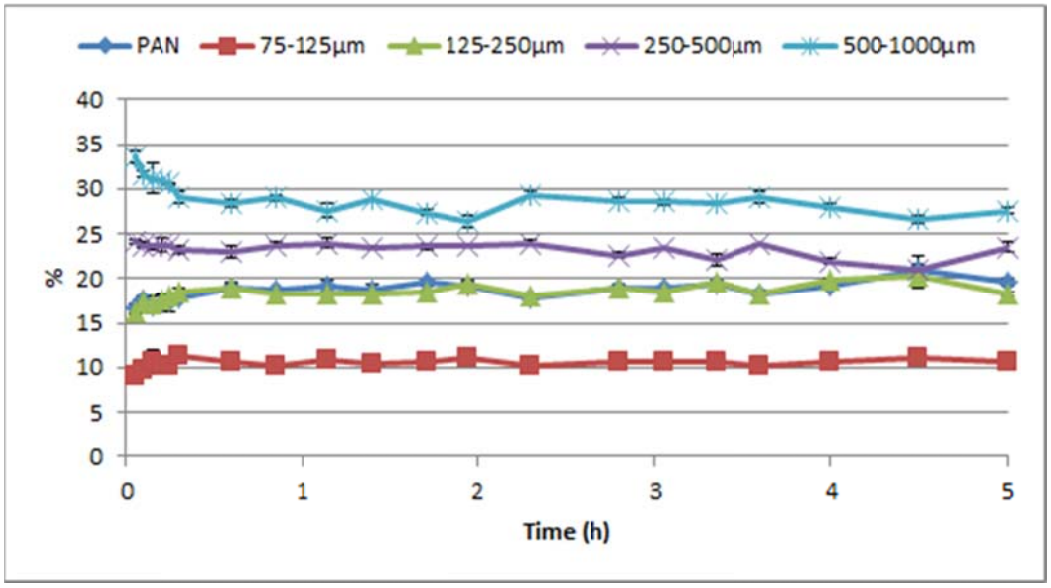


Figure 7: Particle size distribution of milled granules produced by continuous twin screw granulation/drying versus batch fluid bed granulation/drying.

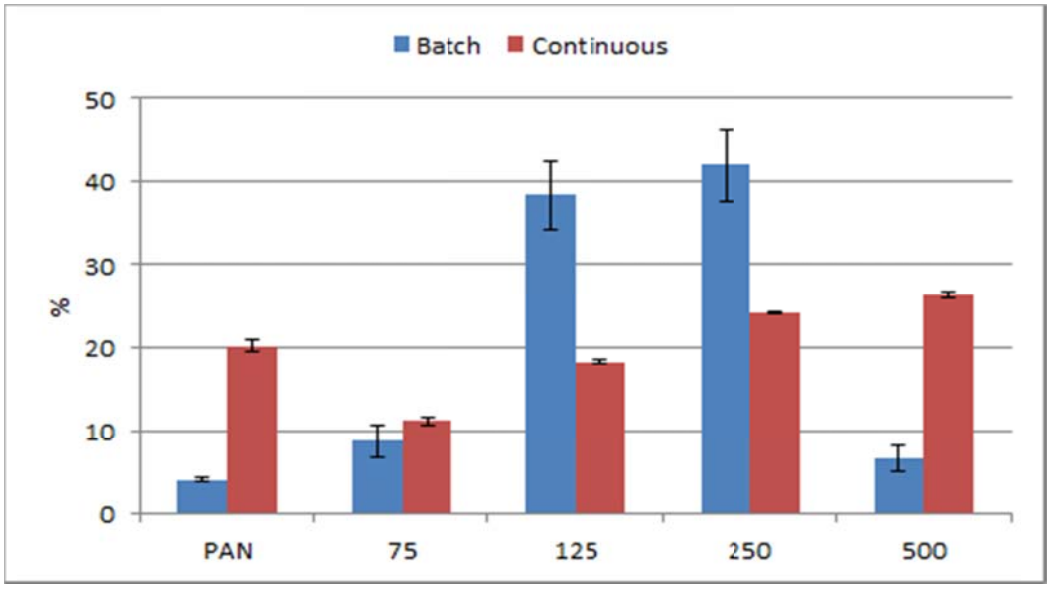
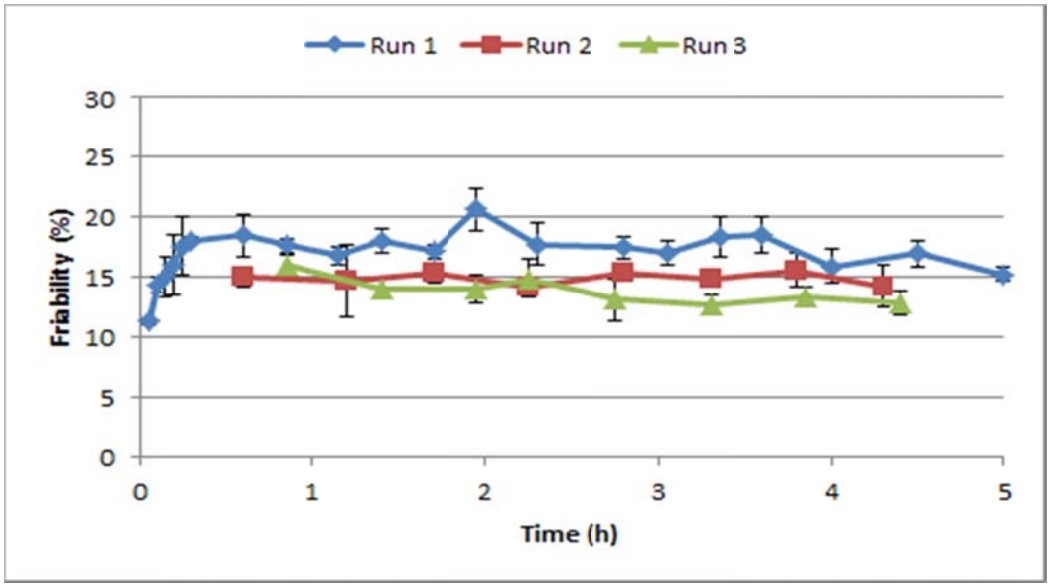


Figure 8: Granule quality attributes in function of process time: friability (a) and Hausner ratio (b).

a



b

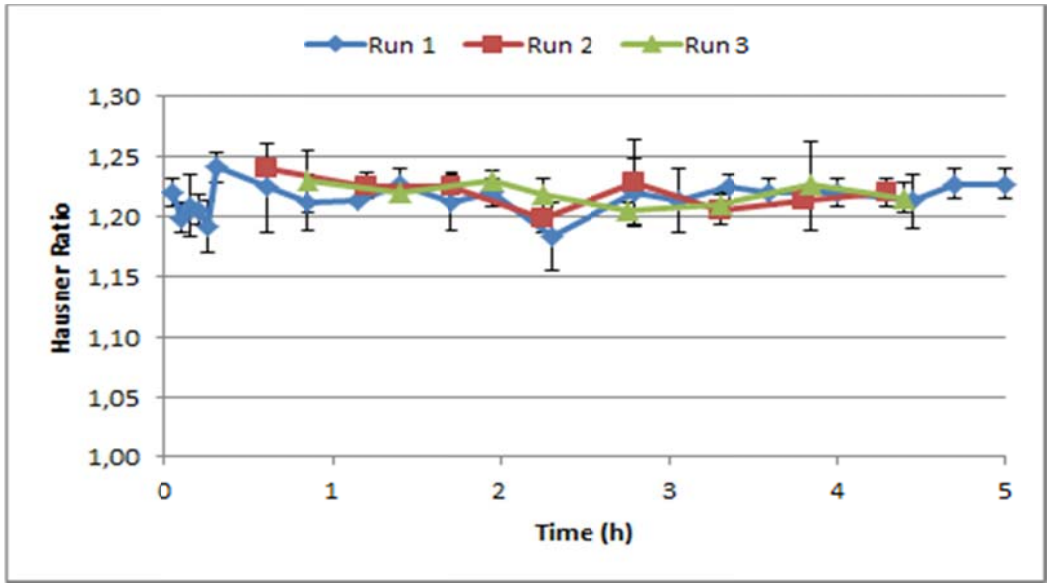
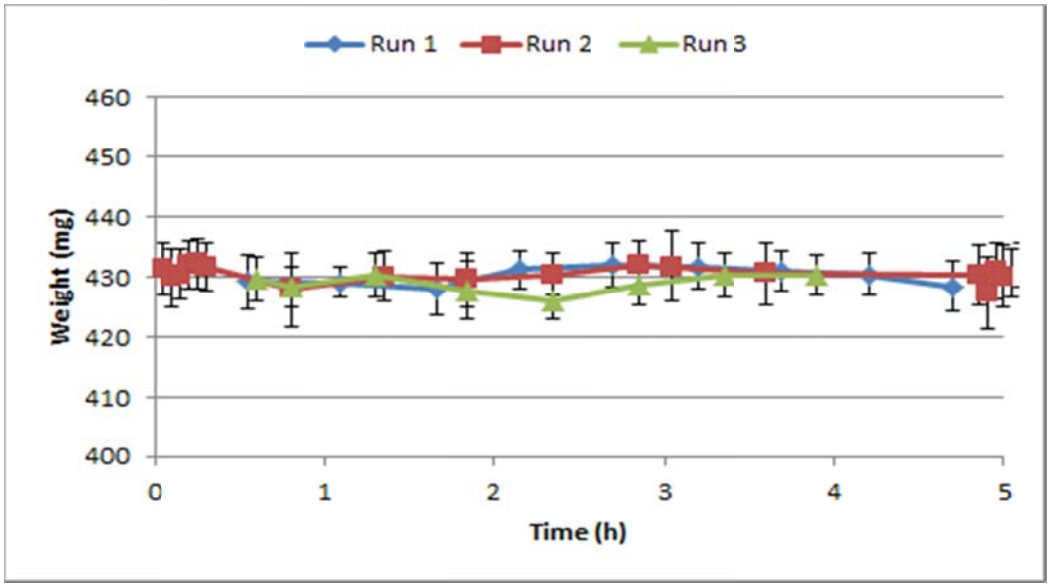


Figure 9: Tablet quality attributes in function of process time: weight uniformity (a) and hardness (b).

a



b

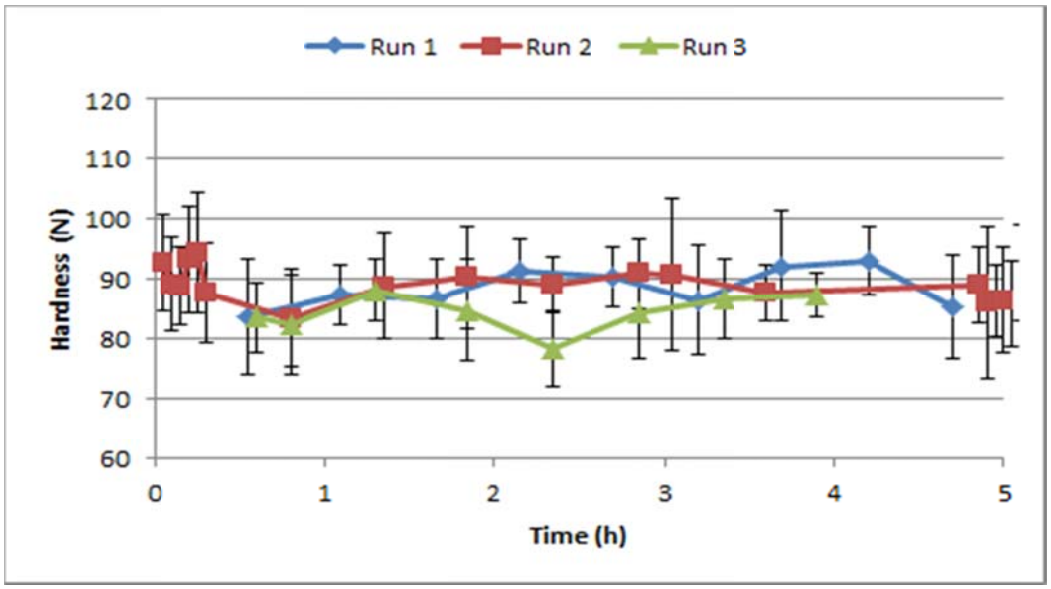


Figure 10: Disintegration time of tablets in function of process time.

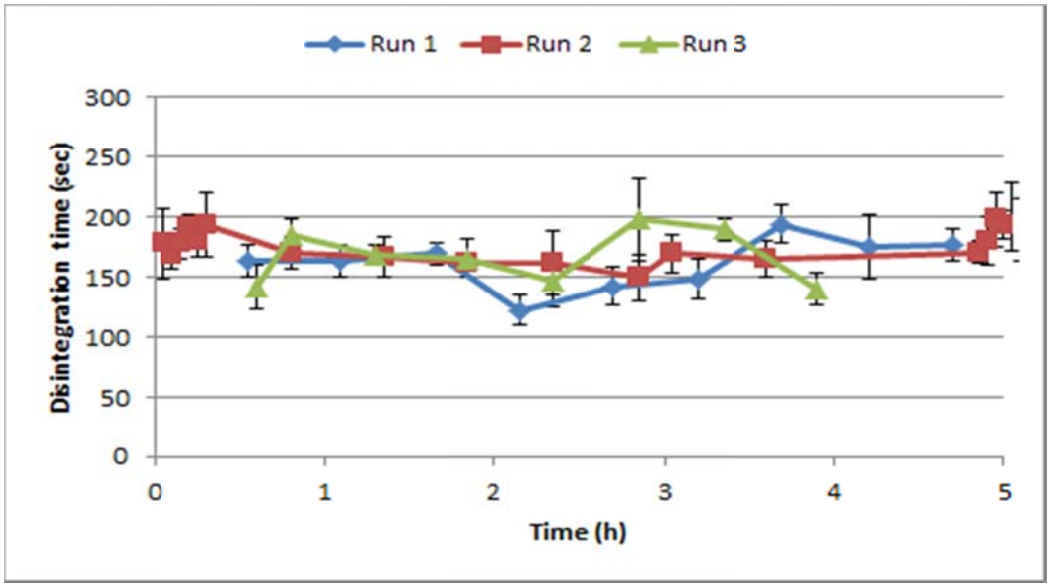
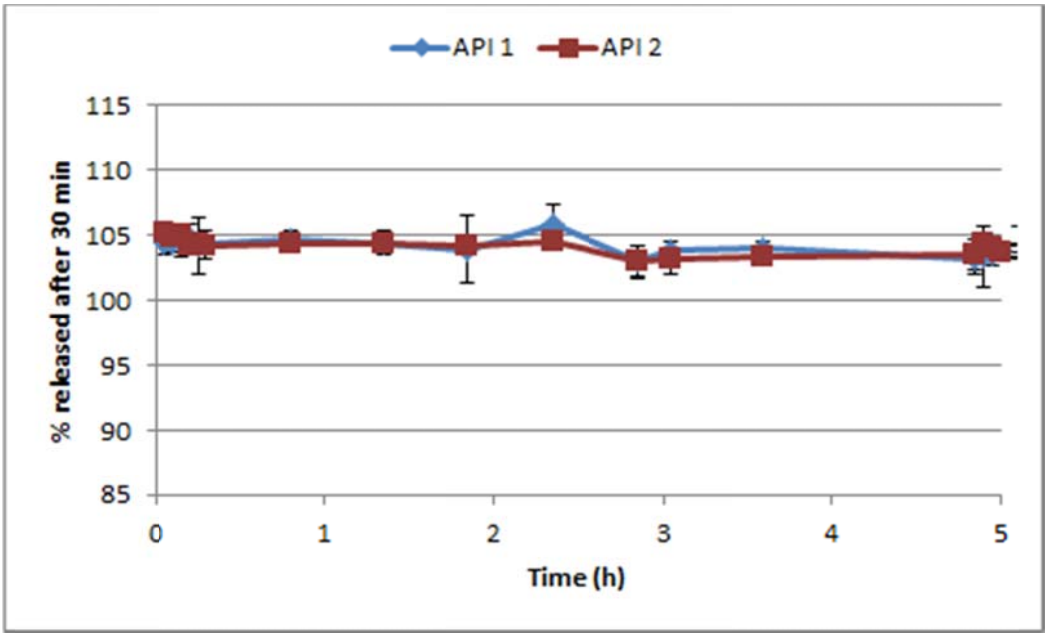


Figure 11: Percentage drug released after 30 min in function of process time for run 2.



Tables

1 Overview of granule and tablet quality attributes derived from the conventional batch process: LOD (n=1), PSD (>500µm, 250µm-500µm, 125µm-250µm, 75µm-125µm and <75µm) (n=3, mean ± SD), bulk density (n=3, mean ± SD), tapped density (n=3, mean ± SD) and Hausner ratio (n=3, mean ± SD) for granules and weight (n=20, mean ± SD), hardness (n=12, mean ± SD), thickness (n=12, mean ± SD), friability (n=8, mean ± SD), disintegration time (n=8, mean ± SD) and % API 1 and 2 released after 30 min dissolution (n=12, mean ± SD) for tablets.

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Quality attribute	Batch 1	Batch 2	Batch 3
Granules			
LOD (%)	1.77	1.93	1.91
> 500µm (%)	6.9 (1.8)	7.7 (0.4)	8.1 (3.8)
250µm-500µm (%)	42.0 (4.4)	43.6 (1.7)	41.9 (4.9)
125µm-250µm (%)	38.3 (4.1)	39.4 (2.6)	42.8 (6.3)
75µm-125µm (%)	8.7 (2.0)	5.9 (2.2)	4.2 (3.4)
<75µm (%)	4.0 (0.2)	3.5 (1.1)	3.2 (0.5)
Bulk density (g/ml)	0.420 (0.000)	0.460 (0.000)	0.523 (0.006)
Tapped density (g/ml)	0.453 (0.006)	0.480 (0.000)	0.570 (0.000)
Hausner ratio	1.08 (0.01)	1.04 (0.00)	1.09 (0.01)
Tablets			
Weight (mg) (n=20)	428.0 (3.4)	429.5 (2.3)	431.8 (2.5)
Hardness (N) (n=12)	99.6 (8.4)	98.3 (8.1)	90.4 (7.2)
Thickness (mm) (n=12)	5.37 (0.03)	5.37 (0.04)	5.32 (0.02)
Friability (%) (n=8)	0.03 (0.01)	0.02 (0.01)	0.02 (0.01)
Disintegration time (sec) (n=8)	218 (31)	285 (28)	176 (11)
% API 1 released after 30 min (n=12)	98.5 (1.0)	99.5 (0.9)	102.5 (0.6)
% API 2 released after 30 min (n=12)	98.3 (1.3)	99.4 (1.0)	102.0 (0.6)