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Continuous integrated production of glucose granules with enhanced flowability and tabletability

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ABSTRACT

Glucose is widely used in both the food and pharmaceutical industry. However, the application of industrially crystallized glucose in solid dosage forms is challenged by its poor flowability and tabletability. To improve these characteristics continuous twin-screw granulation was tested, which has the potential to be integrated into the continuous production of solid glucose from corn starch. A completely continuous manufacturing line (including drying and milling) was developed and the different production steps were examined and synchronized. Our line was supplemented with an in-line applicable near-infrared spectroscopic probe to monitor the moisture content of the milled granules in real-time. The flowability and tabletability of the powder improved significantly, and tablets with acceptable breaking force (greater than 100 N) could be prepared from the granules. The developed continuous line can be easily installed into the industrial solid glucose production process resulting in pure glucose granules with adequate flow properties and tabletability in a simple, continuous and efficient way.

1. Introduction

In the pharmaceutical and food industry compressed tablets, which represent the most popular dosage form thanks to their great endurance, easy packaging and simple (no medical supervision requiring) dosage, are most commonly prepared by direct compression. The direct route for tablet preparation consists of only two main production steps: the blending of the active pharmaceutical ingredients (APIs) and the excipient(s), and the compacting of the mixture by a tablet press. (Silambarasan et al., 2015).

During the direct process, an important factor is the flowability of the powders, which affects the filling of the dies during tableting. Flowability is influenced by numerous conditions, including friction, electrostatic and molecular forces, as well as the shape and size distribution of the particles (Gad, 2007). Besides the adequate flow characteristics, the tabletability of the powders during the tableting is also important. The first element of tableting is the compacting of the powder, which is followed by simultaneous plastic and elastic deformation. Plastic deformation is the beneficial deformation pattern, however, in practice, both of them occur. Elastic deformation makes the crystals try to return to their original form resulting in increased tension and decreased mechanical stability, which can cause the laminar breakage of the tablets, a phenomenon called "capping" (Rana and Hari Kumar, 2011). Materials with the aforementioned behavior have poor compression properties and are not favorable for tableting, thus need to be pre-processed prior. Apart from that, another undesirable phenomenon is the breakage of the crystals during compressing, which prevents the formation of sufficient converging forces. Measuring the tensile strength of the tablets provides valuable information about the robustness of the tablets, whether they would be suitable for further processing (including film coating, packing, transport and handling by the patient). As a general guide, tensile strength of 1.7 MPa at a solid fraction of 0.9 is required (Heasley and Pitt, 2013). A simpler way to characterize the hardness of the tablets is to measure the lowest sufficient force to break the tablets ("breaking force"). Although breaking force is not a suitable parameter for comparing tablets of different sizes and shapes (as the parameter is size-dependent), it is used to determine the mechanical strength of pharmaceutical tablets. The use of the parameter is convenient, as it can be easily and directly measured, and a strong correlation is present between the tensile strength and breaking force. (Gad, 2007; USP35/NF30, 2011) A force of 40 N is considered to be the minimum requirement for oral tablets, however, it should be higher in case of sustained or retarded release tablets and lower in case of chewable tablets. (Gad, 2007; Ganesh and Deshpande, 2011).

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Usually, a correlation can be observed between the breaking force of the tablets and the applied compression force, however in some cases (because of the poor tabletability of the initial powder) after a maximum value, the increasing compression force results in weaker tablets that break horizontally, resulted in the previously mentioned "capping"(Gad, 2007). In some cases, the use of excipient can facilitate the direct compression, otherwise, indirect tablet preparation could be used by adding granulation as an extra downstream processing step into the manufacturing line. Besides improving the flow properties and tabletability granulation can also prevent segregation, making it applicable for both very high (Almutairy et al., 2020) and low (Démuth et al., 2020; Fülöp et al., 2021) drug load dosage forms. Out of the three main types of the technology (dry (Kleinebudde, 2004; Jannat et al., 2016), wet (Dhenge et al., 2012), and melt (Royce et al., 1996)), wet granulation is the most widely used. The procedure can be carried out both in batch production (high shear (Saleh et al., 2005) or fluidized bed wet granulation (Boerefijn and Hounslow, 2005)) and continuously (e.g. twin-screw wet granulation (TSWG) (Keleb et al., 2004)).

Many research and successful applications of TSWG have been published since its first appearance in 1986 (Gamlen and Eardley, 1986; Lindberg et al., 1987; Keleb, 2004; Seem et al., 2015), as well as numerous investigations of the effects of process parameters on product quality (Lindberg et al., 1988a; Lindberg et al., 1988b; Dhenge et al., 2010; Dhenge et al., 2012; El Hagrasy et al., 2013; Vercruysse et al., 2015; Meier et al., 2017; Portier et al., 2020). One of the most important factors is the screw configuration of the equipment, as it determines the course of the processes in the granulator. The geometry determines the properties of the screws, the two most common types of screw elements are the conveying elements (CEs) and kneading elements (KEs), both consisting of many different subtypes (Seem et al., 2015; Portier et al., 2020).

In recent years the TSWG has gotten more attention with the spread of continuous manufacturing (CM) and continuous technologies. Thanks to its many advantages, CM has become a widespread goal in most fields of the chemical industry in the past decades. However, several challenges of the pharmaceutical industry made the shift from batch production a little delayed in that field, despite the many benefits of these technologies. Nevertheless, as both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) have encouraged the development and helped the installation of these technologies by issuing guidelines, more and more researches are in process (Nasr et al., 2017; Korhonen, 2020).

In order to design successful end-to-end CM lines, several process steps need to be connected. Although numerous continuous technologies (including TSWG) were studied extensively, the integration of the technologies is still challenging, with significantly fewer publications in the field (Domokos et al., 2021). Furthermore, CM lines also need to be supplemented with real-time process monitoring to ensure the quality of the final product, therefore are usually paired with in-line Process Analytical Technologies (PAT). ("Food and Drug Administration, 2004. Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.," n.d.) (Vanhoorne and Vervaet, 2020) Various analytical tools – such as near-infrared (NIR) or Raman spectroscopy – are suitable for in-line measurement, therefore can enable the real-time monitoring and control of the critical process parameters. Although some publications (Fonteyne et al., 2013; Martinetz et al., 2018; Fülöp et al., 2021) deal with the integration of the TSWG and the implementation of PAT tools into the system, further research is still in need.

The glucose monohydrate (dextrose), in addition to its wide application in the food industry, is used as a diluent in the pharmaceutical industry. The most commonly used crystalline form is the α-D-glucose monohydrate, produced by acidic or enzymatic hydrolysis of starch, followed by slow crystallization. During the next step of the industrial process, the crystals are separated from the mother liquid by centrifugation, and approximately 14 w/w% water content is reached. It is followed by a drying step to reduce to water content to 8.5–9 w/w%, which is around the theoretical moisture content of the glucose monohydrate (9.08 w/w%) (Schenck, 2006).

The abovementioned industrial crystallization process is widely spread, however, the further usage of the prepared glucose powder has several challenges, needing to be addressed. The powder is hard to handle, has poor flow properties, can pack during storage or transport, and arch during feeding. Furthermore many problems occur at tablet compression as well. The pressed tablets are fragile (break under less than 40 N breaking force), caused by the breakage of the elongated crystals, which results in weak spots and prevent the formation of suitably secure bonds. Moreover, the particle size of prepared glucose powder is usually relatively small – contains a significant fine fraction with particles below 100 μm – causing poor flowability, troublesome and inconsistent loading, thus fluctuant tablet weight. (Moraly et al., 2002) It is generally accepted that the glucose requires mixing of further formulation excipients to improve the flow properties and tabletability, therefore, it became a suitable basis for adequate tablets. The solution to the aforementioned challenge could ease the further use of the glucose powder, enable the effective pressing of the tablets, and widen its application field. Many possible solutions have been investigated in the past decades ("Non-compacting solid anhydrous dextrose - prepd. by shearing and cooling conc. syrup, casting, dehydrating and grinding," 1977; Short and Verbanac, 1978; Moraly et al., 2002; Brys and Meeus, 2008) however most of the processes are operated in batch production and extra excipients are needed in the composition. Despite the examples earlier, because of the disadvantages of the particular technologies, an unsatisfied need is apparent to develop a simple and effective technology suited to convert the glucose monohydrate into a powder form with excellent flow properties and tabletability, preferably with a 100 % glucose content and crystalline purity. Such an invention would make the tablet compression of the powder more effective, improve the quality of the tablets, prevent capping, and enable the formulation of tablets with higher API content, therefore ease its production and widen its application both in the pharmaceutical and food industry.

The main goal of the current research was to develop a scalable technology to enhance the flowability and tabletability of glucose by granulation using a fully continuous, integrated processing line based on TSWG, which can be supplemented with real-time process monitoring via NIR spectroscopy. Furthermore, we aimed to develop a system that can be easily inserted into the widely applied industrial crystalline glucose production lines to achieve a simple and complete process for the production of easy-to-handle glucose granules with 100 % glucose content.

2. Materials and methods

2.1. Materials

α-D glucose monohydrate was obtained from Hungrana (*Szabadegyháza, Hungary*) and magnesium-stearate (used as lubricant) was purchased from Sigma-Aldrich (*Budapest, Hungary*). Distilled water was applied as granulation liquid.

2.2. Continuous integrated granule production line

The production of the glucose granules was carried out in an integrated, continuous manufacturing line (Fig. 1) consisting of a twin-screw wet granulator, fluidized bed dryer, and continuous mill. The further transportation of the milled granules was carried out by a vibratory conveying feeder, whilst the probe of a NIR spectrometer was placed above (for in-line process monitoring).

2.2.1. Feeding

The solid glucose monohydrate was fed into the hopper of the granulator by a twin-screw gravimetric feeder (DDW-MD0-MT type,

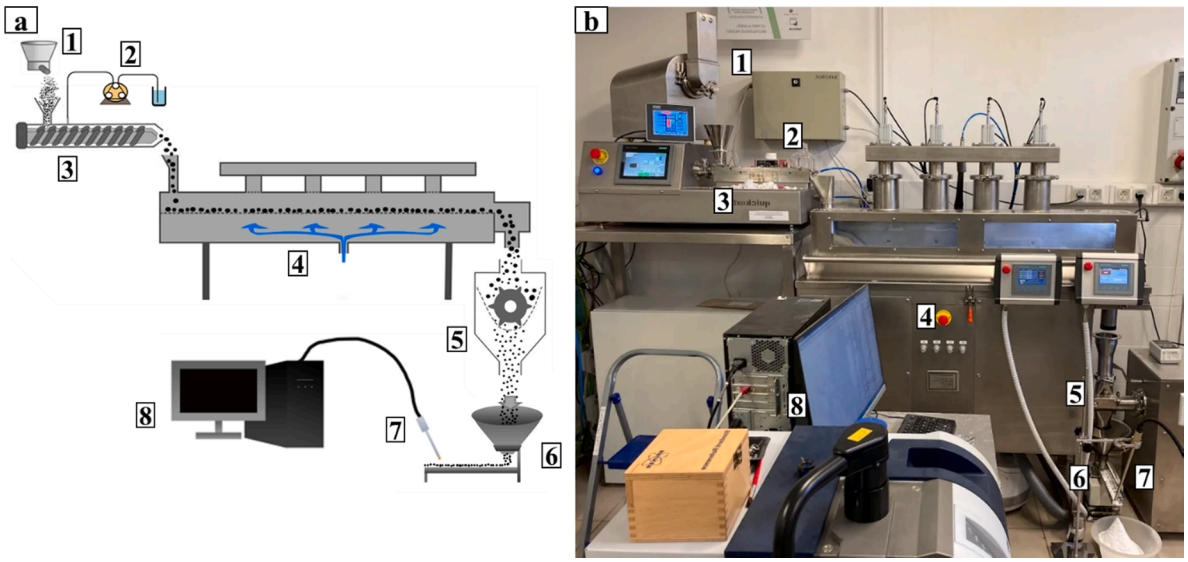

Fig. 1. Schematic drawing. (a) and photo (b) of the continuous manufacturing line (1) gravimetric feeder; (2) peristaltic pump; (3) twin-screw granulator; (4) fluidized bed dryer; (5) oscillating mill; (6) vibratory conveying feeder; (7) NIR probe; (8) computer.

Brabender Technologie, Duisburg, Germany) with a constant feeding rate of 1 kg/h, while the distilled water was added to the second zone of the granulator through a silicone tube with 3.1 mm inner diameter by a peristaltic pump (Watson-Marlow 120 U, Wilmington, MA, US). During the industrial crystallization of the glucose, the last processing step before drying is the centrifugation of the glucose syrup, resulting in 14 w/w% water containing glucose (Schenck, 2006). To make our process easily integrable, we aimed to design a system based on the same water-glucose ratio as the centrifugated material, thus the drying step could be completely skipped, and the remaining water content can be used as granulation liquid. Therefore the initial water content of the used dry glucose monohydrate (including both the crystalline water and additional moisture bond to the surface) was measured by loss on drying (LOD) measurements prior to granulation (revealing that the solid glucose already contained 8.5 w/w% water) and the liquid/solid (L/S) ratio – the feeding rate of the liquid and solid feeders – was adjusted to that, to provide 14 w/w% water in the granulator. Accordingly, the experiments were carried out with a constant 6.4 w/w% L/S ratio.

The exact feeding rate of the peristaltic pump was determined by our previous calibration and was fixed at that proper value through all our experiments. Additionally, experiments with priory wetted glucose were also carried out, where the proper amount of water was added to the dry glucose (to reach 14 % water content), and the wet material was fed into the hopper manually. In that case, the peristaltic pump was not needed.

2.2.2. Granulation

The wet granulation was accomplished in a multifunctional parallel twin-screw granulator (TS16 QuickExtruder, *2000 ltd, Hungary*) with a 16 mm screw diameter and 40 cm length consisting of conveying, kneading, and reverse conveying elements. Experiments were carried out with two screw configurations shown in Fig. 2 – differing only in a reverse conveying element. The granulator was operated in wet granulation mode with 100–200 rpm (revolutions per minute) screw speed, and consisted of 4 heating zones, where the temperature could be individually controlled.

2.2.3. Drying

The granulation was followed by either air-drying on a tray at room

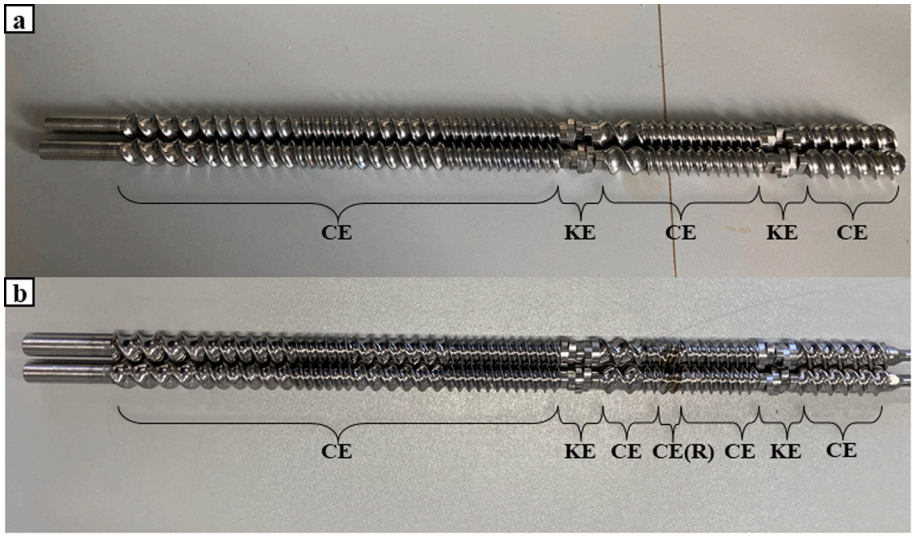

Fig. 2. Screw configurations of the granulator. (a) with only conveying elements (CEs) and kneading elements (KEs) (b) with CEs, KEs and reverse conveying elements (CE_Rs).

temperature (1–3 days) or a continuous horizontal fluidized bed dryer (*Quick 2000 ltd., Hungary*). During the application of the fluidized bed dryer, the transportation of the material was carried out by a perforated metal belt via vibration with 50 Hz intensity. The granules were dried by a vertical airflow, which passed through the perforated conveying belt without interfering with the transport of the granules. The continuous dryer was divided into four drying zones with separate filter bags and separately alterable settings (airflow and temperature). The main part of the drying took place in the first three zones while the last zone was used for cooling, as only the airflow could be adjusted therein, but not the temperature of the supply air. In our experiments, supply air with a flow rate of 120 l/min and temperature varying between 25 and 95 °C was used.

2.2.4. Milling

Next, the dried material was transported into a continuous milling device *(Quick 2000 ltd., Hungary*), operated in oscillating mode with 200 1/min oscillation speed. A sieve with a size of 0.8 mm diameter was applied during the milling, where the large granules were broken down.

2.2.5. Process parameters of the performed experiments

The goal of the preliminary experiments was to determine the adequate granulation parameters before starting the completely continuous production. Therefore, during these experiments, air drying on trays was used, and only the effects of the granulation parameters were evaluated. First, the screw configuration illustrated in Fig. 2a was used, while the granulation temperature (from 60 to 80 °C) and the rotation speed of the granulator (50 to 200 rpm) were changed. As these experiments led to poor results, the screw configuration illustrated in Fig. 2b was used next (Table 1). During experiments 1–6 (with the granulation still coupled with air drying), the effect of the granulation temperature was examined. It was followed by experiments using the adequate granulation temperature coupled with continuous drying on various drying temperatures (experiments 7–10). Finally, scale-up experiments were also performed with the feeding of the previously wetted glucose.

Table 1
Process parameters of the performed experiments with Fig. 2b screw configuration.

Experiment	Feed rate of glucose	Rotation speed of granulator	Granulation temperature	Drying
1	1 kg/h	100 rpm	55 °C	air drying for 3 days
2	1 kg/h	100 rpm	60 °C	air drying for 3 days
3	1 kg/h	100 rpm	65 °C	air drying for 3 days
4	1 kg/h	100 rpm	55 °C	air drying for 1 day
5	1 kg/h	100 rpm	60 °C	air drying for 1 day
6	1 kg/h	100 rpm	65 °C	air drying for 1 day
7	1 kg/h	100 rpm	55 °C	continuous drying at 25 °C
8	1 kg/h	100 rpm	55 °C	continuous drying at 60 °C
9	1 kg/h	100 rpm	55 °C	continuous drying at 85 °C
10	1 kg/h	100 rpm	55 °C	continuous drying at 95 °C
11	3 kg/h*	200 rpm	55 °C	continuous drying at 85 °C
12	3 kg/h*	200 rpm	50 °C	continuous drying at 85 °C

* the glucose and the granulation liquid were previously mixed together.

2.2.6. Near-infrared spectroscopy (NIR)

Supplementing the continuous line, a Bruker MPA II Multi Purpose Fourier-transformed Near Infrared (FT-NIR) Analyzer (Bruker OPTIK GmbH, Germany) with a high intensity NIR source (Tungsten) and PbS detector was used as a PAT tool for monitoring the continuous granulation via the in-line detection of the moisture content of the dried and milled granules. A vibratory conveying feeder with a U-shaped channel (Fritsch Laborette 24, Idar-Oberstein, Germany) was placed under the continuous milling device. The NIR probe was positioned above the channel thus the spectra could be collected directly from the moving material. The spectrum was collected in reflection mode in the 4000–12,500 cm^{-1} spectral range with 8 cm^{-1} resolution and 8 scans accumulated with double-sided, forward–backward acquisition mode. For the spectrum accumulation, OPUS® 7.5 software (Burker Optik GmbH, Germany) was used, and the real-time evaluation of the spectra was carried out with MATLAB 9.7. program (MathWorks, USA) and PLS Toolbox 8.7.1. (Eigenvector Research, USA). Two Matlab scripts developed in-house (Nagy et al., 2017; Gyürkés et al., 2020) were used for the real-time determination of the moisture content: one to import the collected spectra into the Matlab program during the granulation process, and one to perform the chemometric analysis of the spectra using Partial Least Squares (PLS) model developed in PLS Toolbox.

The calibration data were gathered by operating our system with varying process parameters while continuously collecting the spectra in real-time. The granulation temperature, the rotation speed of the granulator, the drying temperature and the L/S ratio were altered in a wide range, thus different moisture contents could be reached. Samples (of approximately 2 g) were taken manually for off-line LOD measurements as a reference method to determine their residual moisture content; therefore, the correlation between the spectra and the moisture content could be determined. Altogether 45 spectra were collected and a residual moisture content range of approximately 6 % to 10 % was covered. The spectra of the completely dry materials were also collected off-line from samples taken out of the drying oven and were used as 0 % calibration values.

2.2.6.1. LOD measurements as a reference method. The amount of the remaining water in the dried and milled granules was determined by LOD (% w/w) measurements. After the continuous manufacturing, the samples were put in an oven for 24 h at 105 °C. An analytical scale was used to measure the mass of the dried and milled granules before and after 24 h of drying, and the LOD was calculated from the difference. Under these conditions, the glucose-monohydrate fully converted into anhydrous form thus the crystal water content was also measured.

2.3. Multivariate data analysis

The calibration curve was determined with the PLS method using the NIR spectra as the independent variable and the moisture content (determined by the LOD measurements) as the dependent variable. The spectra were preprocessed during the building of the PLS model using normalization with Standard Normal Variate (SNV) method and mean centering. For variable selection, interval PLS was used in forward mode with 30 variables per interval, and venetian blinds cross validation method was also applied with 10 data splits and 1 left-out sample per blind. The number of latent variables was chosen based on the root square error of cross-validation ($RMSE_{CV}$), as its value was minimized. The model was evaluated by the coefficient of determination for calibration, cross-validation and prediction (R^2_C, R^2_{CV}, R^2_P), together with the root mean square error of calibration, cross-validation, and prediction

($RMSE_C$, $RMSE_{CV}$, $RMSE_P$). The limit of detection (LoD) and limit of quantification (LoQ), calculated by Eqs. (1) and (2) (De Carvalho Rocha et al., 2012), were also used to characterize the performance of the model.

$$LoD = \frac{3.3 \times \sigma}{S} \quad (1)$$

$$LoQ = \frac{10 \times \sigma}{S} \quad (2)$$

(In the equations, σ indicates the standard deviation (SD) and S is the slope calculated from the measured and predicted concentrations.).

2.4. Characterization of the milled granules

2.4.1. Particle size analysis

The particle size distribution of the milled granules was measured by a Malvern Mastersizer 2000 type laser diffractometer (Malvern Instruments ltd., Worchestershire, UK). The granules were transported into the equipment with a vibratory feeder with 75 % intensity of the vibrational amplitude. The measurement took 30 s with 30 s of background recording. During the measurements, 1.5 bar pressure was applied. The $d_{(0.5)}$ values were used to characterize the particle size, which indicates the 50 % cumulative undersize of the volumetric distribution.

2.4.2. Morphology analysis

JEOL JSM 6380LA (JEOL, Tokyo, Japan) type scanning electron microscope (SEM) was used for examining the morphology and size of the milled granules. The investigated specimen was fixed with conductive double-sided carbon adhesive tape and sputtered with gold to avoid electrostatic charging. The measurements were carried out in high vacuum, with 11 mm working distance and 15 kV accelerating voltage.

Amplival Carl Zeiss type (Jena, Germany) polarized optical microscopy (POM) was also utilized for examining the morphology, furthermore to investigate the crystalline form of the milled granules. The polarized optical microscope was equipped with an OLYMPUS C4040 Z type camera, and DP-Soft software was used for the evaluation. For the measurements, the specimen was dispersed in silicone oil to avoid the aggregation of the particles.

2.4.3. Flow properties

The flow properties of the powder were examined by measuring the required time for samples of 100 g powder to flow out of a funnel with 10 or 15 mm diameter. The standard is the 10 mm diameter, however, the initial unprocessed glucose monohydrate only flow through that funnel with powerful agitation and shaking, therefore a funnel with 15 mm diameter was also used.

2.4.4. Tableting and characterization of tablets

The tabletability of the powder was evaluated by producing tablets from the processed powder and measuring the breaking force of these tablets. After the continuous manufacturing, the milled granules were compressed in a Dott Bonapace CPR6 eccentric tableting machine (*Limbiate, Italy*) using 14 mm round-shaped punches. The targeted tablet weight was 750 mg, and the tablets were prepared with 22–26 kN compression force. The upper and lower punches were set to comply with these criteria before experiments. The breaking force of the tablets (required minimum force to break the tablets) was measured by a Dr. Schleuniger THP-4 M tablet hardness tester (*Dr. Schleuniger Productronic, Switzerland*), and the breaking force of the tablets was registered.

3. Results and discussion

The main goal of our research was to improve the inadequate flowability and tabletability of the crystalline glucose-monohydrate with a completely continuous system, as the initial powder characteristics were so poor, that the unprocessed powder could not flow through a 10 mm diameter funnel nor could be used to compress tablets with over 45 N breaking force. We aimed to produce granulated glucose with satisfying powder characteristics (able to flow through a 10 mm funnel under 10 s and suitable to be compressed into tablets with over 100 N breaking force) and define the most relevant, essential factors of the operations having the greatest impact on the quality of the final granules.

The complete process, consisting of feeding, granulation, drying, milling and tablet compression, was examined while several factors, including the feeding rate, the temperature of the granulation, the rotation speed of the granulator, and the drying condition were altered to discover the most adequate settings of the production. Afterward, the powder properties (therefore the success of our process) were defined by the breaking force of the produced tablets with the addition of the flowability tests of the granules. The effectiveness of the drying was monitored by measuring the remaining moisture content of the milled granules in real-time with NIR spectroscopy. The complete system was operated continuously, and (besides the dry glucose) was also suitable for processing the still wet, centrifugated glucose produced by the industrial crystallization.

3.1. The characterization of the unprocessed glucose

We started our work with the thorough examination of the initial glucose powder. The macroscopic characteristics of the initial glucose monohydrate were investigated using laser diffraction (Fig. 9). Although the observed average particle size (210.0 ± 4.1 μm) was not too small, the large amount (more than 20 %) of particles under 100 μm prevents the free-flowing of the material. The poor flow properties were confirmed by our next experiments, as from the standard 10 mm diameter wide funnel the powder did not flow through without agitation.

The morphology was examined with POM and SEM (Fig. 3) and lengthy crystals were observed. These crystals – besides worsening the flowability – are rigid and poorly deformable, therefore cannot fit together as smoothly as the granules, but instead break during tableting under higher compression forces resulting in weak spots. These properties negatively affect the tablet properties and lead to fragile tablets, breaking at 40 N force. The breakage of the tablets usually occurred laminarly, a phenomenon called capping.

These are the characteristics that needed to be improved by granulation to achieve our goal.

- The size of the lengthy crystallines needs to be reduced in order to achieve better tabletability (and enable the production of tablets with increased breaking force – only breaking when 100 N or higher breaking force is applied to them).
- The construction of granules with good tabletability needs to be accomplished thus the number of particles under 100 μm is decreased ensuring good flowability.

3.2. Pre-experiments with the twin-screw granulator

Before testing the integrated process, the key element of the procedure, the granulation was investigated in detail. In these experiments, the parts of the continuous manufacturing line (the granulation, the drying, the milling and the tablet compression) were operated and examined separately. The aim of these experiments was to examine the granulation process solely, and find the adequate operation parameters, before testing the integrated, continuous production. Firstly, the configuration without the reverse conveying element (Fig. 2a) was used. Many factors were modified in a wide range, nonetheless the tabletability of the final powder remained poor, and the produced tablets were weak (the breaking force of the tables remained under 60 N or was even lower, thus the improvement was unsatisfactory). It became evident that

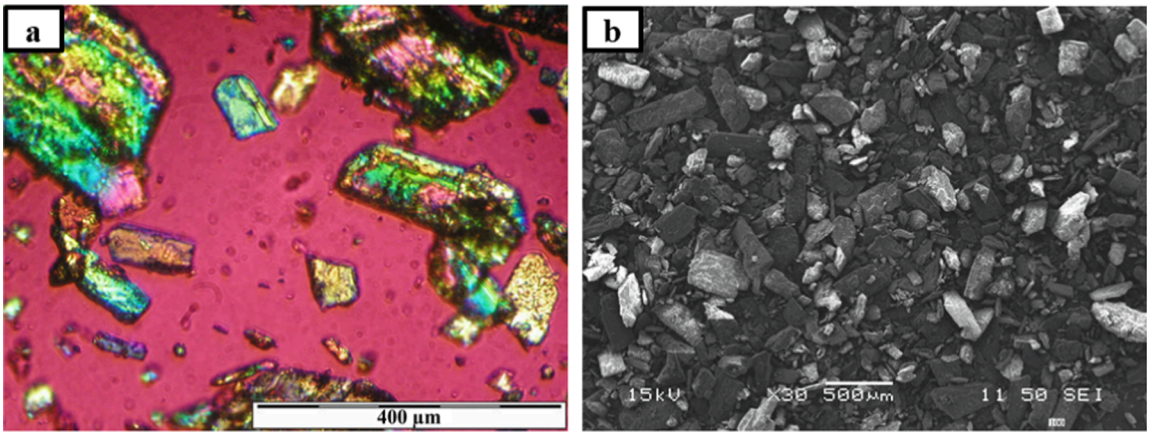

Fig. 3. Polarization optical microscopic and Scanning electron microscopic images of the unprocessed glucose. (a) POM 6,3x magnification; (b) SEM 30 × magnification.

this configuration is not suitable for our goals; therefore, a reverse conveying element was included in the following experiments (Fig. 2b). This element increased the pressure and elongated the residence time in the granulator (measured by the time elapsed between the adding of a coloring agent into the hopper of the granulator and its appearance at the outlet) with 30 s, which is a significant increase, from 40 s to 70 s in case of the 100 rpm rotation speed. For further evaluation, residence time distribution (RTD) could also be measured, however, it was not the focus of our research.

These altered conditions (higher pressure and longer residence time) are believed to lead to the breakage of the previously described long crystals, followed by the aggregation of the particles.

In the first experiments with the Fig. 2b screw configuration (experiments 1–6 illustrated in Table 1) the glucose was fed to the granulator with a constant 1 kg/h feeding and the water was added separately through the feeding rate of the peristaltic pump adjusted to ensure the constant 6.4 w/w% L/S ratio (thus 14 w/w% water) in the granulator. The rotation speed of the granulator was set to 100 rpm, and the temperature of the granulation was examined. The free-flowing granules were dried at room temperature for 1 and 3 days before the milling. It is important to note that with these conditions granulation did not occur under 50 °C as the product remained in powder form, nor above 65 °C – as the product was a completely melt material similar to plasticine. Therefore; the majority of our experiences were carried out within these limits.

With these conditions the lengthy crystals broke prior to tablet compression (during granulation), improving the tabletability of the powder, thus tablets with acceptable breaking force could be produced opposed to the unprocessed glucoseFig. 4.

The lower granulation temperatures positively affected the tabletability of the powder and (after the adequate drying time) resulted in better tablets as shown in Fig. 4. It could have been caused by that the higher temperatures led to the more intense melting of the glucose, thus its later re-crystallization after the granulation process, negatively affecting the tabletability. Even lower temperatures could not be applied, as the flow characteristics of the powder remained unsatisfactory.

These experiences also confirmed the importance of the drying step,

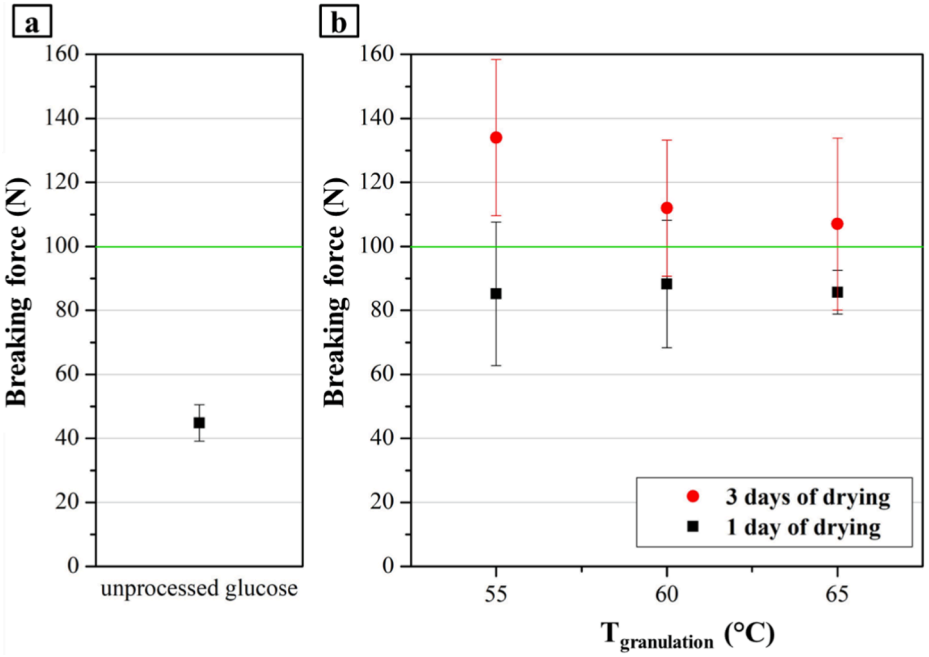

Fig. 4. The breaking force of the tablets compressed from the (a) unprocessed and (b) granulated and milled glucose (produced with different granulation temperatures and drying times).

as it profoundly impacted the tablet properties, thus, it was examined thoroughly in the following experiments.

3.3. Investigation of the continuous manufacturing line

After we found the adequate process parameters of TSWG to successfully improve the tabletability of the glucose, the feeders and the granulator were connected to the continuous drying and milling device. The production speed of each step was harmonized; thus, with the previously described operation parameters, the continuous manufacturing line could be operated together, producing 1 kg granulated glucose every hour. Based on the previous experiments, the temperature of the granulator was set to 55 °C (with the rotation speed set to 100 rpm and the feeding rate of the glucose to 1 kg/h). The continuous drying process was examined with these conditions as the temperature of the drying air was changed between 25 °C and 85 °C (experiments 7–9 illustrated in Table 1). The tabletability was measured by the breaking force of the prepared tablets (Fig. 5). The breaking force of the tablets prepared from the granules dried at 25 °C could not be measured, as the amount of remaining moisture content caused the tablets not to break but deform instantly at the beginning of the measurement (marked with '0N' in Fig. 5). The 60 °C drying air (zone 1–3) resulted in tablets with acceptable breaking force, which could be further improved with higher drying temperature (85 °C). It is evident that the higher drying temperature leads to more effective drying, therefore positively impacting the tablets' breaking force. The characteristics of the powder dried at lower temperatures could also be improved with 1 additional day of air drying. However, the prolonged waiting time caused by the additional drying time is not suited for our production line as our goal was to develop a continuous, integrated technology. Therefore, the lower drying temperatures (25 °C) requiring additional drying were excluded from the further experiments. Drying at 85 °C led to slightly better results, nonetheless satisfactory tablet properties were reached at both temperatures. Operating the manufacturing line at 60 °C would be more energy efficient; however, for scale-up production, the higher temperature would be better, as it would increase the drying capacity.

These results confirmed the conclusion of the prior experiments (Fig. 4) that the high moisture content was indeed the critical factor, affecting the tablet breaking force negatively. Therefore, the following experiments were performed to examine the remaining moisture content of the granules.

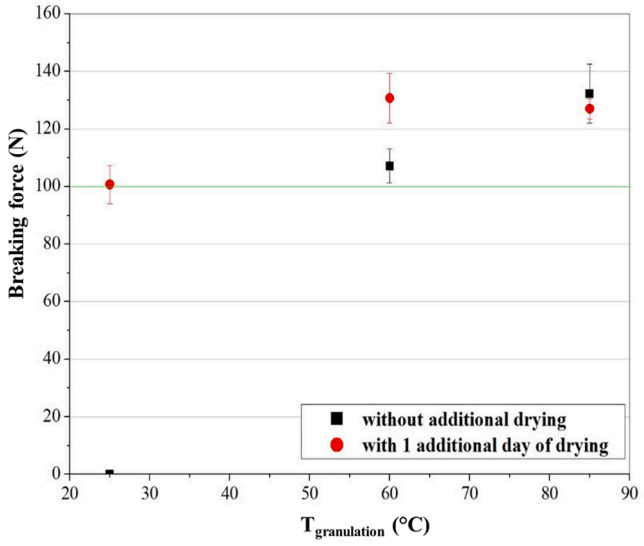

Fig. 5. The breaking force of tablets pressed from granules produced at different drying temperatures (with and without additional drying after the continuous process).

3.4. In-line monitoring of the moisture content of the dried granules

As the definite impact of the drying temperatures and the residual moisture content was confirmed, the continuous line was supplemented with an in-line NIR spectroscope used as an in-line PAT tool to monitor the remaining moisture content of the dried granules.

3.4.1. Development of PLS model for in-line moisture content measurement

To accomplish the real-time moisture content monitoring, a NIR spectra based PLS model was developed first. In the model, 3 latent variables were used, and it explained 97.2 % of the variation. The error of calibration ($RMSE_C$) was 0.443 and the error of cross-validation (($RMSE_{Cv}$) was 0.531 proving the goodness of the model (Table 2). Consequently, the moisture content could be detected with ± 0,5% accuracy.

3.4.2. Real-time monitoring of continuous granulation

The PLS model was used to detect the remaining moisture content of the dried granules in real-time. To accomplish that, the temperature of the drying chamber was raised from 60 °C to 85 °C (as experiment 8–9 in Table 1 was repeated) and then to 95 °C (experiment 10 in Table 1) while the spectra were collected in real-time (Fig. 6). Through the experiment, 20 samples were taken for off-line LOD measurements, and the results (illustrated in Fig. 6 with red symbols) were used for the validation of the model.

The validation data further confirmed the applicability of the model for the in-line process monitoring, as the off-line and in-line measurements led to similar results, and the error of prediction was adequately low (Table 3). Therefore, the moisture content could be successfully detected with the model.

The goal was to completely dry the granules, to reach the theoretical moisture content of the monohydrate (9,08 w/w%), or preferably dry the granules even slightly below that, to ensure that no excess amount of water remains in the final material. As shown in Fig. 6, with 60 °C drying the moisture content remained above (10 w/w%) or around the theoretical moisture content, and with 85° slightly below (8 w/w%) that. Although both experiments were successful (resulted in acceptable granules with satisfactory tabletability), the tablets compressed from the granules dried at 85 °C were harder (Figs. 5 and 6). The breaking force of the tablets compressed from the granules dried at 60 °C could be further improved with 1 additional day of air drying to reach the ones compressed from the granules dried at 85 °C, as shown earlier in Fig. 5. It is believed to be caused by the evaporation of the remaining small amount of water, because the breaking force of the tablets compressed from the completely dry granules (dried at 85 °C) did not change significantly with further air drying. Drying at 95 °C resulted in even lower (6,5 w/w %) remaining moisture content, indicating the higher temperatures were not only unnecessary but led to the partial transition of glucose monohydrate to anhydrous form, lowering the breaking force of the tablets. The solid-state transformation should be further examined in the future; however, it was clearly indicated by the remaining water content. The water content was significantly below the theoretical moisture content of the monohydrate, revealing that the glucose converted into anhydrous form (as these are the most stable forms in these conditions).

Table 2
Performance parameters of the NIR model.

	Model parameters
R^2_C	0.980
R^2_{CV}	0.972
$RMSE_C$ (w/w%)	0.443
$RMSE_{CV}$ (w/w%)	0.531
$Bias_C$ (w/w%)	0.000
$Bias_{CV}$ (w/w%)	0.011
LoD (w/w%)	1.512
LoQ (w/w%)	4.582

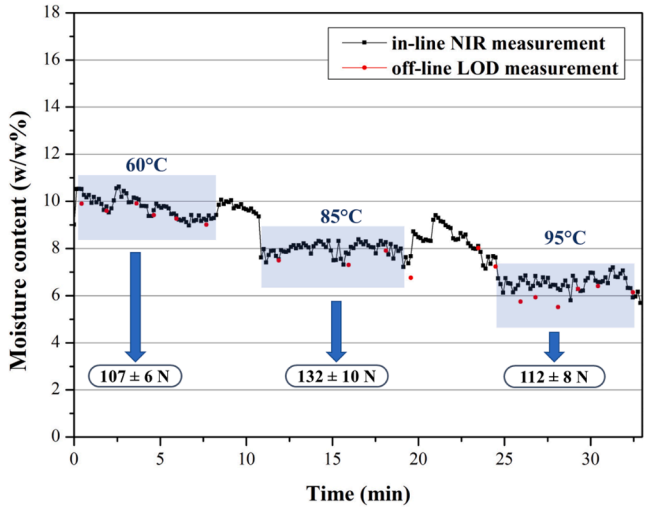

Fig. 6. Monitoring of continuous granulation process by NIR spectra based chemometric model (black symbols) with LOD validation (red symbols). The blue areas indicate periods of steady-state with different drying temperatures, complemented with the breaking force of the tablets (marked with blue arrows) pressed from the granules. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Prediction performance of the NIR model.

	Model parameters
R^2_P	0.957
$RMSE_P$ (w/w%)	0.356
$Bias_P$ (w/w%)	−0.031

Although all three temperatures led to satisfactory results, we deemed the 85 °C drying the best, as it led to completely dry (even slightly overdried) granules and therefore to the hardest tablets. A lower temperature (around 70–75 °C) could possibly lead to complete drying without overdrying the material at all, however at 85 °C the overdrying was not too excessive and the system was robust, therefore we chose that.

3.5. Testing the integrability of our technology to the industrial crystallization line of glucose

Our further goal – apart from developing a technology to improve the flow properties and tabletability, thus the breaking force of the tablets of glucose – was to make the aforementioned technology adaptable into the industrial crystallization technology used to produce glucose-monohydrate from starch.(Schenck, 2006) The last manufacturing step before the drying, the centrifugation leads to the glucose containing about 14 w/w% water (including the crystal water), equal to our experiments. Thus, our process can be modified so that it is suited for directly processing the still wet, centrifugated glucose instead of adding the dry glucose and the water separately (as described in the previous paragraphs). In that way, our system can be inserted right after the centrifugation step, and the drying step can be entirely skipped. That case the system has no need for any additional granulation liquid, the wetted glucose is sufficient for the granulation on its own, making the complete, combined production line shorter and simpler.

For these experiments, we mixed the adequate amount of water with the dry glucose to model the centrifugated, still wet material and fed it manually into the hopper of the granulator. The feed rate was also increased together with the rotation speed of the screws; thus we could examine whether our system could be suitable for scale-up production as well (experiments 11–12 in Table 1). The feed rate of the wet glucose was 3 kg/h, the rotation speed of the granulator 200 rpm and the temperature 55 °C, followed by drying at 85 °C. Experiments with lower granulation temperature (50 °C) were also carried out because we suspected that altered conditions could slightly change the optimal process parameters (Fig. 7).

As opposed to the previous experiments, the breaking force of the tablets pressed from the granules produced at 55 °C (although increased compared to the unprocessed glucose) was below our limit, however, the granulation at 50 °C led to satisfactory results. According to our theory, the conditions in the granulator could have been altered by the higher rotation speed and modified fill level in the granulator (leading to higher shear force and more intense breakage of the crystals in the device) or by the different wetting of the glucose. With previously wetting the material, part of the solid glucose could have dissolved making a viscous syrup and changing the S/L ratio in the granulator. Nevertheless, by slightly modifying the process parameters we managed to achieve good results with the previously wetted material as well, proving that our system is robust enough and can indeed be integrable into the industrial production line. In that case, the manual feeding could be substituted with appropriate industrial feeders, thus the standard deviation could be further decreased.

3.5.1. Further investigation of the physical properties of the granules

Although our main focus was to improve the tabletability of the powders and therefore, the breaking force of the prepared tablets, other characteristics of the granules were also examined to further confirm the improved physical properties.

Our process resulted in enlarged granules illustrated on the SEM and POM images (Fig. 8). These measurements also confirmed the breakage of the previously observed lengthy crystals and the effect that we already suspected as it caused the improvement in the tabletability.

In comparison to the initial unprocessed powder (Fig. 3), the size increase is also notable and was confirmed by laser diffraction measurements (Fig. 9). The average particle size increased significantly and the amount of the smaller particles (below 100 μm) decreased (Fig. 9, Table 4).

In addition to the better tabletability, as described in the previous paragraphs, the granulation also led to improved flow properties. It was confirmed by the shortened required time for the samples to flow out of a funnel.

4. Conclusions

Production of direct tabletable dextrose-monohydrate was

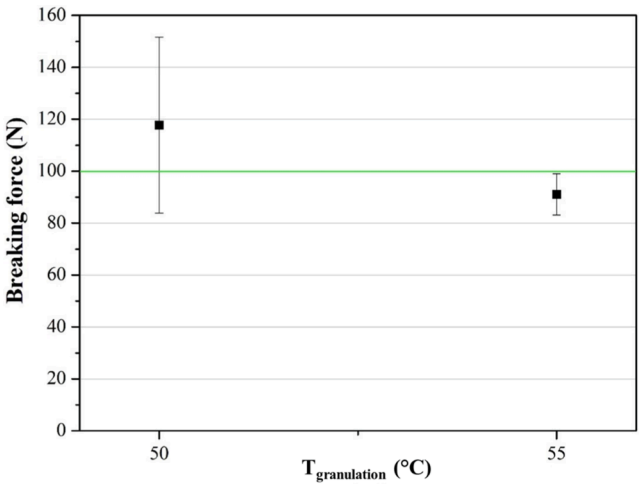

Fig. 7. The impact of the granulation temperature on the breaking force of the tablets produced from the priory wetted glucose during the larger scale production.

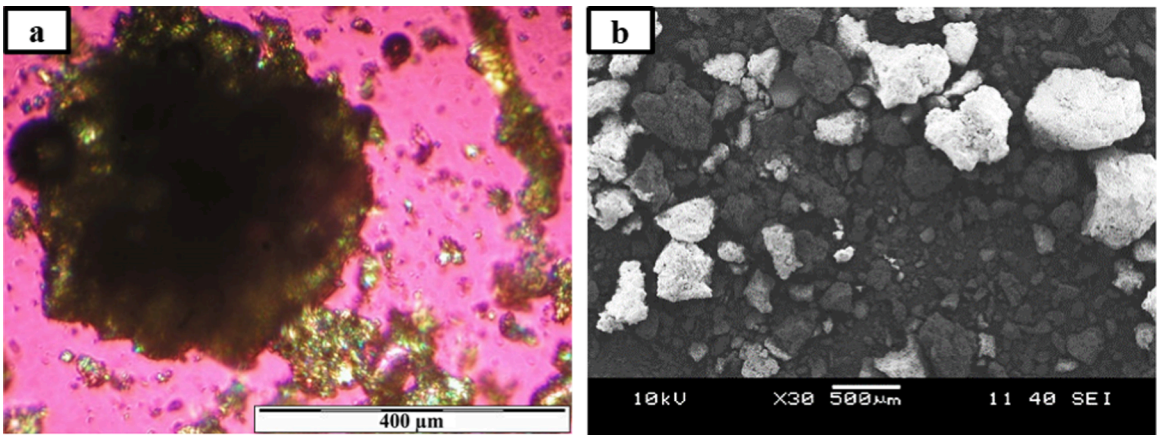

Fig. 8. Polarization optical microscopic (POM) and Scanning electron microscopic (SEM) images of the milled granulated glucose (a) POM 6,3x magnification; (b) SEM 30 × magnification.

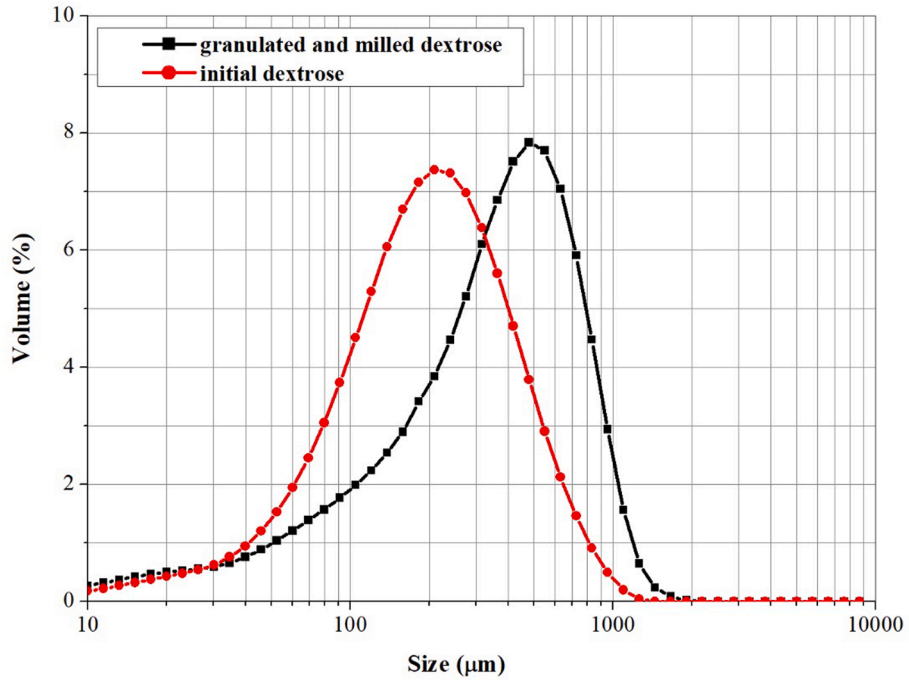

Fig. 9. The comparison of the particle size distribution of the granulated and unprocessed glucose.

Table 4
Flowability of the unprocessed and the granulated and milled glucose.

	Required time to flow out of a 10 mm diameter funnel	Required time to flow out of a 15 mm diameter funnel	Amount of small particles (under 100 µm)
Unprocessed glucose	~30 s (only with agitation)	8.2 ± 0.2 s	20.4 ± 0.8 %
Granulated and milled glucose	11.5 ± 0.2 s	4.6 ± 0.1 s	14.7 ± 0.8 %

successfully achieved by twin-screw granulation. A completely continuous manufacturing line was developed, and the different production steps (including feeding, granulation, drying and milling) were examined and synchronized with each other. The high pressure and shear force in the granulator led to the breakage of the previously lengthy crystals and to a significant increase in the size of the particles causing improved flow properties and tabletability. Therefore, the granulated material could be used to produce tablets with adequate breaking force (requiring over 100 N breaking force to crush them). The system was also supplemented with a non-destructive in-line PAT tool (NIR spectra based chemometric model), validated by off-line measurements (confirming the applicability of the models with satisfactorily low $RMSE_P$ values). The model could be used to measure the moisture content of the dried granules, thus to define the most suitable drying temperature and monitor the remaining moisture content of the granules in order to ensure the proper operation of the system.

The integration of the described system into the industrial production line is also promising. Even though the manual feeding caused minor fluctuations in the process and thus higher standard deviation of the breaking force of the tablets, the production of direct tabletable dextrose from the previously wetted material with higher feed rates was also successfully carried out. The robustness of the system was also proved by these experiments.

In the future, additional scale-up experiments could be carried out

along with a more detailed investigation of the interaction of process parameters to further confirm the industrial applicability of the technology.

CRediT authorship contribution statement

Petra Záhonyi: Investigation, Writing – original draft, Writing – review & editing. **Edina Szabó:** Investigation, Supervision, Writing – original draft. **András Domokos:** Investigation, Writing – review & editing. **Anna Haraszti:** Investigation, Visualization, Writing – review & editing. **Martin Gyürkés:** Investigation, Visualization, Writing – review & editing. **Erzsébet Moharos:** Investigation, Visualization. **Zsombor K. Nagy:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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