Continuous twin screw granulation: influence of process variables on granule and tablet quality

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Abstract

The aim of the current study was to screen theophylline (125 mg) tablets manufactured via twin screw granulation in order to improve process understanding and knowledge of process variables which determine granule and tablet quality. A premix of theophylline anhydrate, α-lactose monohydrate and PVP (ratio: 30/67.5/2.5, w/w) was granulated with demineralized water. Experiments were done using the high shear wet granulation module (based on twin screw granulation) of the ConsiGma^{TM}-25 unit (a continuous tablet manufacturing system) for particle size enlargement. After drying, granules were compressed using a MODUL^{TM} P tablet press (compression force: 10 kN, tablet diameter: 12 mm). Using a D-optimal experimental design, the effect of several process variables (throughput (10 - 25 kg/h), screw speed (600 - 950 rpm), screw configuration (number (2, 4, 6 and 12) and angle (30, 60 and 90 degrees) of kneading elements), barrel temperature (25 - 40°C) and method of binder addition (dry vs wet)) on the granulation process (torque and temperature increase of barrel wall), granule (particle size distribution, friability and flowability) and tablet (tensile strength, porosity, friability, disintegration time and dissolution) quality was evaluated. The results showed that the quality of granules and tablets can be optimized by adjusting specific process variables (number of kneading elements, barrel temperature and binder addition method) during a granulation process using a continuous twin screw granulator.

KEYWORDS: Continuous wet granulation, Twin screw granulation, Process variables, Granule and tablet quality, Experimental design

1. Introduction

In contrast to other industries (plastics, food, chemistry), the pharmaceutical industry has been reluctant to move from batch processing towards continuous processing for several reasons (e.g., high profit margins, stringent regulatory constraints, limited material volume) [1-3]. However, as many patents of drug molecules recently expired or expire in the near future and due to an increasing demand for solid dosage forms, it is expected that the importance of the concept of continuous production will increase over the coming years [4, 5].

As wet granulation is the most popular method to improve material properties (flow, homogeneity, compressibility) prior to tableting, it is obvious that a continuous wet granulation process is of high importance for a manufacturer of solid dosage forms. Several continuous wet granulation techniques were developed which have been reviewed by Vervaet and Remon [1, 4]. Keleb et al. [6] described the use of a laboratory scale co-rotating twin screw extruder without a die block in order to avoid excessive material densification inside the barrel. In this way, wet granules could be obtained in a continuous manner. Based on this research work [6-9], a twin screw granulator was implemented as the high-shear granulation unit in the commercially available industrial scale ConsiGma^{TM}-system (GEA Pharma Systems, Collette^{TM}, Wommelgem, Belgium). This system consists of three modules, as already described by Fonteyne et al. [10] and Chablani et al.[11]: a wet high-shear granulation module, a segmented dryer module and an evaluation module.

Wet granulation via twin screw granulation is an attractive technology for the continuous processing of pharmaceuticals. Twin screw granulators are very flexible in terms of use, offering multiple variables (e.g., screw design, the placement of auxiliary units like feeders and pumps) [12]. Besides, Van Melkebeke et al. [13] successfully demonstrated the possibility to perform melt granulation using the same equipment. However, up-to-now process knowledge (certainly towards specific pharmaceutical formulations) about this innovative manufacturing technique is almost non-existing within the pharmaceutical industry. To improve process understanding, optimize granule quality and increase the process yield, knowledge about the formulation and process variables which determine granule quality is essential. Keleb et al. [8] made a first attempt to modify the screw configuration. By replacing discharge elements with conveying elements having a longer pitch the compression of the granules was reduced and lower amounts of lumps were generated. Shah [14] used a screw

configuration with only conveying and chopping (distributive) elements in order to improve the output and avoid periodic surging of the wet mass as it exited the extruder. Van Melkebeke et al. [7] reported that implementing an extra conveying element after the kneading block improved the granulation yield by reducing the oversized agglomerates. Djuric and Kleinebudde [15] and Thompson and Sun [12] evaluated the impact of different screw elements on continuous granulation with a twin screw extruder. They stated that granule and tablet properties could be influenced by using different designs of screw elements. Dhenge et al. [16] described the influence of screw speed, powder feed rate and liquid-to-solid ratio on the granule properties. In this paper, factors were changed one at a time for each experiment (COST-approach). It was found that alteration of these process variables had a significant impact on the residence time and the average torque during the granulation process, yielding granules with different properties. The liquid-to-solid ratio was recognized as the most influencing factor regarding the granule quality. Djuric and Kleinebudde [17] concluded that for scale-up of continuous twin screw granulation processes the material throughput could not be linearly increased. Further optimization of process variables was needed. In accordance to these results, Dhenge et al. [18] reported that changing the powder feed rate leads to changes in the size, shape, structure, porosity, strength and dissolution time of the granules. Tan et al. [19] used a full-factorial experimental design to describe the effect of granulation liquid composition, injection rate and screw speed on extruder power consumption, granule and tablet properties.

In the current study, an experimental design approach was used to screen theophylline (125 mg) tablets manufactured via twin screw granulation. Design of experiments was used to identify the critical process variables and to study their impact on the granulation process, granule and tablet quality attributes.

2. Materials and methods

2.1. Materials

Theophylline anhydrate was purchased from Farma-Química Sur (Malaga, Spain). α-lactose monohydrate 200M (Caldic, Hemiksem, Belgium) was used as filler for granulation and polyvinylpyrrolidone (PVP) (Kollidon® 30, BASF, Ludwigshafen, Germany) as binder. If PVP was added to the dry premix, distilled

water was used as granulation liquid. Magnesium stearate (Fagron, Waregem, Belgium) was applied as lubricant during tableting.

2.2. Preparation of granules

Granulation experiments were performed using a high-shear co-rotating twin screw granulator without die plate, being the granulation unit of the ConsiGma™-25 unit (Fig. 1). The length-to-diameter ratio was 25:1. In the ConsiGma™-25 unit, the granulation unit is directly linked to a six-segmented fluid bed dryer. As the aim of the current study was to improve process understanding of the granulation step, the fluid bed dryer was not used in order to avoid the impact of dynamic drying on the product properties. 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 [10]. To evaluate the influence of process variables on the granulation process, the torque and temperature of the barrel wall at the work segment of the granulator were recorded. The equipment has an in-built torque gauge. The torque values obtained after equilibration of the process were averaged to give the overall torque during each run. 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. During processing, the powder premix was gravimetrically dosed by a twin screw feeder (KT20, K-Tron Soder, Niederlenz, Switserland). Granulation liquid was gravimetrically pumped into the screw chamber using two peristaltic pumps (Watson Marlow, Comwall, UK) and silicon tubing (internal and external diameter of 1.6 and 4.8 mm, respectively) connected to a 1.6 mm nozzle. Liquid was added in front of the first kneading element. PVP was used as a binder, 2.5% (w/w) in granules, based on dry mass. To evaluate the dissolution properties, theophylline anhydrate (30%) was added as a model drug to the formulation. The water concentration (9%, calculated on wet mass) was kept constant for all experiments. For each run, after equilibration of the system, 800g of wet granules were collected at the outlet of the granulator, spread on a tray and oven-dried at 40°C during 24h. After drying, the total granule batch was divided into two parts of 400g. One part was analysed for particle size distribution as such and the other part was milled through a 1400µm screen at 800rpm using a Quadro comil U10 (Quadro Engineering, Ontario, Canada), which

is part of the evaluation module of the ConsiGma™-25 system. The response parameters when investigating the influence of process variables on granule quality were: particle size distributions before and after milling, and friability and flowability of the milled granules.

2.3. Preparation of tablets

Tablets were made using the milled granulation product. Before tableting, the granules were blended with 0.5% (w/w) magnesium stearate in a tumbling mixer (W.A. Bachofen, Basel, Switserland). Tablets (417 mg) were prepared using a MODUL™ P tablet press (GEA Pharma Systems, Courtoy™, Halle, Belgium) equipped with a round concave (radius: 24mm) Euro B punch of 12 mm diameter at a compression force of 10 kN per tablet. Tensile strength, porosity, friability, disintegration time and dissolution of the tablets were tested.

2.4. Design of experiments

Preliminary experiments were carried out to determine the experimental ranges for the DOE factors throughput, screw speed and barrel temperature at different number and angle of kneading elements. When 12 kneading elements were used, two kneading zones each consisting of 6 kneading elements had to be used (Fig. 2). Both kneading zones were separated by a conveying element having the same length as one kneading zone. In this way, accumulation of material due to the retaining character of the kneading elements could be limited. An extra conveying element was implemented after the second kneading block in order to reduce the amount of oversized agglomerates, as reported by Van Melkebeke et al. [7]. Nevertheless, as the use of 12 kneading elements at an angle of 90 degrees at different process settings resulted in excessive formation of lumps or even blockage of the system due to excessive friction, this combination of factor levels had to be excluded from the design. For all experiments, the distance between liquid addition and first kneading element was kept constant. An 18-experiment D-optimal design was used to evaluate the influence of 6 process variables on the granulation process, granule and tablet properties: total throughput (10 - 25 kg/h), screw speed (600 - 900 rpm), screw configuration (number (2, 4, 6 and 12) and angle (30, 60 and 90 degrees) of kneading elements), barrel temperature (25 - 40°C) and method of binder addition (dry vs wet). D-optimal designs are used for screening and optimization instead of

the classical factorial designs when the experimental space is irregular and/or when several (multilevel) qualitative factors are examined, as is the case for this study [20]. Three replicates of the design center point were run. The different factor settings for each run are listed in Table 1. The results were evaluated with MODDE 9.0 software (Umetrics, Umeå, Sweden).

2.5. Evaluation of granules

2.5.1. Particle size analysis

Sieve analysis was performed using a Retsch VE 1000 sieve shaker (Haan, Germany). Granules were placed on the shaker during 5 min at an amplitude of 2 mm using a series of sieves (150, 250, 500, 710, 1000, 1400 and 2000 µm). The amount of granules retained on each sieve was determined. All granule batches were measured in duplicate. The amount of fines and oversized agglomerates were defined as the fractions <150 and >1400 µm, respectively. After milling, the amount of coarse granules was defined as the fraction between 710 and 1400 µm. The yield of the granulation process was defined as the fraction between 150 and 1400 µm.

2.5.2. 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 <250µm 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 $((I_{wt} – F_{wt}) / I_{wt})*100$.

2.5.3. 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 compressibility index (C%) was calculated from the bulk and tapped density using the following equation,

$C\% = \{(\rho_f - \rho_i) / \rho_f\} * 100$

where ρ_i is the bulk density and ρ_f is the tapped density.

2.6. Tablet evaluation

The hardness, thickness and diameter of tablets (n=10) was determined (Sotax HT 10, Basel, Switserland) after a 24 h storage period at 21 °C and 30% RH. The tablet tensile strength T was calculated using the equation described by Fell and Newton [21],

$T = 2 F / \pi d t$

where F, d and t denote the diametral crushing force, the tablet diameter and the tablet thickness, respectively. Tablet porosity was calculated (n=3) using tablet apparent density and the helium density of the former granules.

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.

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 demineralised water (pH = 5) 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. 5 ml samples were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min after starting the dissolution. The drug content was determined at 272 nm using an UV-1650PC double beam spectrophotometer (Shimadzu Benelux, Antwerp, Belgium).

3. Results and discussion

3.1. Evaluation of granulation process

Generally, conveying elements are used in a screw design to move material with minimal mechanical energy imparted, while kneading elements intensively mix solid and liquid components during continuous wet granulation. Kneading elements operate fully filled with material and may be partially or fully dependent on pressure-driven flow, as described by Thompson and Sun [12]. Because of their retaining character for the mass flow through the barrel, increasing the number of kneading elements led to more friction inside the barrel and consequently higher torque values (Fig. 3). As the granulation process generates friction and heat, the temperature of the barrel wall at the work segment of the granulator was monitored during each run. Using more kneading elements caused a higher temperature increase at the barrel wall (0.0 to 21.5°C) (Table 2) as a result of the higher amount of heat generated by friction. If the level of barrel temperature was low (25°C) and a higher number of kneading elements was used, the contribution of the heat generated by friction to the temperature of the barrel wall during processing was high (e.g. run 7, 8 and 13).

Increasing the throughput (kg/h) resulted in a higher filling degree which required more energy input to rotate the screws at the predefined screw speed, yielding higher torque values (Fig. 3). In contrast to Tan et al. [19], no significant impact of screw speed on torque was observed. In the current study, the screw speed was varied between 600 and 950 rpm. As the difference of screw load at lower versus higher screw speed is low, no significant differences in extent of shear and compaction forces experienced by the material inside the barrel were observed. Changing the angle of kneading elements or the binder addition method had no significant effect on torque. As described above, the combination of 12 kneading elements at an angle of 90 degrees was excluded from the design due to the formation of lumps or even blockage of the system. It seems that the angle of kneading elements only becomes an important factor when a higher amount of kneading elements is used.

During start-up of each run, the torque and temperature of the barrel wall increased until equilibrium was reached. This can be explained by the gradual layering of the barrel wall at the work segment with wet mass during this phase. The time needed for the torque and temperature of barrel wall to equilibrate gives a good indication of the time needed for the granulation process to reach steady state conditions. It was found that when a higher number of kneading elements was used, the time to reach equilibrium was higher (0 to 9 min) (Table 2). Using a

feedback control system material loss during start-up can be minimized. This system regulates the temperature of the barrel jacket during the granulation process in order to compensate for the temperature increase of the barrel wall due to friction.

3.2. Influence of process variables on granule quality

Particle size distributions of granules before and after milling were determined. A significant relationship between amount of fines and amount of oversized agglomerates and three process variables was detected: number of kneading elements, barrel temperature and binder addition method (Fig. 4a and b). By increasing the number of kneading elements, the powder was more intensively mixed with the granulation liquid, yielding less fines (0.9 to 20.2% <150µm) and more oversized agglomerates (19.5 to 82.3% >1400µm) (Table 2). This was also described by Thompson and Sun [12] and Djuric and Kleinebudde [15]. The same effects on particle size distribution were observed at a higher barrel temperature due to an increased solubility rate of the powder mixture in the granulation liquid. Because of the low residence time during twin screw granulation, the binder was more effective when it was already dissolved in the granulation liquid. Although changing the throughput led to different degrees of barrel filling and torque values, no significant impact on the particle size distribution was detected. No significant effect for angle of kneading elements and screw speed on particle size distribution was found. According to Thompson and Sun [12], the angle of kneading elements only affected the particle size distribution if the filling degree of the barrel was high (70%). Dhenge et al. [16] already mentioned the minimal effect of screw speed on the size of the granules. As the same process variables had an opposite effect on the amount of fines and the amount of oversized agglomerates (Fig. 4a and b), the changes in yield before milling could not be explained by the variation of a specific process variable. Milling of the granules resulted in breakage of oversized agglomerates and extra formation of fines (19.2 ± 3.4%). As a higher number of kneading elements and barrel temperature led to less fines before milling, as already described above, and a lower increase of fines by milling, the process yield after milling could be increased (55.0 to 84.7%) by adjusting these process variables (Fig. 5).

For all granules, the friability, an estimate for granule strength, was low (1 to 11%). However, using more kneading elements and higher barrel temperature

yielded less friable granules (Fig. 6). Kneading elements improved the distribution of granulation liquid through the powder bed and densified the material, resulting in stronger granules which are less liable to mechanical stress [7]. Besides, by increasing the barrel temperature, more theophylline and lactose dissolved in the granulation liquid which formed solid bridges after recrystallisation during drying.

The results for bulk and tapped density are shown in Fig. 7. The bulk densities ranged from 0.553 to 0.667 g/ml, and the tapped densities from 0.632 to 0.728 g/ml. The number of kneading elements significantly affected granule bulk and tapped density. Increasing the number of kneading elements resulted in higher bulk and tapped densities. When a higher number of kneading elements were used more irregular shaped coarse granules were formed, in agreement with Thompson and Sun [12], leading to a better packing of the granules when poured into the cylinder. The compressibility index was used to describe the flowability of the granules. Compressibility indices marginally differed from each other and did not exceed 15%, indicating a good flowability of the granules [22]. No significant relationships between the flow properties and any of the process variables were detected.

3.3. Influence of process variables on tablet quality

Tablets were made from the milled fraction of the granules. No extragranular disintegrant was added to the formulation in order to avoid the loss of significant relationships between process variables and tablet properties. In accordance to Djuric and Kleinebudde [15], shortening of the kneading section during twin screw granulation yielded granules with a lower density. Compression of these granules resulted in tablets with a higher tensile strength (1.24 to 1.78 MPa) (Table 3) due to the lower resistance towards deformation during compression.

For all tablets, the friability was low (0.17 to 0.30%). However, barrel temperature had statistically significant impact on the tablet friability. A higher barrel temperature during granulation resulted in tablets with a lower friability. Regarding the porosity of the tablets (19.1 to 24.8%), no significant process variables were detected.

The use of more kneading elements during granulation created granules with a higher density [15]. Because of the increased density, the percolation of liquids

inside these granules is hampered resulting in tablets with a higher disintegration time (470 to 1256 sec). Besides, elongation of the kneading zone during granulation decreased the amount of fines, which are important for disintegration.

Next to the disintegration time, it was investigated if process variables could significantly influence the drug release profile, as this is the most important characteristic for tablets. As the aim of this study was to compare drug release profiles of tablets made from granules produced with different process settings, no disintegrant was added to the formulation. Again, the number of kneading elements showed a significant impact on the dissolution results (Fig. 8). Similar to the disintegration results, tablets made from denser granules (i.e. higher number of kneading elements) showed a slower drug release profile (69.8 to 86.6% released after 45min). These results were in agreement with the conclusions made by Dhenge et al. [18]. In this paper, it was noticed that at increased powder feed rate denser granules were produced which took longer time to release the salt embedded in them.

4. Conclusions

This study was designed to screen theophylline (125mg) tablets manufactured via twin screw granulation. Using a D-optimal experimental design, the effect of several process variables on the granulation process, granule and tablet quality was evaluated. No significant relationships for angle of kneading elements and screw speed were found. Increased throughput and number of kneading elements resulted in higher torque values during granulation. More friction due to elongation of the kneading zone resulted in a higher temperature increase of the barrel wall. A higher number of kneading elements and barrel temperature resulted in less fines, more oversized agglomerates and less friable granules. As barrel temperature had an important effect on the granule properties, this parameter should be carefully controlled, especially when using good water soluble components e.g. lactose. Because of the short residence time during twin screw granulation, the binder was more effective when it was already dissolved in the granulation liquid. The tensile strength, disintegration time and dissolution profile of tablets depended on the number of kneading elements. Increasing the number of kneading elements yielded denser granules which were less deformable during compression. Percolation of liquids inside these granules is hampered, resulting in tablets with a longer disintegration time and a slower drug release. The results

showed that the quality of granules and tablets can be optimized by adjusting specific process variables (number of kneading elements, barrel temperature and binder addition method) during a granulation process using a continuous twin screw granulator.

Figures

1 Consigma™-25 granulation unit: high-shear twin screw granulator (a) with K-Tron KT20 loss-in-weight feeder (b) and gravimetric liquid addition on both screws (c).

2 Detail of twin screws with feed segment (a), liquid addition position (b) and work segment (c).

3 Contour plot for torque as a function of throughput (kg/h) and number of kneading elements.

4 Effect plots for particle size distribution of granules before milling: fines (a) and oversized agglomerates (b). Numb: Number of kneading elements; T: Barrel temperature; Bind (wet): Binder addition via granulation liquid; Scr: Screw speed; Angle: Angle of kneading elements; Thr: throughput.

5 Contour plot for yield (150-1400µm) of milled granules as a function of barrel temperature (°C) and number of kneading elements.

6 Surface plot for friability of milled granules as a function of barrel temperature (°C) and number of kneading elements.

7 Bulk and tapped densities of milled granules.

8 Effect plot for percentage drug released after 45 min. Numb: Number of kneading elements; Angle: Angle of kneading elements; Thr: throughput; T: Barrel temperature; Scr: Screw speed; Bind (wet): Binder addition via granulation liquid.

Tables

Figure 1: Consigma^{TM}-25 granulation unit: high-shear twin screw granulator (a) with K-Tron KT20 loss-in-weight feeder (b) and gravimetric liquid addition on both screws (c).

Figure 2: Detail of twin screws with last part of feed segment (a), liquid addition position (b) and work segment (c).

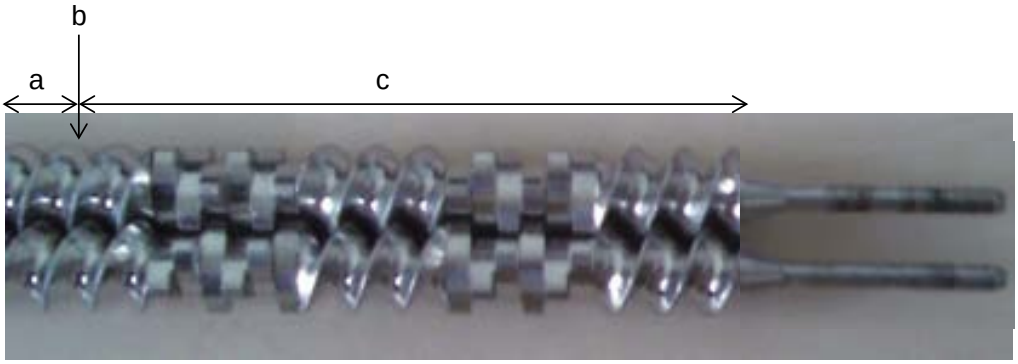


Figure 3: Contour plot for torque as a function of throughput (kg/h) and number of kneading elements.

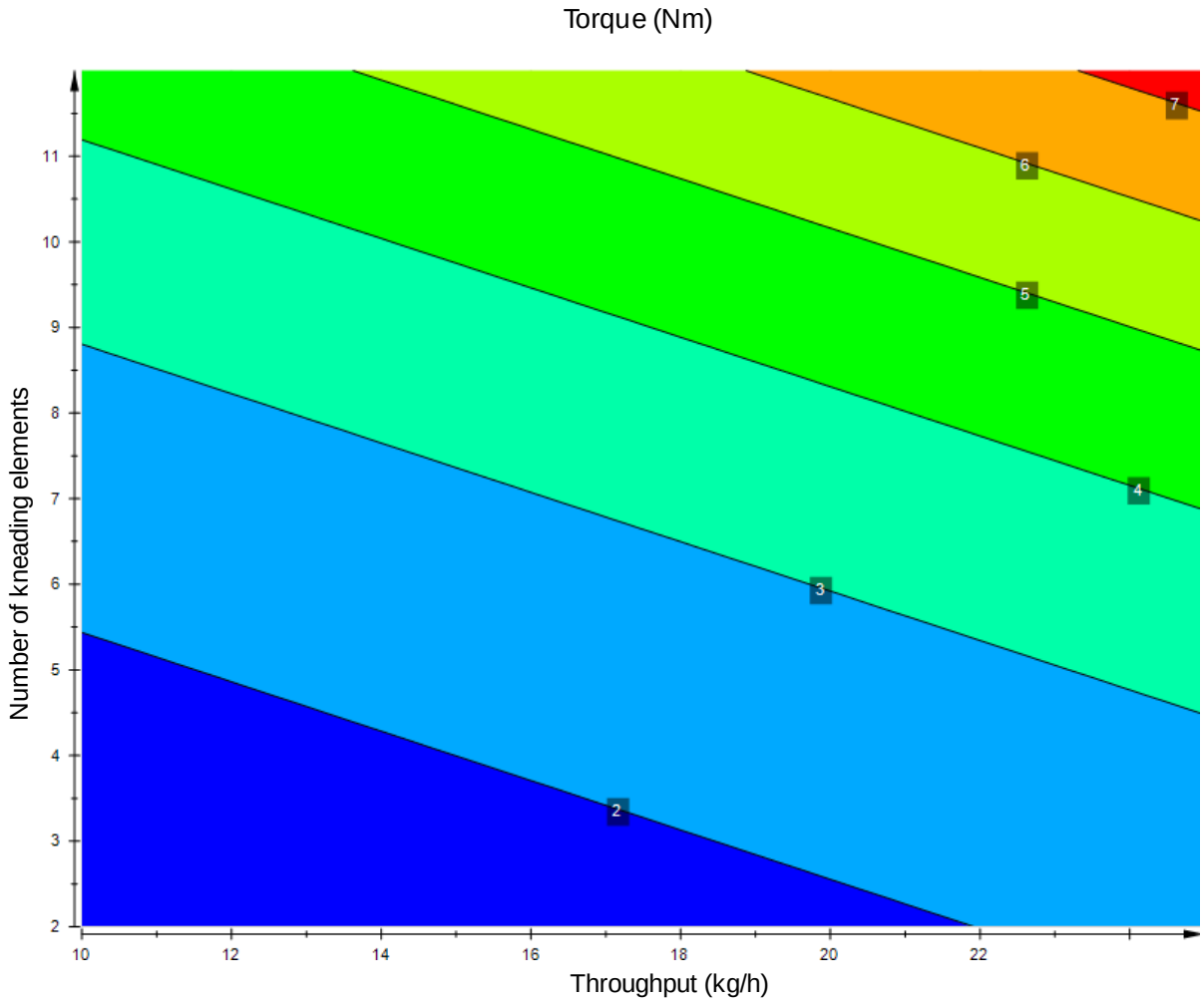
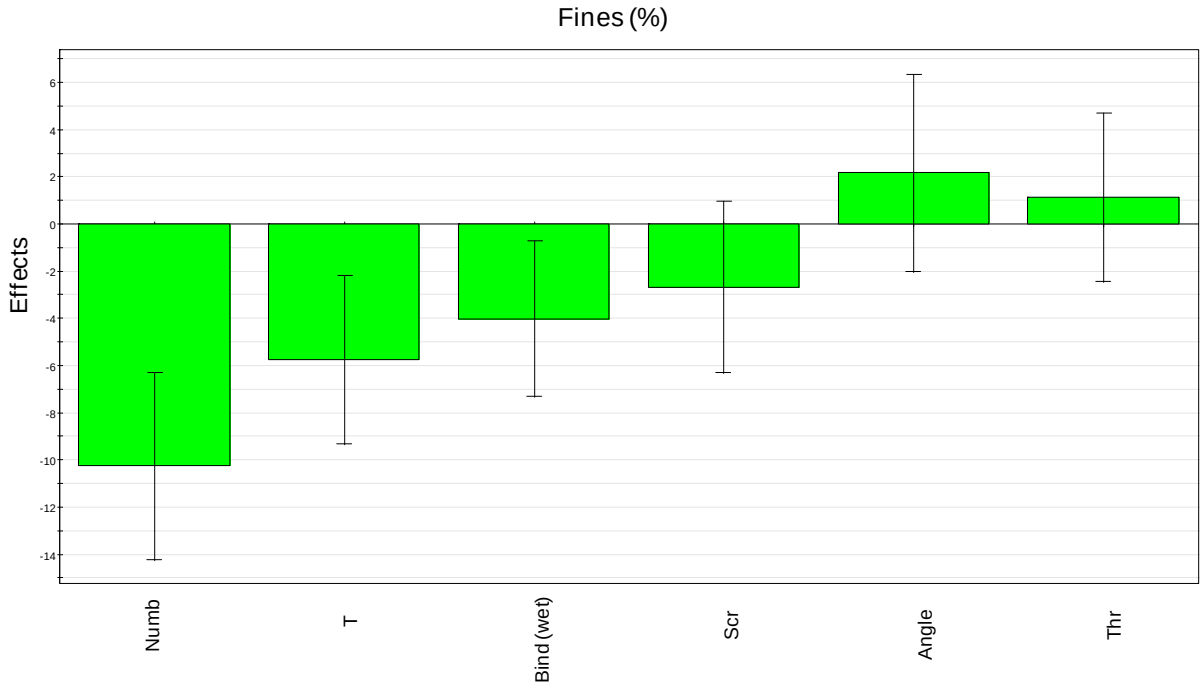


Figure 4: Effect plots for particle size distribution of granules before milling: fines (a) and oversized agglomerates (b). Numb: Number of kneading elements; T: Barrel temperature; Bind (wet): Binder addition via granulation liquid; Scr: Screw speed; Angle: Angle of kneading elements; Thr: throughput.

a



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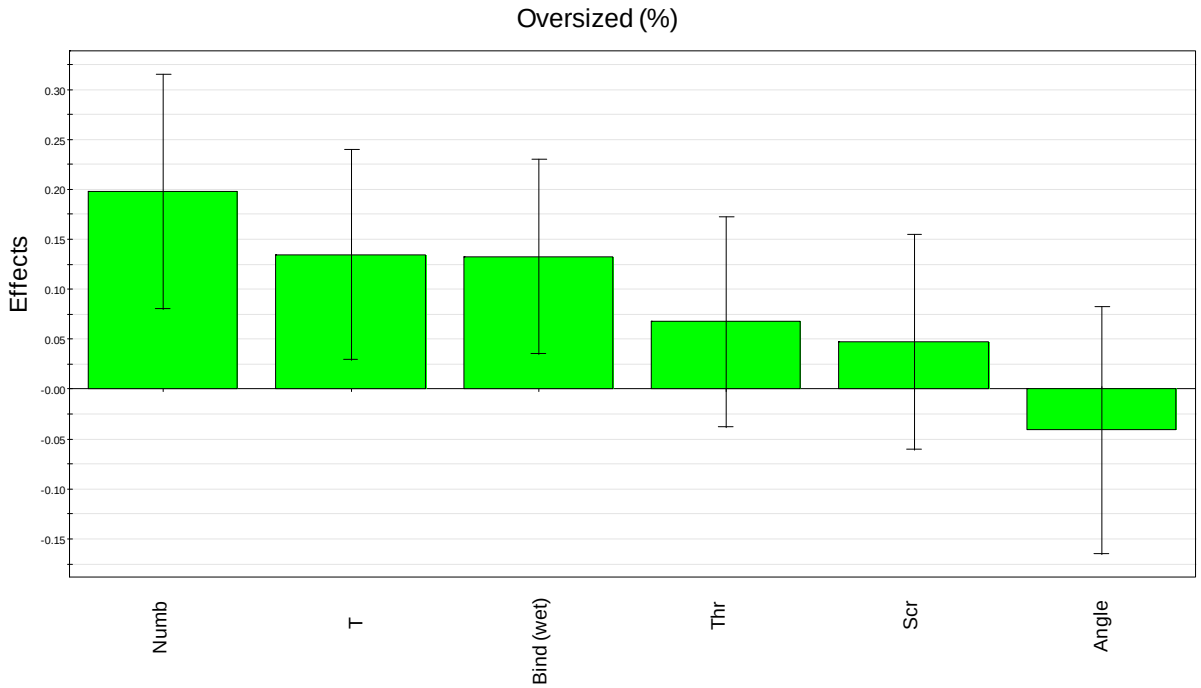

Figure 5: Contour plot for yield (150-1400µm) of milled granules as a function of barrel temperature (°C) and number of kneading elements.

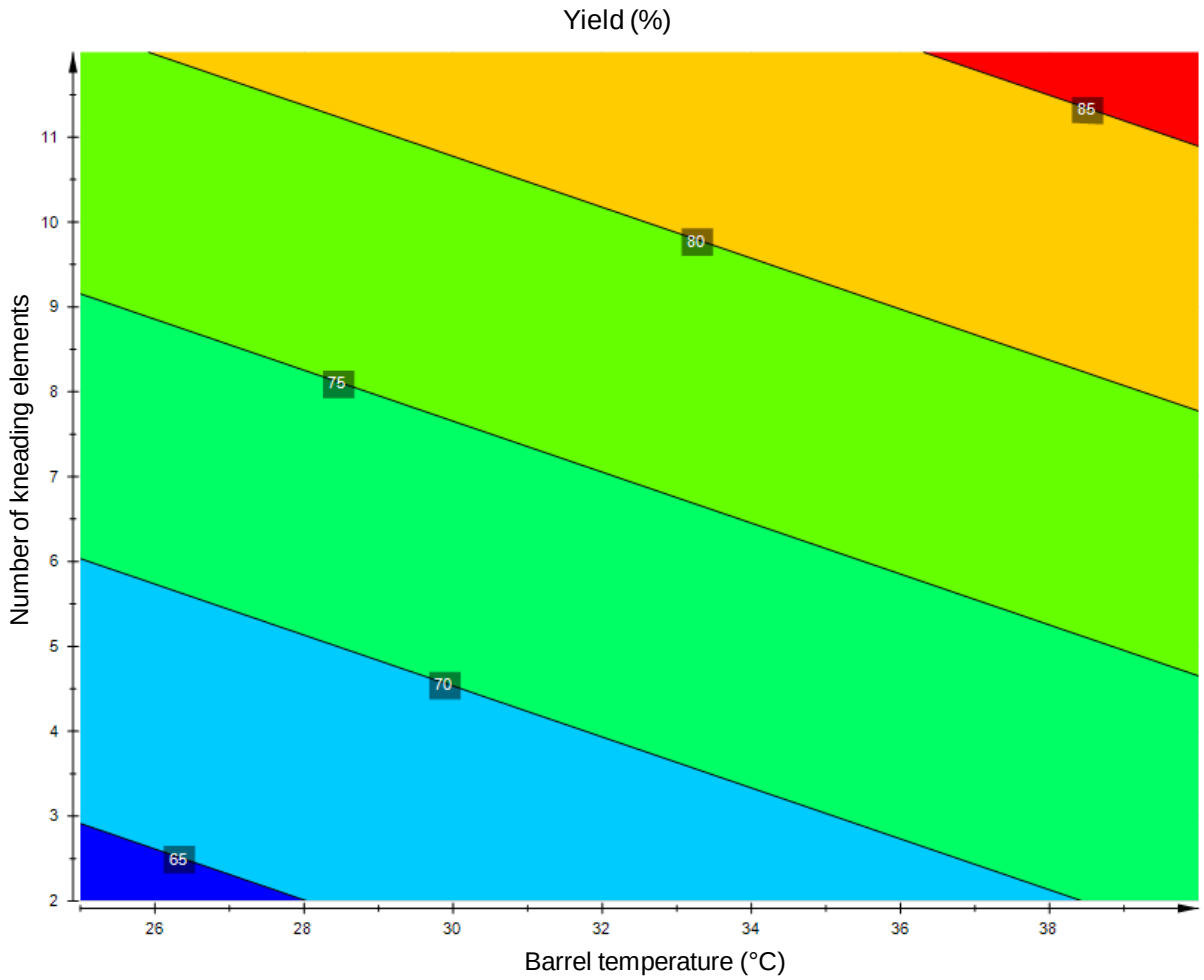

Figure 6: Surface plot for friability of milled granules as a function of barrel temperature (°C) and number of kneading elements.

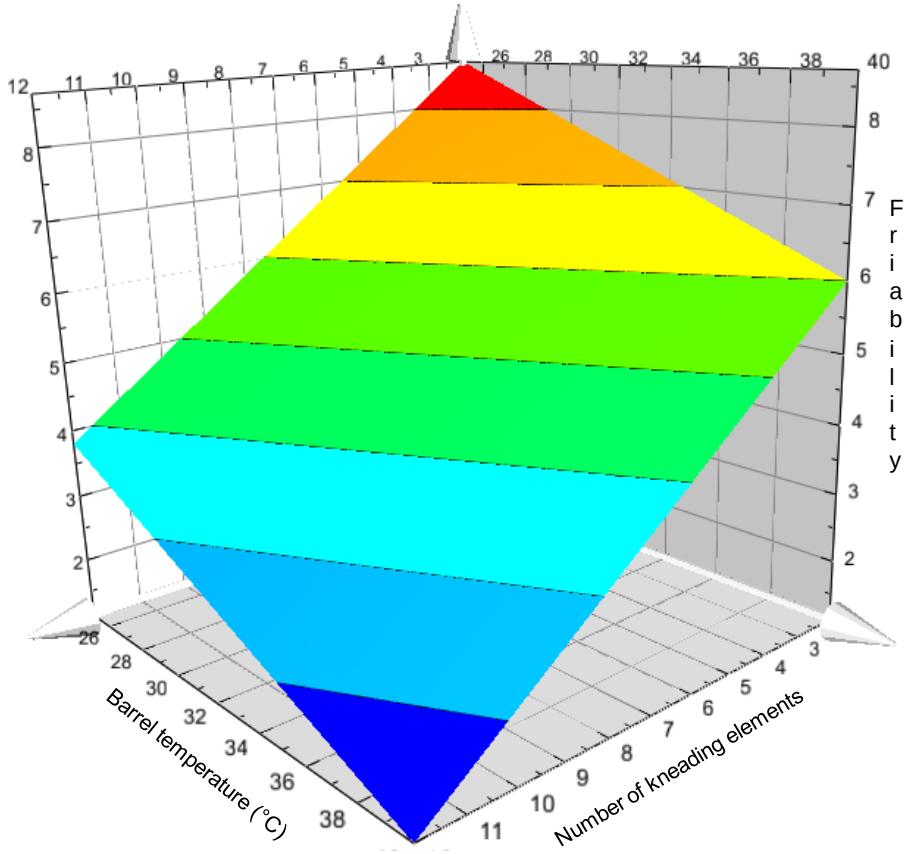

Figure 7: Bulk and tapped densities of milled granules.

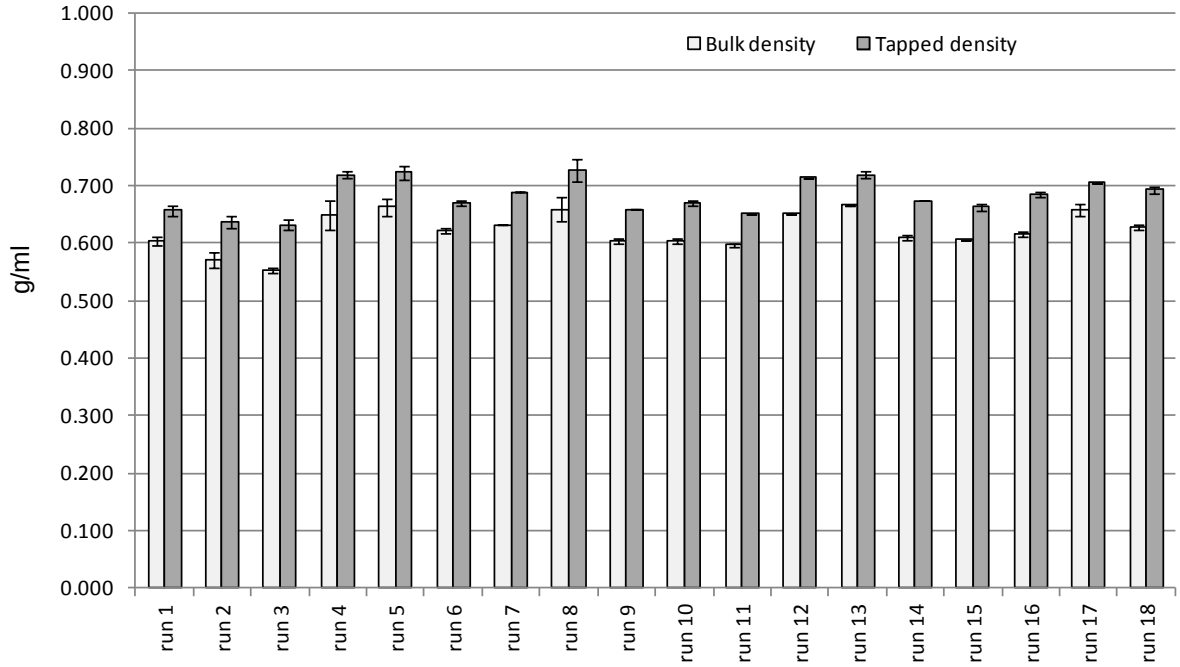

Figure 8: Effect plot for percentage drug released after 45 min. Numb: Number of kneading elements; Angle: Angle of kneading elements; Thr: throughput; T: Barrel temperature; Scr: Screw speed; Bind (wet): Binder addition via granulation liquid.

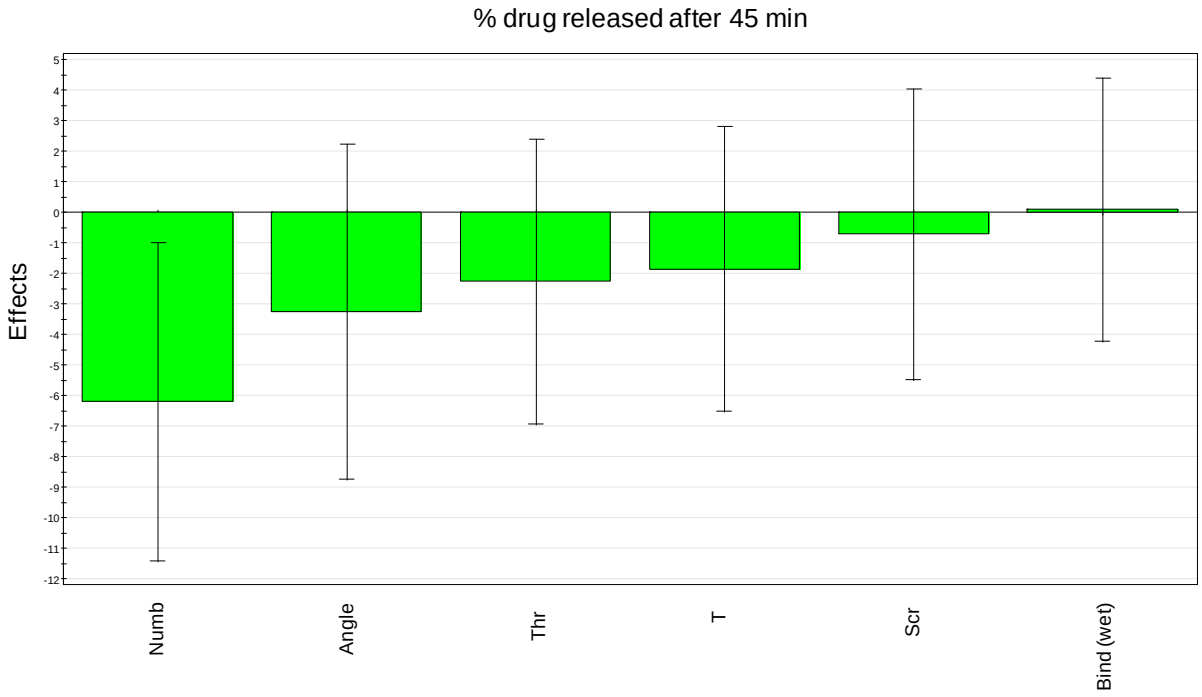

Table 1: Overview of factor settings from the experimental design.

Run	Throughput (kg/h)	Screw speed (rpm)	Kneading elements		Barrel T (°C)	Binder addition
			Number	Angle (°)		
1	17.5	775	4	60	32.5	wet
2	25	600	2	90	25	wet
3	25	950	2	30	40	dry
4	10	600	12	30	40	dry
5	25	600	12	30	40	wet
6	25	950	2	30	25	wet
7	25	600	12	60	25	dry
8	25	950	12	30	25	dry
9	25	600	2	90	40	dry
10	10	600	2	30	25	dry
11	10	950	2	90	25	dry
12	25	950	6	90	40	wet
13	10	950	12	30	25	wet
14	17.5	775	4	60	32.5	wet
15	17.5	775	4	60	32.5	wet
16	10	950	2	30	40	wet
17	10	600	6	90	40	wet
18	10	950	12	60	40	dry

Table 2: Characterization of granulation process and granules from the experimental design.

	Process			Unmilled granules			Milled granules				
Run	Torque (Nm)	Barrel T increase (°C)	Time to steady state (sec)	<150µm (%)	150-1400µm (%)	>1400µm (%)	<150µm (%)	710-1400µm (%)	150-1400µm (%)	Friability (%)	Compressibility (%)
1	1.5	0.0	250	6.6	51.1	42.2	29.3	18.5	70.7	8 ± 0	8 ± 1
2	2.2	0.0	100	20.2	48.8	30.9	45.0	13.0	55.0	10 ± 1	10 ± 1
3	2.1	0.0	25	10.8	55.8	33.3	35.2	15.0	64.8	7 ± 0	12 ± 1
4	4.0	10.0	350	1.3	41.3	57.5	15.7	30.9	84.3	3 ± 0	10 ± 3
5	7.3	10.3	335	0.9	33.7	65.4	15.3	33.2	84.7	3 ± 0	8 ± 1
6	2.4	0.4	165	11.3	47.1	41.5	33.9	20.1	66.1	9 ± 1	7 ± 1
7	5.6	12.5	285	11.2	60.0	28.8	29.3	19.1	70.7	2 ± 0	8 ± 0
8	6.6	21.5	535	1.8	43.6	54.6	17.9	28.1	82.1	9 ± 1	9 ± 1
9	1.9	0.0	35	16.5	51.4	32.1	36.6	16.8	63.4	11 ± 1	9 ± 1
10	1.3	0.3	60	14.6	57.7	27.7	34.1	18.2	65.9	9 ± 0	10 ± 0
11	0.9	0.1	45	19.0	61.5	19.5	37.6	15.6	62.4	9 ± 0	9 ± 1
12	4.9	6.2	250	1.0	16.7	82.3	18.2	28.6	81.8	1 ± 0	9 ± 0
13	4.5	20.2	335	2.4	46.2	51.4	19.5	28.1	80.5	4 ± 0	7 ± 1
14	1.7	0.1	215	8.7	51.8	39.5	31.1	17.6	68.9	7 ± 1	10 ± 1
15	1.4	0.0	275	11.0	54.4	34.6	33.3	17.0	66.7	7 ± 0	9 ± 1
16	1.3	0.0	200	7.6	53.9	38.5	27.4	20.0	72.6	5 ± 0	10 ± 1
17	4.4	6.0	300	1.6	52.4	46.1	17.2	27.7	82.8	3 ± 0	7 ± 2
18	2.8	8.5	385	2.4	53.4	44.2	17.9	26.7	82.1	3 ± 0	9 ± 0

Table 3: Characterization of tablets from the experimental design.

Run	Tensile strength (MPa)	Porosity (%)	Friability (%)	Disintegration time (s)	% release after 45 min
1	1.78 ± 0.04	19.0 ± 2.1	0.25	772 ± 80	73.8 ± 3.1
2	1.48 ± 0.06	15.2 ± 1.9	0.30	730 ± 66	76.8 ± 4.3
3	1.57 ± 0.09	17.9 ± 0.5	0.26	828 ± 25	73.7 ± 5.6
4	1.32 ± 0.05	16.0 ± 1.9	0.24	927 ± 49	72.2 ± 2.1
5	1.36 ± 0.05	19.4 ± 1.0	0.23	649 ± 45	71.1 ± 2.2
6	1.43 ± 0.06	19.0 ± 0.8	0.26	605 ± 75	73.9 ± 1.9
7	1.45 ± 0.04	16.1 ± 1.1	0.27	774 ± 44	74.0 ± 2.0
8	1.24 ± 0.06	16.9 ± 1.1	0.23	766 ± 57	77.8 ± 5.5
9	1.52 ± 0.06	17.2 ± 1.2	0.22	834 ± 59	73.4 ± 4.8
10	1.52 ± 0.08	15.7 ± 1.0	0.27	470 ± 50	82.1 ± 6.0
11	1.61 ± 0.06	18.8 ± 0.2	0.26	529 ± 59	77.4 ± 1.4
12	1.54 ± 0.07	17.5 ± 0.3	0.19	825 ± 108	71.9 ± 4.4
13	1.27 ± 0.08	16.6 ± 0.6	0.23	938 ± 78	70.9 ± 3.5
14	1.52 ± 0.04	20.1 ± 0.7	0.21	536 ± 43	81.7 ± 1.7
15	1.51 ± 0.05	19.6 ± 0.9	0.19	557 ± 37	76.5 ± 1.3
16	1.63 ± 0.07	19.9 ± 1.1	0.21	485 ± 62	86.6 ± 3.4
17	1.35 ± 0.09	17.9 ± 0.9	0.19	765 ± 61	73.1 ± 6.0
18	1.44 ± 0.08	18.4 ± 0.4	0.17	1256 ± 49	69.8 ± 3.7

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