Journal Pre-proofs

Research paper

Integrated continuous melt granulation-based powder-to-tablet line: process investigation and scale-up on the same equipment

Petra Záhonyi, Fekete Dániel, Edina Szabó, Lajos Madarász, Árnika Fazekas, Anna Haraszti, Zsombor K. Nagy

PII: S0939-6411(23)00158-3
DOI: https://doi.org/10.1016/j.ejpb.2023.06.005
Reference: EJPB 14040

To appear in: *European Journal of Pharmaceutics and Biopharmaceutics*

Received Date: 26 March 2023
Revised Date: 5 June 2023
Accepted Date: 10 June 2023

Please cite this article as: P. Záhonyi, F. Dániel, E. Szabó, L. Madarász, A. Fazekas, A. Haraszti, Z.K. Nagy, Integrated continuous melt granulation-based powder-to-tablet line: process investigation and scale-up on the same equipment, *European Journal of Pharmaceutics and Biopharmaceutics* (2023), doi: https://doi.org/10.1016/j.ejpb.2023.06.005

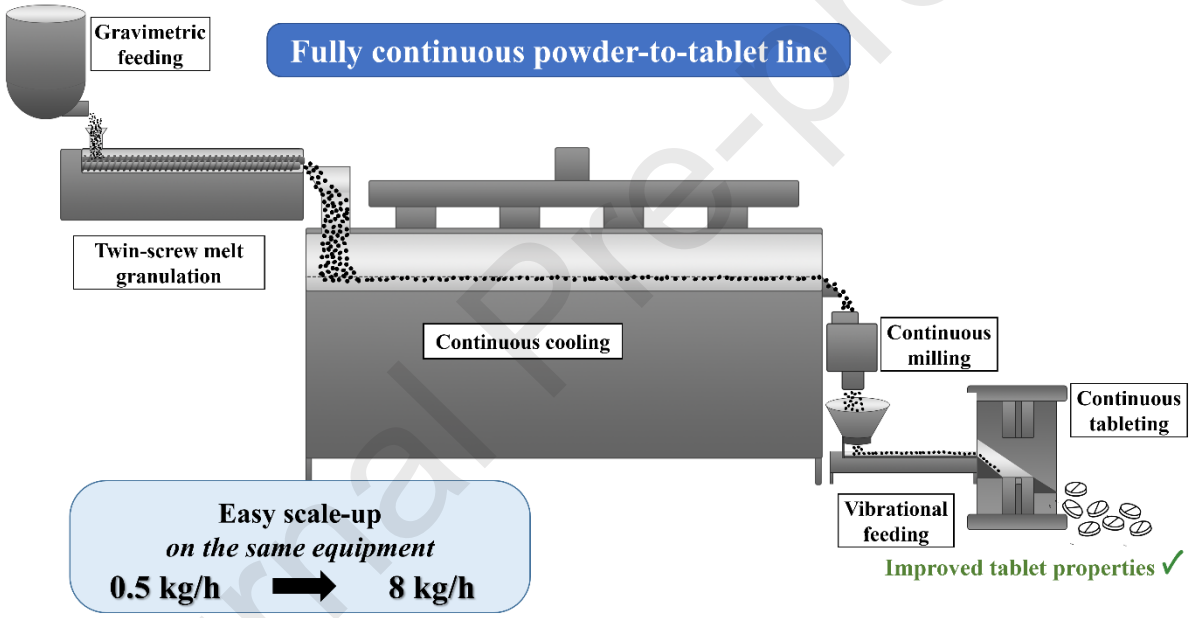
Integrated continuous melt granulation-based powder-to-tablet line: process investigation and scale-up on the same equipment

Petra Záhonyi[1]; Fekete Dániel[1]; Edina Szabó[1]; Lajos Madarász[1]; Árnika Fazekas[1]; Anna Haraszti[1]; Zsombor K. Nagy[1*]

[1]Department of Organic Chemistry and Technology, Faculty of Chemical Technology and Biotechnology, Budapest University of Technology and Economics, Műegyetem rkp. 3., H-1111 Budapest, Hungary

*Corresponding author: Tel: +36 1 463-1424; E-mail: zsknagy@oct.bme.hu

Graphical abstract



Abstract

In the last decades, continuous manufacturing (CM) has become a research priority in the pharmaceutical industry. However, significantly fewer scientific researches address the investigation of integrated, continuous systems, a field that needs further exploration to facilitate the implementation of CM lines. This research outlines the development and optimization of an integrated, polyethylene glycol aided melt granulation-based powder-to-tablet line that operates fully continuously. The flowability and tabletability of a caffeine-containing powder mixture were improved through twin-screw melt granulation resulting in the production of tablets with improved breaking force (from 15 N to over 80 N), excellent friability, and immediate release dissolution. The system was also conveniently scaleable: the production speed could be increased from 0.5 kg/h to 8 kg/h with only minimal changes in the process parameters and using the same equipment. Thereby the frequent challenges of scale-up can be avoided, such as the need for new equipment and separate optimization.

Keywords

continuous manufacturing, twin-screw granulation, melt granulation, integrated continuous process, scale-up

Highlights

- Fully continuous melt granulation-based powder-to-tablet line was developed
- The flowability and tabletability were improved significantly
- Caffeine-loaded tablets with increased breaking force (from 15 N to over 80 N) were produced
- The tablets had excellent friability and immediate release dissolution
- Scale-up production (from 0.5 kg/h to 8 kg/h) was accomplished with the same system

1. Introduction

Continuous manufacturing (CM) has become a widespread tendency in the pharmaceutical industry in the past decades. Although the shift from batch production is delayed in the field compared to the other chemical industry sectors, CM's many advantages support the change. That includes more efficient production, smaller equipment sizes and reduced investment and operation expenses.[1] The connected production steps eliminate the need for transport and storage between operations units, resulting in shorter, more energy-efficient supply chains with decreased degradation risk of sensitive active pharmaceutical ingeredients (APIs) and safety risk of hazardous materials.[2–6]

The scale-up of continuous technologies is also more convenient. In many cases, the commercial-scale equipment can be used for all the experiments, eliminating the need for time- and energy-consuming separate laboratory- and commercial-scale optimization.[7,8] Moreover, this flexibility can expedite the time-to-market of the product, and enable a sudden increase in production.[3,4]

During tablet pressing, an essential part of most pharmaceutical formulation processes, the handling of poorly flowable powders poses a significant challenge. To overcome this issue, twin-screw granulation (TSG), a continuous technology can be applied. TSG improves the physical properties (for example flowability, compressibility and bulk density) of the material as well as tabletability and content uniformity, making the technology a critical part of many formulation processes.[9–11]

In particular, a type of TSG, twin-screw melt granulation (TSMG) has great potential since it has many advantages compared to the other types of granulation. The use of organic and aqueous solvents and the need for the extra process steps (including the wetting and the drying) can be eliminated, making the process less time- and energy-consuming, more environmentally friendly and suitable to moisture-sensitive APIs compared to the more widely used wet granulation. Moreover, it could also lead to a narrower range of granule sizes as well as improved flowability and compactibility.[12,13]

Thanks to these advantages, more and more publications address TSMG. The technology has been successfully applied to produce high-dosage immediate-release tablets[14,15] and sustained release tablets[16–19], enhance the solubility[20,21] and for simultaneous cocrystallization and formulation of cocrystal API[22]. Although these publications only examine the TSMG process in isolation from other operational units, the downstream processing of the granules towards tableting was also investigated in great detail by W. Grymonpré et al., providing evidence of the technology's robustness.[23] However, even they did not use connected continuous manufacturing lines, but instead the granules were manually transferred for milling. Thus, while complex systems based on similar technologies, for example hot-melt extrusion[24] have already been thoroughly investigated, the challenges regarding the implementation of TSMG still need to be further examined.

Further proving the importance of the technology, TSMG has also been applied at commercial scale. Using TSMG, immediate release tablets were produced from metformin granules (Eucreas™)[15] and elagolix granules (Orilissa® and Oriahnn®)[25]. The technology was also used by Novartis to produce fevipiprant containing tablets for Phase 1-3 trials, and (in spite of the termination of the product[26]) the data about the commercial scale transfer from

the pilot scale production was published. The publication revealed numerous challenges connected to the different equipment used for the scale-up. [27]

Although numerous research has been published about continuous technologies and TSMG, and there are marketed products manufactured this way, the integration of the different processing steps is still underexamined. Therefore, this research aimed to investigate how TSMG can be connected to other operation units, and develop a manufacturing line that can run undisturbed, fully continuously from powder to tablet. Furthermore, as the scale-up is also a critical part of all pharmaceutical processes, our goal was to eliminate this risk by using the same system for small- and larger-scale production. According to the authors' best knowledge, no publications have yet investigated the development of such a melt granulation-based fully continuous powder-to-tablet line, that can be easily scaled up using the same equipment. However, the efficacy of such systems has a great potential in the pharmaceutical industry, and can support the spread of the commercial application of CM lines.

2. Materials and methods

2.1. Materials

Our model system comprised caffeine (API) and polyethylene-glycol (binder) as key components. The caffeine-anhydrous and crosslinked polyvinylpyrrolidone (crospovidone, Kollidon® CL) were obtained from BASF (Ludwigshafen, Germany), the lactose monohydrate (Granu-Lac® 230) was provided by Meggle Pharma (Wasserburg, Germany) and polyethylene-glycols with different molecular weight (PEG 3000, PEG 6000 and PEG 20 000) were supplied from Merck Ltd. (Budapest, Hungary). PEG was applied as a melting agent acting as granulation liquid in the granulator at elevated temperatures (>60 °C).

2.2. Continuous powder-to-tablet line

First, all the materials (caffeine, lactose, crospovidone and polyethylene-glycol) were homogenized manually, before starting the continuous production. Before blending with the other materials, the polyethylene-glycol was milled to reduce its particle size using a continuous oscillating milling device (described later in this section) with a sieve size of 800 µm. The composition of the mixture was the following: 65% lactose, 15% caffeine, 15% polyethylene-glycol and 5% crospovidone.

The tablet production was carried out in an integrated, continuous manufacturing line based on melt granulation (Figure 1). The line consisted of a gravimetric feeder (a DDW-MD0-MT type gravimetric feeder (Brabender Technologie, Germany) for experiments 1-7 detailed in Table 1, and a K-SFS-24 type gravimetric feeder (K-tron, Switzerland) for experiments 8-10), a TS16 type twin-screw granulator (QuickExtruder, 2000 Ltd, Hungary), a horizontal fluidized bed dryer/cooler (used to cool down the granules) (Quick 2000 Ltd., Hungary), a continuous oscillating milling device with a sieve size of 0.8 mm (QUICKmill Lab multifunctional milling machine, Quick 2000 Ltd., Hungary), a vibratory conveying feeder equipped with a U-shaped chute (LABORETTE 24 type vibratory feeder, Fritsch GmbH, Germany) and a Dott Bonapace CPR6 eccentric tableting machine (Limbiate, Italy). The reason for application of two different feeders was that higher mass flow rates were able to be achieved only with the K-tron gravimetric feeder. However, the feeding was not the critical part of the system thus both could be used for similar purposes. Between experiments 1-4, 5-7, and 8-10, the hopper was emptied and freshly filled. During these intervals, changes in the process parameters were carried out without stopping the system. After each alteration the

material was not collected for 5 minutes (waste) to reach the steady state. Subsequently, 0.5 kg of material was produced at each process parameter, and samples were collected manually throughout the entire 0.5 kg. In some cases, the refill of the feeder was carried out during production. Despite the feeders operating in gravimetric mode, they automatically switched to volumetric feeding for the refill (which only took 10-20 seconds), thus allowing the refill to be carried out without disturbing the process.

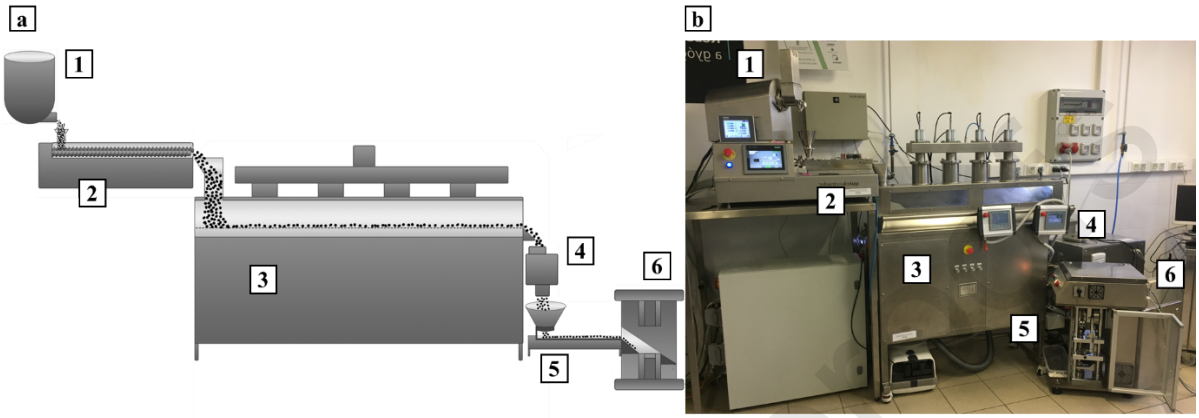


Figure 1: The (a) schematic drawing and (b) photo of the continuous manufacturing line consisting of (1) gravimetric feeder; (2) twin-screw granulator; (3) horizontal fluidized bed dryer used for cooling; (4) oscillating mill; (5) vibratory conveying feeder; (6) tableting device.

The granulator consisted of 4 heating zone, and had a 16 mm screw diameter and 400 mm length (25 L/D). The screw configuration, including both conveying (CEs) and kneading elements (KEs) is illustrated in Figure 2.

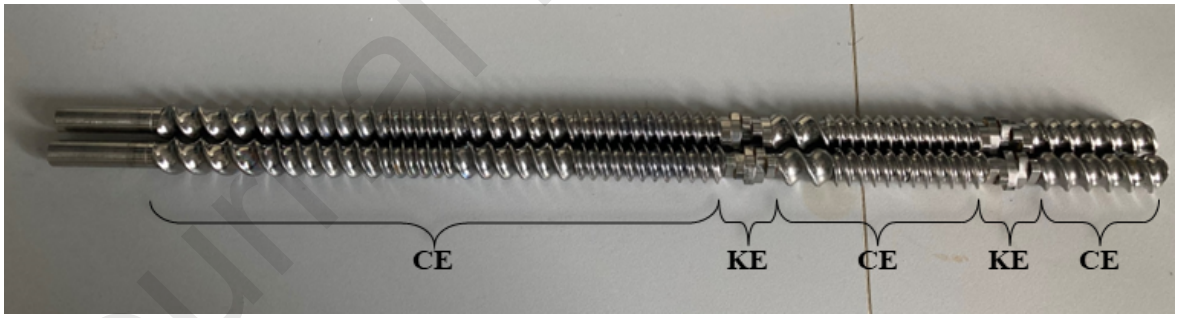


Figure 2: Screw configurations of the granulator

The operation parameters of the feeders and the granulator are summarized in Table 1. During experiments 1-4, the tableting was performed separately (with the tableting device still operating in continuous mode), as the goal of these experiments was to find the optimal operation parameters. Experiments 5-10 were carried out with the connected, fully continuous system. During all the experiments shown in Table 1, the pre-blend mixture contained PEG 20 000 as a melting binder, and the other types of polyethylene-glycol with different molecular weight were only used for pre-experiments.

Table 1: The process parameters of the performed experiments

Experiment number	Feed rate of the pre-blend mixture (kg/h)	Rotation speed of granulator (rpm)	Granulation temperature (°C)
1	0.5	100	40
2	0.5	100	60
3	0.5	100	80
4	0.5	100	100
5	0.5	100	120
6	1	200	120
7	3	600	120
8	4.5	900	120
9	8	900	120
10	8	900	150

The granules were cooled down to room temperature with the above-mentioned continuous horizontal fluidized bed dryer/cooler. In order to use the equipment for cooling instead of drying, the temperature of the supply air was kept at room temperature. In the cooler the material transport was carried out via a vibrating perforated metal belt (vibrating with 50 Hz frequency) and the granules were cooled by vertical air passing through the small, perforated holes of the conveying belt. The cooler consisted of four zones with individually alterable airflow rates and separate filter bags. All the experiments were carried out with 120 l/min airflow rate at each zone.

The above-desribed mill was operated with a 150 1/min oscillation speed to break down the larger particles (sieve size: 0.8 mm). The same equipment was also used for the milling of the PEG earlier, prior to the homogenization of the pre-blend.

At the end of the continuous powder-to-tablet line, the target tablet weight was 600 mg (90 mg caffeine dose) and 14 mm round-shaped punches were used. Tablets were also pressed from the pre-blend mixture (physical mixture) for comparison. During the compression of the

physical mixture and the pre-experiments, various compression forces were applied. During experiments 1-10, 5 kN compression force was used (with the upper and lower punches set to comply with that criterion before the experiments).

2.3. Thermal imaging camera

The effectiveness of the cooling system was investigated with the help of a FLIR T660 type thermal imaging camera (FLIR, USA). The temperature of the granulator, the granulated material and the cooled granules were investigated after applying different granulation temperatures and feed rates. A conventional thermometer was also placed into the material flow and was used to validate the measurements.

2.4. Powder characterization

Samples were collected from the physical mixture and the milled granules. The characterization of these samples was carried out off-line.

2.4.1. Particle size analysis

The particle size distribution of the physical mixture, the granules and the milled granules was measured by an off-line Malvern Mastersizer 2000 type laser diffractometer (Malvern Instruments Ltd., UK), with a detection range of 0.02-2000 µm. A vibratory Malvern Scirocco 2000 dry powder feeder transported the powders into the equipment with 75% intensity of the vibrational amplitude, where 0.4 bar pressure was applied. Around 1-2g samples were measured, and each measurement lasted 30 seconds with 30 seconds of background recording. Every sample was measured in triplicate, and both the average and the standard deviation of d(0.1), d(0.5) and d(0.9) values were calculated, indicating the 10%, 50% and 90% of cumulative undersize of the volumetric distribution.

2.4.2. Morphology

The morphology of the physical mixture, the granules and the milled granules was examined with a JEOL JSM 6380LA (JEOL, Japan) type scanning electron microscope (SEM). Prior to the measurement, each specimen was fixed with conductive double-sided carbon adhesive tape and sputtered with gold to avoid electrostatic charging. During the experiments, the applied accelerating voltage and working distance were 15 kV and 10 mm, respectively.

2.4.3. Flow properties

The flow properties were investigated by measuring the bulk and tapped densities of the materials with an ERWEKA SVM12 type tapped density tester (Erweka, Germany). The flowability and compressibility was determined based on the calculated Hausner's Ratios[28] and Carr's Indexes[29]. One measurement was carried out for each experiment. The flow properties were further investigated by measuring the required time for 100 g samples of powders to flow out of a funnel with 10 mm diameter. Three separate measurements were carried out for each sample.

2.5. Characterization of the tablets

2.5.1. Characterization of the mechanical properties

A Dr. Schleuniger THP-4M diametral tablet crushing tester (Dr. Schleuniger® Pharmatron, Switzerland) was used for measuring the breaking force of the tablets (required minimum force to break the tablets). In case of each sample multiple measurements were carried out (5 independent tablets were measured, and the average breaking force was calculated). In some cases, the tensile strength was also determined for comparative reasons with the following formula:

$$\sigma_x = \frac{2F}{\pi DH} \quad (1)$$

In Eq. (1) σ_x denotes the tensile strength of the tablet, F the breaking fore, D the diameter and H the height of the tablets (determined by measuring 5 individual tablets and calculating their average). Although several limits exist for the tensile strength of tablets, around 1 MPa is usually considered adequate[30–32]. The friability of the tablets was examined with a Pharma Test PTF 20E type friability tester (Pharma Test, Germany). One measurement using 10 tablets and applying 100 rotation rounds was carried out for each experiment.

2.5.2. In vitro dissolution tests

A Hanson SR8-Plus dissolution tester (Hanson Research, USA) was used for the *in vitro* dissolution studies of the drug-loaded tablets. The measurements were carried out using the paddle method (United States Pharmacopoeia II), with 900 mL distilled water used as dissolution medium. The distilled water was kept at a constant temperature of 37 ± 0.5 °C and was stirred at 100 rpm. The concentration of the dissolved caffeine was measured on-line by an Agilent 8453 UV–Vis spectrophotometer (Hewlett-Packard, USA), connected to the dissolution tester through flow cells. The measurements took two hours with minimum 10 sampling points (after 2, 5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 minutes). The concentration of the dissolved caffeine was calculated in real-time using a preliminarily built calibration at a wavelength of 272 nm, with 100% dissolution value corresponding to the total dissolution of target dose of the API (90 mg). In case of each sample, 3 tablets were measured parallelly.

3. Results and discussions

3.1. Pre-experiments with PEGs of different molecular weights

The initial physical mixture containing caffeine as model API had small average particle size (Figure 3) and bad flow and compression properties (Table 4). The tablets pressed from the untreated powder also had poor properties. These tablets broke under 15 N breaking force and broke down completely during the friability measurements, and these properties could not be adequately improved by increasing the compression force (Figure 5a). As granulation excipients were used, the direct compression (DC) was not further examined (the formulation was not optimal for DC). Instead, the goal was to improve these poor initial properties of the powder mixture typically used for melt granulation using TSMG.

First, the adequate binder needed to be determined for the granulation. For these pre-experiments, three separate pre-blends were made containing PEG 3000, PEG 6000 and PEG 20 000. During these pre-experiments, the granulation was carried out separately (applying 100 rpm rotation speed and 120°C granulation temperature), and the granules were cooled on trays at room temperature (not in the horizontal fluidized bed cooler).

The measured particle size distribution suggested that granulation was successful in all cases, as it increased the average particle size and decreased the ratio of fine particles compared to the physical mixture (Figure 3). It was revealed that the bigger molecular weight of the binder affected the process positively, and monomodal particle size distribution was only reached when using PEG 20 000.

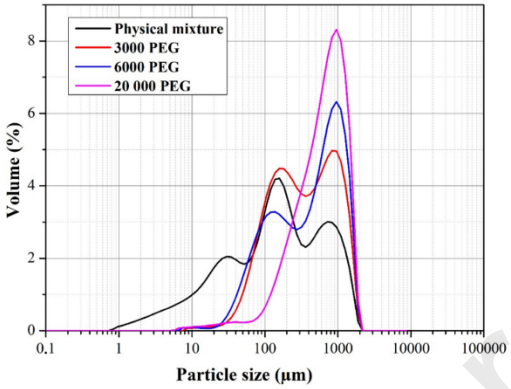


Figure 3: The particle size distribution of the physical mixture (containing PEG 20 000) and the granules containing PEGs of different molecular weights, granulated at 120°C with 100 rpm rotation speed and 0.5 kg/h production speed.

The breaking force of the tablets prepared after granulation increased significantly in all cases and the friability was also adequate, less than 1% (Table 2).[33] However, it was the best when PEG 20 000 was used, as in that case, the weight loss was under 0.3 %, meaning that these tablets were even suitable for film coating.[34,35] The lubrication efficiency of the tablet compression was also investigated by measuring the lubrication value (the ratio of the maximum lower punch force to the maximum upper punch force) during tablet pressing. As in case of well-lubricated powders, the force exerted by the upper punch and the one transmitted to the lower punch are essentially the same, the higher lubrication values indicate efficient lubrication (typically over 0.9 the lubrication is considered excellent)[36]. The lubrication values of the prepared tablets were found to be above 0.9 in all cases, confirming that the use of PEG in the applied amount (15 m/m%) leads to adequate lubrication. These results demonstrated that no additional lubricating agent was required.

Table 2: The breaking force of the tablets compressed from the physical mixture and the granules produced at 120°C granulation temperature and 100 rpm rotation speed using 10 kN compression force, and the results of the friability tests.

	The breaking force of tablets (N)	**Friability of tablets (%)**
Physical mixture	15	cannot be measured
PEG 3000	122	0.51%

PEG 6000	146	0.61%
PEG 20 000	168	0.15%

Although all tablets could be considered immediate release (Q=80% in 30 minutes)[37], the dissolution rate of the tablets containing PEG 20 000 was slightly delayed compared to the other tablets (Figure 4). In spite of that, using PEG 20 000 still seemed to be the best option for the continuous system, as it led to the best granule and tablet properties. The final goal was to carry out experiments with scalable production; therefore, a robust system needed to be designed. Thus, the powder mixture containing PEG 20 000, was chosen for the following experiments.

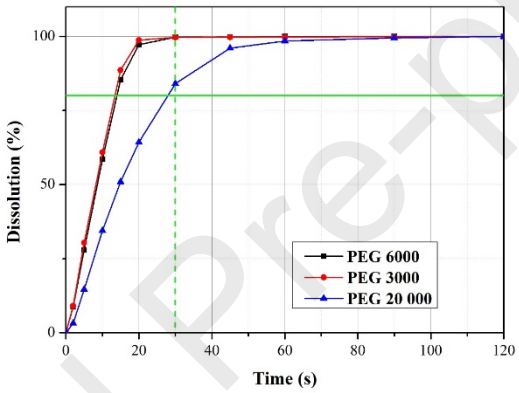


Figure 4: Investigation of the effect of different binders on the dissolution of the tablets (900 mL distilled water dissolution medium, 37±0.5°C, 100 rpm, paddle method, 90 mg API content, n = 3).

To further ensure that all the tablets are going to be immediate release, the dissolution rate needed to be improved. As the breaking force of the tablets (compressed with 10 kN force) improved significantly (Table 2), using lower compression force was suspected to possibly accelerate the dissolution rate while still leading to tablets with adequate mechanical strength. Therefore, the correlation between the compression force and the breaking force (Figure 5a) and dissolution rate (Figure 5b) was investigated. It was revealed, that even with 5 kN compression force 100 N breaking force could be achieved. Based on the size of the tablets, which indicates over 1.09 MPa tensile strength, showing a significant increase from the physical mixture (0.16 MPa). The friability of the tablets (compressed with 5 kN, 10 kN and 20 kN) was also measured, which was excellent in all cases (the weight loss was under 0.3%), as shown on Figure 5c. These experiments revealed that the tablets pressed with 5 kN compression force had excellent tablet properties (high breaking force, low friability and immediate dissolution). Thus, it was chosen for our system.

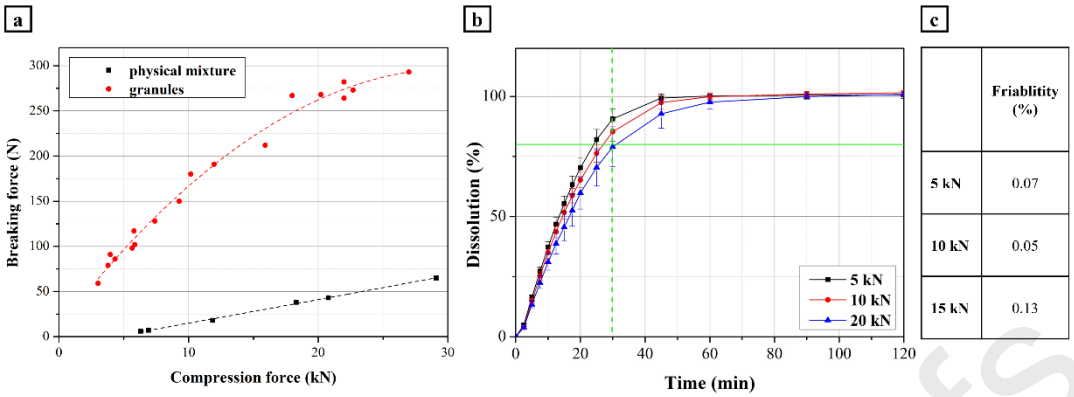


Figure 5: Investigation of the effect of the compression force on the (a) breaking force, the (b) dissolution (900 mL distilled water dissolution medium, 37±0.5°C, 100 rpm, paddle method, 90 mg API content, n = 3) and the (c) friability of the tablets prepared with PEG 20 000.

3.2. Effect of the granulation temperature

Afterward, all the experiments were carried out with the continuous manufacturing line using PEG 20 000 and applying 5 kN compression force during tablet compression. The effect of the granulation temperature was investigated (Experiments 1-4), in order to find the optimal for our system.

During these experiments, the efficiency of the continuous cooler was examined with the thermal imaging camera and thermometers (Figure 6). The cooling was found to be effective in all cases, as the granules had cooled to room temperature after the cooling step (Table 3).

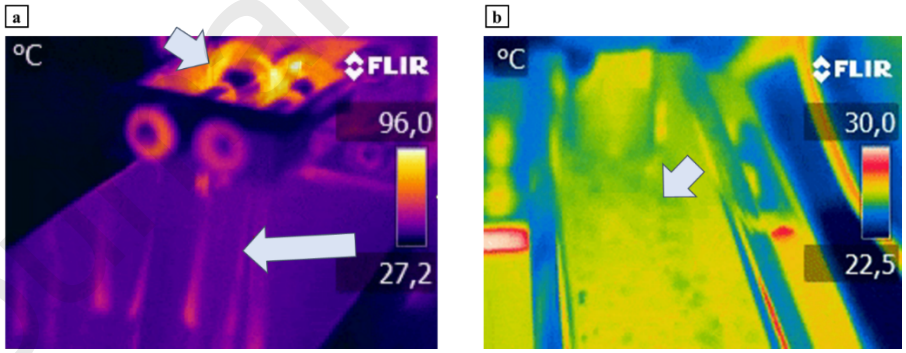


Figure 6: The temperature of the granules (a) before and (b) after cooling (granulated at 120°C), with light blue arrows showing the material.

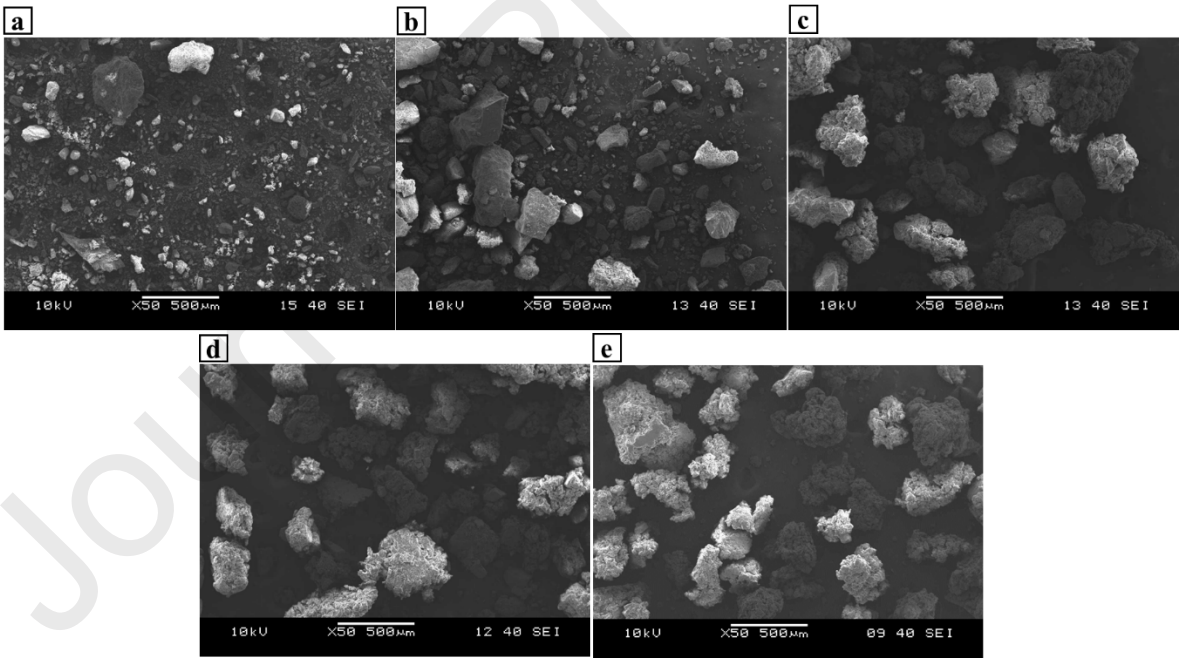
Table 3: The temperature of the granules (produced with 0.5 kg/h production speed) after cooling in the horizontal fluid bed cooler.

	Temperature of the granules before cooling (°C)	**Temperature of the granules after cooling (°C)**

Granulated at 60°C	50	24
Granulated at 80°C	60	25
Granulated at 100°C	75	27
Granulated at 120°C	95	27

305

306 The microscopic characteristics of the milled granules were examined with SEM (Figure 7).
307 The increase in the particle size can be observed in all cases of granulation, and after 80°C the
308 granule formation is definite, as the aggregation of the initial particles can be clearly
309 recognized. These properties were believed to lead to improved flow and compression
310 properties.



311

312 Figure 7: SEM images of the (a) physical mixture and the milled granules produced at (b) 60°C, (c)
313 80°C, (d) 100°C and (e) 120°C granulation temperatures.

314 The macroscopic characteristics of the milled granules were evaluated via laser diffraction
315 (Figure 8). According to the laser diffraction measurements, the granulation process
316 effectively improved the particle size distribution in all cases, transforming the initial
317 multimodal particle size distribution towards a predominantly unimodal distribution.
318 Although in most cases, a small local maximum remained beside the prominent peak, the

improvement is notable. Over 80°C, the amount of fine particles (under 100 µm) decreased drastically, and the average particle size also increased with the temperature. The particle size distributions of the milled granules produced at 80 and 100°C were both similarly good; furthermore, at 120°C, an even more distinct increase in the average particle size could be observed.

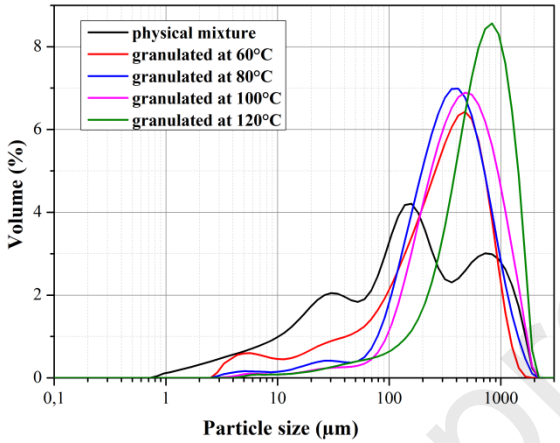


Figure 8: The particle size distribution of the physical mixture and the milled granules produced at different granulation temperatures.

The investigation of the flowability and compressibility of the milled granules confirmed that these properties of the powder were improved significantly by granulation. The results of these measurements are summarized in Table 4.

Table 4: The flowability of the physical mixture and the milled granules produced at different granulation temperatures.

	Carr index (%)	**Hausner ratio (-)**	**Flowability**	**Required time for 100 g powder to flow out of a 10 mm diameter funnel (s/100 g)**
Physical mixture	28.65	1.40	Poor	Does not flow through
Granulated at 60°C	21.62	1.28	Passable	8.50 ± 0.15 s
Granulated at 80°C	13.17	1.15	Good	4.48 ± 0.08 s
Granulated at 100°C	10.45	1.12	Good	4.67 ± 0.07 s
Granulated at 120°C	8.17	1.09	Excellent	4.44 ± 0.02 s

The improvement in the flowability and compressibility is notable even at 60°C, however granulation at 80°C and 100°C led to significantly better flowability and compressibility. These properties could be further improved (to excellent flow and compression properties) by applying 120°C granulation temperature. The improved properties are supposedly caused by the granule formation assisted by the melted and dispersed PEG binding together the particles. The deformability of the particles also improved, making them fit together more properly and improving cohesion. It is assumed, that the positive correlation between the temperature and the granule properties is caused by the more effective melting and dispersion of the binder. It leads to more efficient granulation (increased granule formation and growth that was observed earlier on Figures 7 and 8), and later enhanced granule properties.

Tablets compressed from the milled granules with 5 kN compression force were also examined, and the positive effect of the increased temperatures was also confirmed. The characterization of the tablets was carried out, and the results are shown in Table 5. Except for the 60°C granulation temperature (in which case the tablets were crushed in the friability tester similarly to the tablets compressed from the physical mixture), the friability of all the tablets was excellent. However, the breaking force was the highest (indicating over 1.09 MPa tensile strength) when 120°C granulation temperature was used.

Table 5: The breaking force of the tablets compressed from granules produced at different temperatures using 5 kN compression force, and the results of the friability tests (10 tablets tested with 100 rotations) of the same tablets.

	The breaking force of tablets (N)	**Friability of tablets (%)**
Granulated at 60°C	4.0 ± 0.0	cannot be measured
Granulated at 80°C	63.3 ± 2.3	0.09%
Granulated at 100°C	75.7 ± 4.7	0.08%
Granulated at 120°C	99.9 ± 10.7	0.07%

The dissolution of the tablets was also examined with the exception of the ones granulated at 60°C, as those tablets were too fragile; thus, those were excluded from the following measurements (Figure 9). The dissolution rate of the tablets was satisfactory in all cases. Therefore, the 120°C granulation temperature was chosen for the scale-up experiments, because of the superior physical properties of the tablets, particularly the breaking force and friability.

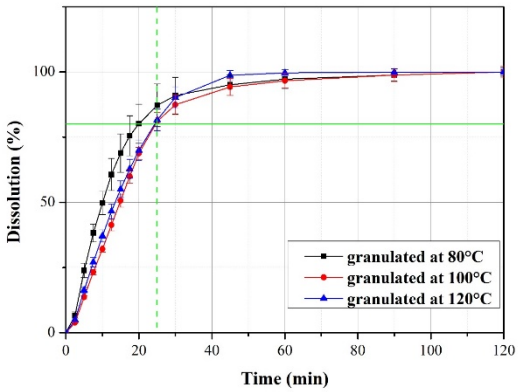


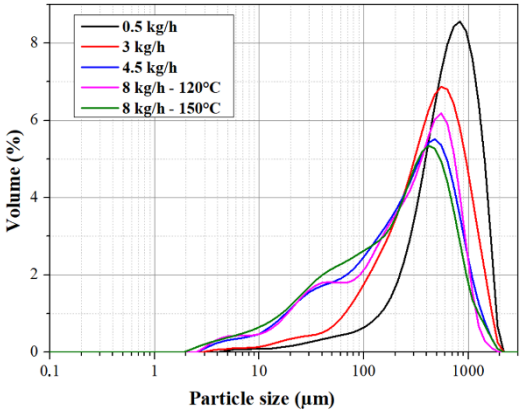
Figure 9: Investigation of the effect of the temperature on the dissolution of the tablets (900 mL distillated water dissolution medium, 37±0.5°C, 100 rpm, paddle method, 90 mg API content, n = 3).

3.3. Scale-up experiments

To accomplish the scaling-up using the same production line, the feed rate of the physical mixture was increased from 0.5 kg/h up to 8 kg/h in several steps (Experiments 4-7). The rotation speed of the granulator was increased proportionally with the feed rate to aid the transport of the material and to keep a consistent fill level inside the granulator. However, the maximum rotation speed of the granulator was reached at 900 rpm (with 4.5 kg/h feed rate); therefore, this rotation speed was applied even at higher feed rates. It is important to note, that over 3 kg/h a slight accumulation was observed at the hopper of the tableting device. Although it did not pose a significant challenge during our experiments (because of the smaller batch sizes) for longer productions larger tableting device (for example rotary tableting device that is widespread and well-acquainted in the pharmaceutical industry) could be applied.

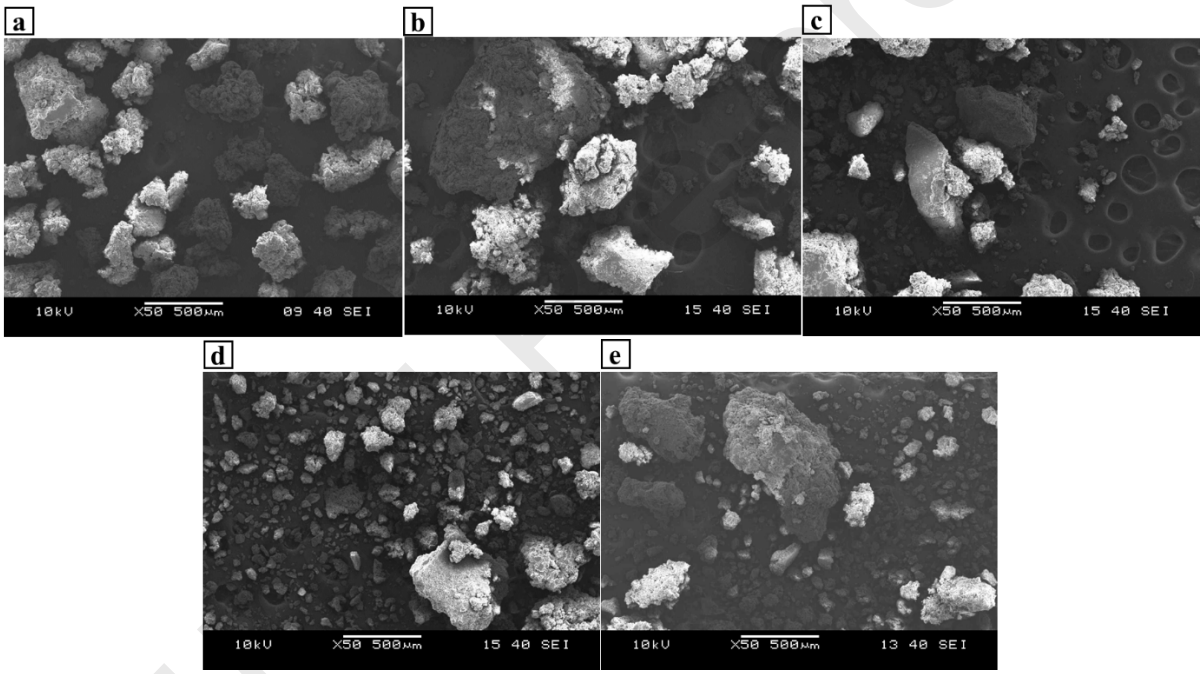
The temperature of the cooled granules was measured upon leaving the continuous cooler with thermal imaging and conventional thermometers. As the measured temperature was close to room temperature (27-28°C), the capacity of the cooler was proved to be adequate for the scale-up production. During the experiment, a decrease was noticed in the flowability and tabletability of the granules in the case of 8 kg/h production speed. This negative effect could be caused by the increased amount of material in the barrel required to be heated with the same heat transfer area. It led to less effective heating and thus, less effective granulation in the equipment. Therefore, an extra experiment (Experiment 8) was carried out, where the 8 kg/h production speed was paired with higher granulation temperature (150°C instead of 120°C).

Samples were collected from the milled granules and the tablets as well, to investigate the granule (Table 6, Figures 10 and 11) and tablet (Table 7 and Figure 12) properties.



387

388 Figure 10: The particle size distribution of the milled granules produced with different
389 production speed and granulation temperatures.
390



391

392 Figure 11: SEM images of the milled granules produced at 120°C granulation temperature with (a)
393 0.5 kg/h (b) 3 kg/h (c) 4.5 kg/h (d) 8 kg/h production speed and (e) produced at 150°C granulation
394 temperature with 8 kg/h production speed.

395 Table 6: The flow and compression properties of the physical mixture and the milled
396 granules prepared with different production speeds and granulation temperatures (Experiment
397 4-8).

Production speed (kg/h)	Rotation speed of the granulator (rpm)	Granulation temperature (°C)	Carr index (%)	Hausner ratio (-)	Flowability	Required time for 100 g powder to flow out of a 10 mm diameter funnel (s/100 g)
0.5	**100**	**120**	8.17	1.09	Excellent	4.44 ± 0.02 s
3	**600**	**120**	8.68	1.10	Excellent	4.646 ± 0.04 s
4.5	**900**	**120**	9.78	1.11	Excellent	4.582 ± 0.01 s
8	**900**	**120**	12.35	1.14	Good	6.123 ± 0.05 s
8	**900**	**150**	9.39	1.10	Excellent	4.729 ± 0.17 s

Although the higher production speed increased the amount of fine particles (Figure 10), the formation of granules can be observed in all cases, as shown in Figure 11. In case of 8 kg/h, the flow properties of the powder worsened slightly, but the negative effect could be reversed with the use of higher granulation temperature (Table 6). Therefore, good granule properties could be reached with 8 kg/h feed rate as well.

Similarly to the granule properties, the physical properties of the tablets also worsened when the feed rate was raised to 8 kg/h (with 120°C granulation temperature). The breaking force of the tablets decreased to 63.2 N (indicating 0.66 MPa tensile strength), but it could be improved by applying higher granulation temperature (Table 7).

Table 7: The breaking force of the tablets compressed from granules produced with different production speeds and different temperatures using 5 kN compression force, and the results of the friability tests (10 tablets tested with 100 rotations) of the same tablets.

Production speed (kg/h)	Rotation speed of the granulator (rpm)	Granulation temperature (°C)	The breaking force of tablets (N)	Friability of tablets (%)
0.5	**100**	**120**	99.9 ± 10.7	0.07

3	**600**	**120**	83.3 ± 10.0	0.01
4.5	**900**	**120**	88.2 ± 8.1	0.12
8	**900**	**120**	63.2 ± 10.8	0.25
8	**900**	**150**	85.4 ± 18.7	0.13

With 150°C granulation temperature the scale-up was successful, as no significant difference was observed regarding tablet and granule properties between the ones produced at 8 kg/h and 0.5 kg/h. The breaking force was over 80 N (indicating over 0.8 MPa tensile strength) and the tablet friability was under 0.3%. Finally, the immediate release dissolution testing of the tablets produced with these process parameters (8 kg/h and 150°C) was also carried out. The dissolution rate was adequate, and the tablets were immediate-release tablets like the ones produced at 0.5 kg/h (Figure 12). Thus, the scale-up to a production speed, that is 16 times faster than the original was successful.

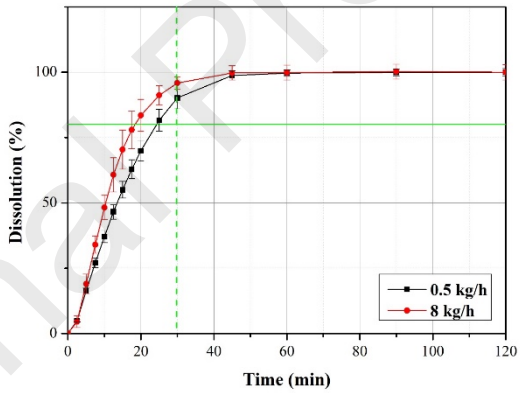


Figure 12: Investigation of the dissolution of the tablets produced with different production feeds (900 mL distillated water dissolution medium, 37±0.5°C, 100 rpm, paddle method, 90 mg API content, n = 3).

4. Conclusions

A fully continuous powder-to-tablet line based on twin-screw melt granulation was developed. The poor flow and compression properties of the initial powder mixture of API and granulation excipients were improved significantly, as well as the poor tablet properties. Therefore, adequate tablets were produced with excellent friability, increased breaking force, and immediate release dissolution. The different production steps (including feeding, granulation, cooling, milling and tablet pressing) were connected and synchronized. The line was also easily scalable: the scale up from 0.5 kg/h to 8 kg/h could be carried out with the same equipment, the previous good powder and tablet properties could be reached.

Our research showed the benefits of both TSMG and CM, and how easily a continuous line can be developed and operated successfully. Moreover, with the applied line, convenient scale-up could be achieved up to 16 times the initial production speed with minimal changes in the process parameters. It further demonstrated the advantages of CM, as the need for different equipment and, more importantly, separate optimization for the different scale experiments – which is almost always necessary during batch production – can be eliminated.

Acknowledgments

This research was supported from grant by National Research, Development and Innovation Office of Hungary (grant number: FK-132133). The scientific research publicized in this article was reached with the sponsorship of Gedeon Richter Talentum Foundation in framework of Gedeon Richter Excellence PhD Scholarship of Gedeon Richter. This project was supported by the ÚNKP-22-3-I-BME-182 and ÚNKP-22-5-BME-301 New National Excellence Program of the Ministry for Culture and Innovation from the source of the National Research, Development and Innovation Fund. This paper was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Science. Project no. TKP-9-8/PALY-2021 has been implemented with the support provided by the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-EGA funding scheme.

Declarations of interest: none.

References

[1] S.D. Schaber, D.I. Gerogiorgis, R. Ramachandran, J.M.B. Evans, P.I. Barton, B.L. Trout, Economic analysis of integrated continuous and batch pharmaceutical manufacturing: A case study, Ind. Eng. Chem. Res. 50 (2011) 10083–10092. https://doi.org/10.1021/ie2006752.

[2] J.S. Srai, T. Harrington, L. Alinaghian, M. Phillips, Evaluating the potential for the continuous processing of pharmaceutical products-a supply network perspective, Chem. Eng. Process. Process Intensif. 97 (2015) 248–258. https://doi.org/10.1016/j.cep.2015.07.018.

[3] J.S. Srai, C. Badman, M. Krumme, M. Futran, C. Johnston, Future supply chains enabled by continuous processing-opportunities and challenges May 20-21, 2014 continuous manufacturing symposium, J. Pharm. Sci. 104 (2015) 840–849. https://doi.org/10.1002/jps.24343.

[4] S.L. Lee, T.F. O'Connor, X. Yang, C.N. Cruz, S. Chatterjee, R.D. Madurawe, C.M.V. Moore, L.X. Yu, J. Woodcock, Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production, J. Pharm. Innov. 10 (2015) 191–199. https://doi.org/10.1007/s12247-015-9215-8.

[5] K. Plumb, Continuous processing in the pharmaceutical industry: Changing the mind set, Chem. Eng. Res. Des. 83 (2005) 730–738. https://doi.org/10.1205/cherd.04359.

[6] L. Rogers, K.F. Jensen, Continuous manufacturing-the Green Chemistry promise?, Green Chem. 21 (2019) 3481–3498. https://doi.org/10.1039/c9gc00773c.

[7] G. Allison, Y.T. Cain, C. Cooney, T. Garcia, T.G. Bizjak, O. Holte, N. Jagota, B. Komas, E. Korakianiti, D. Kourti, R. Madurawe, E. Morefield, F. Montgomery, M. Nasr, W. Randolph, J.L. Robert, D. Rudd, D. Zezza, Regulatory and quality considerations for continuous manufacturing May 20-21, 2014 continuous manufacturing symposium, J. Pharm. Sci. 104 (2015) 803–812. https://doi.org/10.1002/jps.24324.

[8] H. Leuenberger, New trends in the production of pharmaceutical granules: Batch versus continuous processing, Eur. J. Pharm. Biopharm. 52 (2001) 289–296. https://doi.org/10.1016/S0939-6411(01)00199-0.

[9] G. Fülöp, A. Domokos, D. Galata, E. Szabó, M. Gyürkés, B. Szabó, A. Farkas, L. Madarász, B. Démuth, T. Lendér, T. Nagy, D. Kovács-Kiss, F. Van der Gucht, G. Marosi, Z.K. Nagy, Integrated twin-screw wet granulation, continuous vibrational fluid drying and milling: A fully continuous powder to granule line, Int. J. Pharm. 594 (2021). https://doi.org/10.1016/j.ijpharm.2020.120126.

[10] B. Démuth, G. Fülöp, M. Kovács, L. Madarász, M. Ficzere, Á. Köte, B. Szabó, B. Nagy, A. Balogh, K. Csorba, G. Kaszás, T. Nagy, A. Bódis, G. Marosi, Z.K. Nagy, Continuous manufacturing of homogeneous ultralow-dose granules by twin-screw wet granulation, Period. Polytech. Chem. Eng. 64 (2020) 391–400. https://doi.org/10.3311/PPch.14972.

[11] B.K. Almutairy, E.S. Khafagy, A. Alalaiwe, M.F. Aldawsari, S.M. Alshahrani, B.B. Alsulays, A.S. Alshetaili, S.M. Alshehri, M.H. Fayed, Enhancing the poor flow and tableting problems of high drug-loading formulation of canagliflozin using continuous green granulation process and design-of-experiment approach, Pharmaceuticals. 13 (2020) 1–17. https://doi.org/10.3390/ph13120473.

[12] G. Dalziel, E. Nauka, F. Zhang, S. Kothari, M. Xie, Assessment of granulation technologies for an API with poor physical properties, Drug Dev. Ind. Pharm. 39 (2013) 985–995. https://doi.org/10.3109/03639045.2012.687744.

[13] J. Kowalski, O. Kalb, Y.M. Joshi, A.T.M. Serajuddin, Application of melt granulation technology to enhance stability of a moisture sensitive immediate-release drug product, Int. J. Pharm. 381 (2009) 56–61. https://doi.org/10.1016/j.ijpharm.2009.05.043.

[14] J.F. Kelleher, A.M. Madi, G.C. Gilvary, Y.W. Tian, S. Li, A. Almajaan, Z.S. Loys, D.S. Jones, G.P. Andrews, A.M. Healy, Metformin Hydrochloride and Sitagliptin Phosphate Fixed-Dose Combination Product Prepared Using Melt Granulation Continuous Processing Technology, AAPS PharmSciTech. 21 (2020) 1–14. https://doi.org/10.1208/s12249-019-1553-2.

[15] J.P. Lakshman, J. Kowalski, M. Vasanthavada, W.-Q. Tong, Y.M. Joshi, A.T.M. Serajuddin, Application of Melt Granulation Technology to Enhance Tabletting Properties of Poorly Compactible High-Dose Drugs, J. Pharm. Sci. 100 (2011) 1553–1565. https://doi.org/10.1002/jps.

[16] V.R. Kallakunta, R. Tiwari, S. Sarabu, S. Bandari, M.A. Repka, Effect of formulation and process variables on lipid based sustained release tablets via continuous twin screw granulation: A comparative study, Eur. J. Pharm. Sci. 121 (2018) 126–138.

https://doi.org/10.1016/j.ejps.2018.05.007.

[17] T. Monteyne, P. Adriaensens, D. Brouckaert, J.P. Remon, C. Vervaet, T. De Beer, Stearic acid and high molecular weight PEO as matrix for the highly water soluble metoprolol tartrate in continuous twin-screw melt granulation, Int. J. Pharm. 512 (2016) 158–167. https://doi.org/10.1016/j.ijpharm.2016.07.035.

[18] D.C.T. Tan, W.W.L. Chin, E.H. Tan, S. Hong, W. Gu, R. Gokhale, Effect of binders on the release rates of direct molded verapamil tablets using twin-screw extruder in melt granulation, Int. J. Pharm. 463 (2014) 89–97. https://doi.org/10.1016/j.ijpharm.2013.12.053.

[19] J.M. Keen, C.J. Foley, J.R. Hughey, R.C. Bennett, V. Jannin, Y. Rosiaux, D. Marchaud, J.W. McGinity, Continuous twin screw melt granulation of glyceryl behenate: Development of controlled release tramadol hydrochloride tablets for improved safety, Int. J. Pharm. 487 (2015) 72–80. https://doi.org/10.1016/j.ijpharm.2015.03.058.

[20] H.K. Mamidi, S. Palekar, P.K. Nukala, S.M. Mishra, M. Patki, Y. Fu, P. Supner, G. Chauhan, K. Patel, Process optimization of twin-screw melt granulation of fenofibrate using design of experiment (DoE), Int. J. Pharm. 593 (2021) 120101. https://doi.org/10.1016/j.ijpharm.2020.120101.

[21] K.E. Steffens, K.G. Wagner, Dissolution enhancement of carbamazepine using twin-screw melt granulation, Eur. J. Pharm. Biopharm. 148 (2020) 77–87. https://doi.org/10.1016/j.ejpb.2020.01.006.

[22] R. Shaikh, G.M. Walker, D.M. Croker, Continuous, simultaneous cocrystallization and formulation of Theophylline and 4-Aminobenzoic acid pharmaceutical cocrystals using twin screw melt granulation, Eur. J. Pharm. Sci. 137 (2019) 104981. https://doi.org/10.1016/j.ejps.2019.104981.

[23] W. Grymonpré, G. Verstraete, V. Vanhoorne, J.P. Remon, T. De Beer, C. Vervaet, Downstream processing from melt granulation towards tablets: In-depth analysis of a continuous twin-screw melt granulation process using polymeric binders, Eur. J. Pharm. Biopharm. 124 (2018) 43–54. https://doi.org/10.1016/j.ejpb.2017.12.005.

[24] S. Sacher, S. Celikovic, J. Rehrl, J. Poms, M. Kirchengast, J. Kruisz, M. Sipek, S. Salar-Behzadi, H. Berger, G. Stark, M. Horn, J.G. Khinast, Towards a novel continuous HME-Tableting line: Process development and control concept, Eur. J. Pharm. Sci. 142 (2020) 105097. https://doi.org/10.1016/j.ejps.2019.105097.

[25] Y. Qiu, Y. Gong, A. Ruggles, J.A. Baird, K. Chwalisz, C. Owens, J.W. Thomas, J. Castelli-Haley, K. Gordon, M.C. Snabes, A.M. Soliman, O.A. Flores, R. Jain, J. Wing-Keung Ng, J.D. North, H. Palac, P.M. Peloso, L.A. Williams, H. Zu, Y. Hu, US 2019 / 0054027 A1 Solid Pharmaceutical formulations forb treating endometrosis, uterine fibrosis, polycystic ovary syndrome or adenomyosis, 2019.

[26] M. Castro, E. Kerwin, D. Miller, A. Pedinoff, L. Sher, P. Cardenas, B. Knorr, D. Lawrence, D. Ossa, W. Wang, J.F. Maspero, Efficacy and safety of fevipiprant in patients with uncontrolled asthma: Two replicate, phase 3, randomised, double-blind, placebo-controlled trials (ZEAL-1 and ZEAL-2), EClinicalMedicine. 35 (2021)

100847. https://doi.org/10.1016/j.eclinm.2021.100847.

[27] C. Vicente Martin, S. Stocker, M. Bautista, V. Rogue, C. Steib-Lauer, H.G. Häcker, D. Spickermann, S. Hirsch, S.S. Dhareshwar, Commercial scale transfer of a twin-screw melt granulation process for high drug load fevipiprant tablets, Drug Dev. Ind. Pharm. 48 (2022) 211–225. https://doi.org/10.1080/03639045.2022.2104307.

[28] H.H. Hausner, Friction conditions in a mass of metal powder, Int. J. Powder Met. 3 (1967) 7–13.

[29] R.L. Carr Jr, Evaluating flow properties of solids, Chem. Eng. 18 (1965) 163–168.

[30] V.A. Belousov, Selection of optimum pressing pressures in tablettizing medical powders, Khim. Farm. Zh. 10 (1976) 105–111.

[31] J. Mužíková, S. Muchová, A. Komersová, V. Lochař, Compressibility of tableting materials and properties of tablets with glyceryl behenate, Acta Pharm. 65 (2015) 91–98. https://doi.org/10.1515/acph-2015-0006.

[32] K.G. Pitt, M.G. Heasley, Determination of the tensile strength of elongated tablets, Powder Technol. 238 (2013) 169–175. https://doi.org/10.1016/j.powtec.2011.12.060.

[33] The United States Pharmacopeial Convention, USP 1216 Tablet Friability, The United States of Pharmacopoeia. 32 (2016) 22–24. http://www.usppf.com/pf/pub/index.html.

[34] M. Levina, C.. R. Cunningham, The effect of core design and formulation on the quality of film coated tablets, Pharm. Technol. Eur. 17 (2005) 29–37.

[35] S.C. Porter, Preventing Film Coating Problems by Design, Pharm. Technol. 40 (2016) 42–45.

[36] U.I. Leinonen, H.U. Jalonen, P.A. Vihervaara, E.S.U. Laine, Physical and lubrication properties of magnesium stearate, J. Pharm. Sci. 81 (1992) 1194–1198. https://doi.org/10.1002/jps.2600811214.

[37] Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances Guidance for Industry, (2018). fda.gov.

Integrated continuous melt granulation-based powder-to-tablet line: process investigation and scale-up

Petra Záhonyi[1]; Fekete Dániel[1]; Edina Szabó[1]; Lajos Madarász[1]; Árnika Fazekas[1]; Anna Haraszti[1]; Zsombor K. Nagy[1*]

[1]1Department of Organic Chemistry and Technology, Faculty of Chemical Technology and Biotechnology, Budapest University of Technology and Economics, Műegyetem rkp. 3., H-1111 Budapest, Hungary

*Corresponding author: Tel: +36 1 463-1424; E-mail: zsknagy@oct.bme.hu

Highlights:

- Fully continuous melt granulation-based powder-to-tablet line was developed
- The flowability and tabletability were improved significantly
- Caffeine-loaded tablets with increased breaking force (from 15 N to over 80 N) were produced
- The tablets had excellent friability and immediate release dissolution
- Scale-up production (from 0.5 kg/h to 8 kg/h) was accomplished with the same system

Integrated continuous melt granulation-based powder-to-tablet line: process investigation and scale-up

Petra Záhonyi[1]; Fekete Dániel[1]; Edina Szabó[1]; Lajos Madarász[1]; Árnika Fazekas[1]; Anna Haraszti[1]; Zsombor K. Nagy[1]*

[1]1Department of Organic Chemistry and Technology, Faculty of Chemical Technology and Biotechnology, Budapest University of Technology and Economics, Műegyetem rkp. 3., H-1111 Budapest, Hungary

*Corresponding author: Tel: +36 1 463-1424; E-mail: zsknagy@oct.bme.hu

Abstract

In the last decades, continuous manufacturing (CM) has become a research priority in the pharmaceutical industry. However, significantly fewer scientific researches address the investigation of integrated, continuous systems, a field that needs further exploration to facilitate the implementation of CM lines. This research outlines the development and optimization of an integrated, polyethylene glycol aided melt granulation-based powder-to-tablet line that operates fully continuously. The flowability and tabletability of a caffeine-containing powder mixture were improved through twin-screw melt granulation resulting in the production of tablets with improved breaking force (from 15 N to over 80 N), excellent friability, and immediate release dissolution. The system was also conveniently scaleable: the production speed could be increased from 0.5 kg/h to 8 kg/h with only minimal changes in the process parameters and using the same equipment. Thereby the frequent challenges of scale-up can be avoided, such as the need for new equipment and separate optimization.