European Journal of Pharmaceutics and Biopharmaceutics 71 (2009) 155–160

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

# Comparison of two twin-screw extruders for continuous granulation

D. Djuric [a,1], B. Van Melkebeke [b,1], P. Kleinebudde [a], J.P. Remon [b], C. Vervaet [b,*]

[a] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany
[b] Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium

ARTICLE INFO

*Article history:*
Received 29 February 2008
Accepted in revised form 29 June 2008
Available online 17 July 2008

*Keywords:*
Continuous granulation
Twin-screw extruder
Process parameter
Granule quality
Tablet properties

ABSTRACT

A comparison was made between two twin-screw extruders (APV Baker and Leistritz Micro) used for continuous wet granulation. Both extruders had similar screw configurations, based on the length-to-diameter ratio of the screws, existing out of a conveying zone of 20 D, i.e. 20 times the screw diameter and a granulation zone of 4 D. The kneading blocks in the granulation zone were 2.2 and 2.5 D for the Leistritz and APV extruders, respectively. An experimental design was used to investigate the influence of process parameters (total input rate and screw speed) and extruder type on granule and tablet quality. Dicalcium phosphate and $\alpha$-lactose monohydrate were used as water-insoluble and water-soluble excipients, respectively. For dicalcium phosphate, the amount of fines (<125 μm), median granule size and granule friability were significantly influenced by extruder type and total input rate. For lactose, the amount of oversized agglomerates and median granule size were significantly affected by extruder type and total input rate. The granule formulations were properly agglomerated on both the extruders, although the extruder type had an important influence on the granule properties, which was more pronounced for dicalcium phosphate. This study shows that a given formulation cannot simply be interchanged between the two extruders without further work on the geometrics of the extruders.



## 1. Introduction

The popularity of continuous processes is increasing in the pharmaceutical industry [1]. This way of processing offers several advantages, such as improved process efficiency due to reduction of costs and time. Furthermore, scale-up is avoided as the amount of material processed can be increased by simply prolonging the process time [2]. Extruders for pharmaceutical granulation were introduced by Gamlen and Eardley [3] and Lindberg et al. [4]. While Gamlen and Eardley utilised a single screw extruder, Lindberg et al. already used a twin-screw extruder and characterised the process for an effervescent granulation. In a more recent study, hydrophobic materials were agglomerated with a planetary screw extruder [5]. The use of a twin-screw extruder for continuous granulation was patented by Ghebre-Sellasie et al.[6]. Keleb et al. [7] compared a twin-screw extruder with a high-shear granulator and made the first attempt to modify the screw configuration. Another study utilized a modified twin-screw extruder for melt granulation [8] using polyethylene glycol as meltable binder for an immediate release formulation. A recent study from Van Melkebeke et al. [9] validated the granulation process using a twin-screw extruder. Djuric and Kleinebudde [10] evaluated systematically the impact of different screw elements on the granulation process.

However, a comparison of different extruder types is still missing. Therefore, the purpose of this study was to compare two continuous granulators: a statistical design of experiments was run on two twin-screw extruders, namely an APV Baker extruder with 19 mm screw diameter and a Leistritz Micro with 27 mm screw diameter. For comparison, water-soluble and water-insoluble granules were processed.

## 2. Materials and methods

### 2.1. Materials

Dicalcium phosphate anhydrate (DI-CAFOS PA, C92-04, Chemische Fabrik Budenheim, Budenheim, Germany) and $\alpha$-lactose monohydrate (Pharmatose 200 M, DMV, Veghel, The Netherlands) were granulated with 11% and 7.5% (w/w) granulation liquid, respectively. Povidone (Kollidon K30, BASF, Ludwigshafen, Germany) as binder (2.5%, w/w, in dried granules) was dissolved in demineralised water to prepare the granulation liquid.

### 2.2. Methods

#### 2.2.1. Granulation setup

A Leistritz Micro 27GL/28D co-rotating twin-screw extruder (Leistritz Extrusionstechnik GmbH, Nuremberg, Germany) with

* Corresponding author. Laboratory of Pharmaceutical Technology, Ghent University, 9000 Ghent, Belgium. Tel.: +32 92 64 80 69; fax: +32 9 222 82 36.
*E-mail address:* chris.vervaet@ugent.be (C. Vervaet).

[1] These authors contributed equally to this paper.

0939-6411/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2008.06.033

a screw diameter of 27 mm was used for granulation in an open configuration without a die plate. During processing, powder was gravimetrically dosed by a twin-screw feeder (K-CL-KT 20, K-Tron Soder, Niederlenz, Switzerland). Granulation liquid was supplied by a peristaltic pump (504U, Watson Marlow Limited, Falmouth, United Kingdom) in combination with a flow through a metering device (Promass 80, Endress + Hauser, Weil am Rhein, Germany).

For comparison, a second co-rotating twin-screw extruder (MP19 TC25, APV Baker, Newcastle-under-Lyme, United Kingdom) with a screw diameter of 19 mm was used. During granulation, the powder volume in the volumetrically dosing feed hopper (DDSR 20, Brabender Technologie KG, Duisburg, Germany) was maintained at a constant level (85–100% of the total feeder capacity). The granulation liquid was pumped into the extruder barrel using a peristaltic pump (505L, Watson Marlow Limited, Falmouth, United Kingdom). Powder and liquid feed rates were determined prior to each experiment by repeatedly ($n = 3$) weighing the powder and liquid amount delivered over a period of 5 min.

After extrusion of 2 kg wet material, the granules were oven dried at 60 °C for 4 h. For both the extruders similar screw configurations were used based on the length-to-diameter (L/D) ratio of the screws (Fig. 1). The total length of the screw was 24 D. It consisted of a conveying zone with a length of 20 D and a granulation zone with a length of 4 D. Granulation liquid was added at the end of the conveying section. In case of the Leistritz extruder, the granulation zone was equipped with 2.2 D long kneading blocks with 30° and 60° advance angle and a 1.8 D long conveying section for the discharge of granules. For the APV extruder, the kneading blocks had a length of 2.5 D. The kneading block consisted of 10 disks, with a staggering angle increasing from 30° (4 disks) over 60° (5 disks) to 90° (1 disk). The conveying section for the discharge of the granules was 1.5 D long.

### 2.2.2. Design of experiments

A 12-run full factorial design was used on both the extruders to evaluate 2 variables on 3 levels: total input rate (A) (2, 4 and 6 kg/h) and screw speed (B) (150, 225 and 300 rpm). Four replicates of the centre point (level 0, i.e. 4 kg/h and 225 rpm) were run. The different factor settings of the trials and the results for dicalcium phosphate and α-lactose monohydrate are shown in Tables 1 and 2. All factor level combinations were carried out in a randomized order. To evaluate the results, the extruder type was included as a qualitative factor (factor C), using −1 as a coded value for the APV extruder and +1 for the Leistritz extruder. The results were evaluated with the programme MODDE 7.0 (Umetrics, Umeå, Sweden). All confidence levels were 95%.

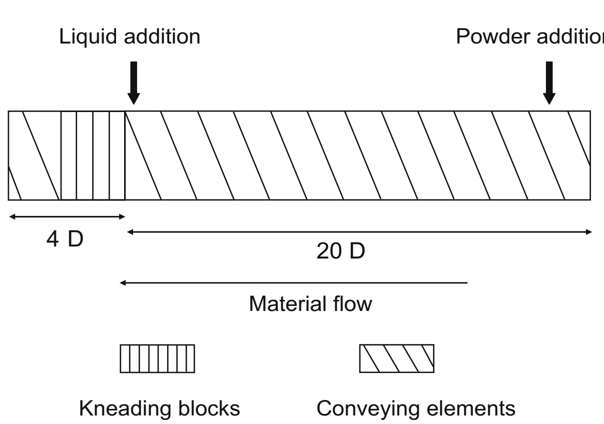


**Fig. 1.** Screw configuration of both extruders.

### 2.2.3. Particle size distribution

The total granule batch was divided into 2 parts. Each part was placed on a sieve shaker (Retsch VE 1000, Haan, Germany) for 5 min at an amplitude of 2 mm using a sieve of 3150 μm. The particles retained on the 3150 μm sieve were considered as oversized agglomerates. The percentage of oversized agglomerates was calculated from the total weight of an agglomerate fraction and the total granule weight.

The particle size distribution of the fraction <3150 μm was determined using a series of sieves (125, 250, 500, 710, 1000, 1400 and 2000 μm). A granule sample of approximately 100 g was placed on the sieve tower, and the sieves were shaken during 10 min at an amplitude of 2 mm. The amount of fines was defined as the fraction <125 μm. Using the cumulative particle size distribution the median particle size (d50) was interpolated.

### 2.2.4. Friability

Granule friability was determined in duplicate with an air jet sieve [11] (LS-N 200, Hosokawa Alpine, Augsburg, Germany) using a 125 μm sieve.

During air jet sieving, particles are fluidised and bounced against the sieve lid. These movements induce mechanical stress onto the granules during determination. With a higher negative pressure during sieving particle movements and thus mechanical stress are increasing.

Prior to determination, fines (granule fraction <125 μm) of the granule samples (sample mass approximately 10 g) were removed to assure the same starting conditions. Oversized agglomerates were not included in the granule samples. Determination was performed by sieving at a negative pressure of 600 Pa for 1 min. The friability was defined as the mass loss in percent after sieving at a negative pressure of 2000 Pa for 10 min.

### 2.2.5. Flowability

Granule flowability was measured using a computer-controlled ring shear cell tester RST-01.pc with RST-CONTROL 95

**Table 1**
Characterisation of dicalcium phosphate granules processed on the APV and Leistritz extruder using a full factorial design of experiments

| Experiment | Total input rate [kg/h] | Screw speed [rpm] | Fines [%] | Oversized agglomerates [%] | Friability [%] | Flowability ffc |
|---|---|---|---|---|---|---|
| APV1 | 6 | 300 | 22.1 | 0.1 | 14.6 | 10.8 |
| APV 2 | 4 | 225 | 22.4 | 0.3 | 18.7 | 13.3 |
| APV 3 | 4 | 150 | 21.7 | 0.3 | 17.6 | 10.8 |
| APV 4 | 2 | 300 | 26.8 | 0.3 | 19.9 | 9.7 |
| APV 5 | 2 | 150 | 26.7 | 0.2 | 19.6 | 9.6 |
| APV 6 | 6 | 150 | 16.7 | 0.3 | 9.4 | 12.7 |
| APV 7 | 6 | 225 | 25.9 | 0.3 | 13.4 | 8.2 |
| APV 8 | 2 | 225 | 26.3 | 0.4 | 15.2 | 13.8 |
| APV 9 | 4 | 225 | 22.4 | 0.3 | 18.4 | 11.7 |
| APV 10 | 4 | 300 | 26.1 | 0.2 | 17.1 | 11.2 |
| APV 11 | 4 | 225 | 22.1 | 0.3 | 15.3 | 12.5 |
| APV 12 | 4 | 225 | 19.3 | 0.3 | 15.9 | 12.3 |
| Leistritz 1 | 6 | 300 | 3.2 | 6.5 | 4.8 | 14.7 |
| Leistritz 2 | 4 | 225 | 10.9 | 3.6 | 7.6 | 9.2 |
| Leistritz 3 | 4 | 150 | 2.2 | 3.8 | 4.6 | 13.2 |
| Leistritz 4 | 2 | 300 | 5.7 | 3.9 | 7.8 | 10.1 |
| Leistritz 5 | 2 | 150 | 13.3 | 1.0 | 13.0 | 13.2 |
| Leistritz 6 | 6 | 150 | 2.7 | 6.5 | 3.9 | 13.8 |
| Leistritz 7 | 6 | 225 | 3.1 | 6.9 | 3.3 | 14.6 |
| Leistritz 8 | 2 | 225 | 7.8 | 4.5 | 6.8 | 14.2 |
| Leistritz 9 | 4 | 225 | 3.3 | 9.2 | 3.0 | 9.8 |
| Leistritz 1 0 | 4 | 300 | 2.6 | 9.1 | 3.0 | 11.1 |
| Leistritz 11 | 4 | 225 | 2.6 | 8.8 | 3.3 | 19.1 |
| Leistritz 12 | 4 | 225 | 3.5 | 8.7 | 4.4 | 10.8 |

**Table 2**
Froude number and tip speed values calculated for both extruders

| Screw speed [rpm] | Froude number | | Tip speed [m/s] | |
|---|---|---|---|---|
| | APV | Leistritz | APV | Leistritz |
| 150 | 0.012 | 0.017 | 0.15 | 0.21 |
| 225 | 0.027 | 0.039 | 0.22 | 0.32 |
| 300 | 0.048 | 0.069 | 0.30 | 0.42 |

(Schulze Schuettgutmesstechnik, Wolfenbüttel, Germany). Flowability of bulk material is characterised by its unconfined yield strength ($\sigma_c$) dependent on the consolidation stress ($\sigma_1$). The ratio of these two values, the flowability function $ff_c$, is used to quantify the flowability.

$$ff_c = \frac{\sigma_1}{\sigma_c} \quad (1)$$

Flowability improves with increasing $ff_c$ value according to Jenike [12]. Values for the $ff_c$ function were calculated using the RST-CONTROL 95 software.

All the granule batches were measured in triplicate after storage at 21 °C and 45% relative humidity for at least 24 h. A representative sample of the batch was used. Measurements were conducted with consolidation stress values of approximately 11 kPa. A constant preshearing at 5 kPa assured the same working conditions for all measurements. To calculate a yield locus that describes the strength of a bulk material, samples were sheared at four different normal loads (1, 2, 3 and 4 kPa). In order to assure that the samples were unaffected by the measurement, the first normal load at 1 kPa was repeated at the end of a measurement cycle. The difference between the two measurements at 1 kPa normal load was in all cases <5%, and thus the granule samples were assumed to be unaffected by the determination [13].

*2.2.6. Compression of tablets*

A pneumohydraulic tablet press [14] (FlexiTab, Roeltgen, Solingen, Germany) was used for the production of 12 mm flat faced tablets. The granule fraction 125–1250 µm was compressed in order to solely evaluate the deformation potential of agglomerated material, avoiding the influence of fines. The granules were compressed at a force of 20 kN. Tablet masses were 405 ± 5 mg for lactose and 505 ± 5 mg for dicalcium phosphate granules. A lubricant was not added to the granules. Instead a pure magnesium stearate tablet (every third tablet) was compressed for lubrication of die and punches prior to compression of granules [15].

*2.2.7. Tablet tensile strength*

Tablets were stored at 21 °C and 45% relative humidity for 48 h prior to characterisation. The dimensions of the flat faced tablets were measured with an electronic micrometer (Mitutoyo, Tokyo, Japan). Tablet porosity was calculated using tablet apparent density and the helium density of the former granules. The crushing strength of ten tablets was measured with a radial strength tester (HT-1, Sotax, Basel, Switzerland) at a constant speed of 1 mm/s. Tablet tensile strength was calculated according to Fell and Newton [16].

## 3. Results and discussion

Although continuous granulation using a twin-screw extruder has already been investigated, different twin-screw extruders have not yet been compared. In this study a comparison was made with two different twin-screw extruders, using water-soluble and water-insoluble materials.

*3.1. Granulation of dicalcium phosphate*

*3.1.1. Particle size distribution*

Fig. 2a and b shows the surface plots for the amount of fines in function of screw speed and total input rate for both the extruders. Next to total input rate, the extruder type had a significant influence ($p < 0.05$) on the amount of fines. When increasing the total input rate the amount of fines decreased. The APV extruder produced granules with the amount of fines from 16.7% to 26.8%, whereas the Leistritz extruder created amounts of fines ranging from 2.2% to 13.3% (Table 1). This can be explained with the free chamber volume, which was calculated using the element weight divided by the metal density. This volume was put into relation to the extruder cylinder volume. The free chamber volume was determined for the screw section after the liquid addition where the agglomeration occurs. The granulation zone of the APV extruder has approximately a free chamber volume of 51%; the Leistritz extruder offers 24% free volume for the material. Thus, a higher densification level is reached within the granulation zone of the Leistritz extruder, leading to coarser granules and to lower amounts of fines. The difference in a screw diameter can be the another reason for this phenomenon. Since the diameter of the Leistritz extruder is larger compared to the APV extruder, a higher tip speed is obtained at the same screw speed. For high-shear mixers it is known from the literature [17] that increasing the tip speed leads to a higher mechanical stress, resulting in coarser granules.

Since a number of parameters have been introduced to compare the granulators of different sizes [18,19], the Froude number (Fr) (Eq. (2)) was used in this study to determine the dynamic similarity of both the extruders.

$$\mathrm{Fr} = \frac{N^2 D}{g} \quad (2)$$

$N$ represents the revolutions per min, D the diameter of the impeller or screw and $g$ is the gravitational constant.

Although this dimensionless number (taking into account centrifugal force to the gravitational force) was initially used to compare different types of high-shear granulators, its application was extended to granulation using an extruder. The Froude numbers found for both the extruders (Table 2) were lower than for the high-shear granulators, due to different machine designs. Although the Froude numbers were low, a difference was detected at all screw speed settings. The Leistritz extruder resulted in higher Froude-numbers indicating higher centrifugal forces during agglomeration, due to higher tip speed values which induce a higher mechanical stress onto the granules during processing.

The median granule size (d50) was significantly influenced by total input rate (A) and extruder type (C), given by the experimental designing:

$$d50 = 708.3 + 120.1 * A + 253.6 * C + 99.75 * A * C \quad (3)$$

Furthermore, an interaction between the total input rate and the extruder type could be detected. This relation becomes more obvious using the interaction plot (Fig. 3), where the median granule size is shown in function of the total input rate. Whereas the Leistritz extruder produced much larger granules, only a limited effect was observed in case of the APV extruder when increasing the total input rate. The different behaviours of the two extruders can be explained by their difference in free chamber volume. The higher free chamber volume of the APV extruder allowed increasing the total input rate with little effect on the median granule size. In contrast the Leistritz extruder did not show this variability.

Particle size distributions of the centre points confirmed the results for the median particle size: granules produced by the

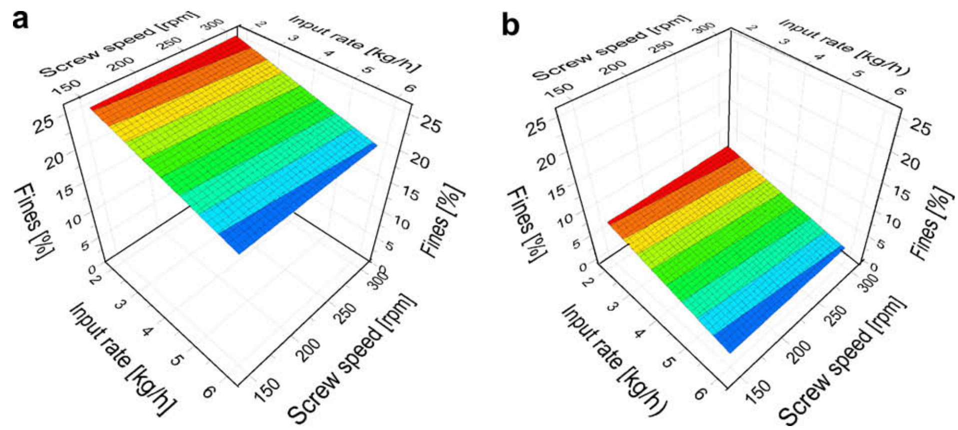


**Fig. 2.** (a) Surface plot for the amount of fines of dicalcium phosphate granules produced by the APV extruder ($R^2_{adj}$ = 0.916, $Q^2$ = 0.899). (b) Surface plot for the amount of fines of dicalcium phosphate granules produced by the Leistritz extruder ($R^2_{adj}$ = 0.916, $Q^2$ = 0.899).

Leistritz extruder were coarser than the APV granules (Fig. 4). While the granule fraction smaller than 2000 μm ($F_{<2000}$ μm) was comparable for both the extruders, the differences in particle size became more obvious for the smaller fractions: $F_{<1400}$ μm for the Leistritz extruder was 68 ± 3%, compared to 88 ± 2% for the APV extruder. In Fig. 4, the full lines depict the particle size distributions for the APV extruder ($n$ = 4) and the Leistritz extruder ($n$ = 3). The dotted line represents a deviating run for the Leistritz extruder, which was not included in the calculation of the mean. A reason for this deviation could not be found. Finally, no significant influence was observed for the amount of oversized agglomerates (>3150 μm).

### 3.1.2. Friability

Granule friability, indicating granule strength [20], was determined by stressing granule samples with an air jet sieve. Fig. 5a and b shows the surface plots for the friability measurements of dicalcium phosphate granules in function of screw speed and total input rate. For both extruders, granule friability was significantly affected by the total input rate: a higher input rate yielded lower friability values as a higher filling level of the extruder barrel resulted in a higher densification during agglomeration. Processing the same formulation on the Leistritz extruder produced granules with lower friabilities as its lower free chamber volume led to a higher densification. The screw speed had no significant influence for both the extruders in this study.

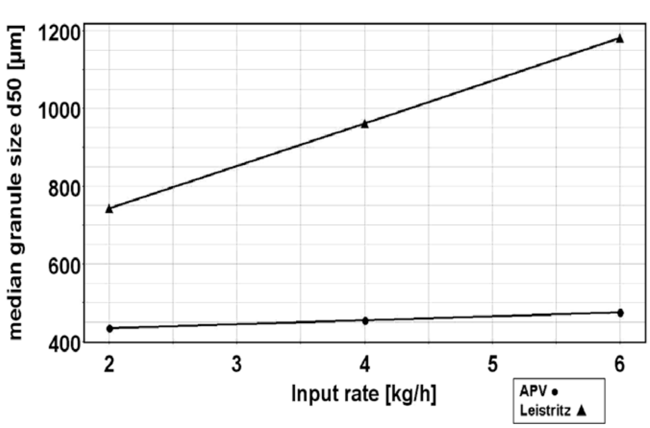


**Fig. 3.** Interaction plot for the median particle size of dicalcium phosphate granules ($R^2_{adj}$ = 0.832, $Q^2$ = 0.79).

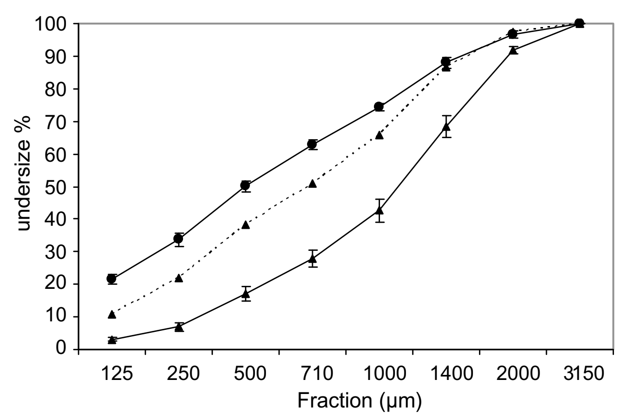


**Fig. 4.** Cumulative curves of the centre points (225 rpm, 4 kg/h) of dicalcium phosphate granules. ●, APV extruder ($n$ = 4, mean ± SD); ▲, Leistritz extruder ($n$ = 3, mean ± SD), dotted line represents deviating run of Leistritz experiments.

### 3.1.3. Flowability

Flowability values of dicalcium phosphate granules determined by the ring shear cell tester are shown in Table 1. Both the extruders produced granules with good flow properties with $ff_c$ values around 10 or higher. Low amounts of fines and a sufficient agglomeration of the primary dicalcium phosphate particles (initial $ff_c$ = 3) resulted in an improved flow behaviour. A significant difference could not be detected between the granules produced on different extruders.

### 3.1.4. Tablet tensile strength

Fig. 6 shows the tensile strength values of dicalcium phosphate tablets in consideration to their tablet porosity. Tablets resulting from the granules produced with the APV extruder showed tensile strength values between 0.9 and 1.3 MPa, whereas values for the tablets from the Leistritz extruder ranged from 1.2 to 1.7 MPa. Significant differences were not detected since values and standard deviations for the tablet tensile strength were overlapping.

Slight differences were found for the tablet porosity as the APV extruder yielded higher tablet porosities (15.3–15.8%) compared to a range from 13.3% to 14.2% for the Leistritz extruder. Due to the brittle deformation behaviour of dicalcium phosphate, the mechanical pre-treatment was more intense during agglomeration in the Leistritz extruder. Compression as a second mechanical treatment enhanced the material consolidation and resulted in

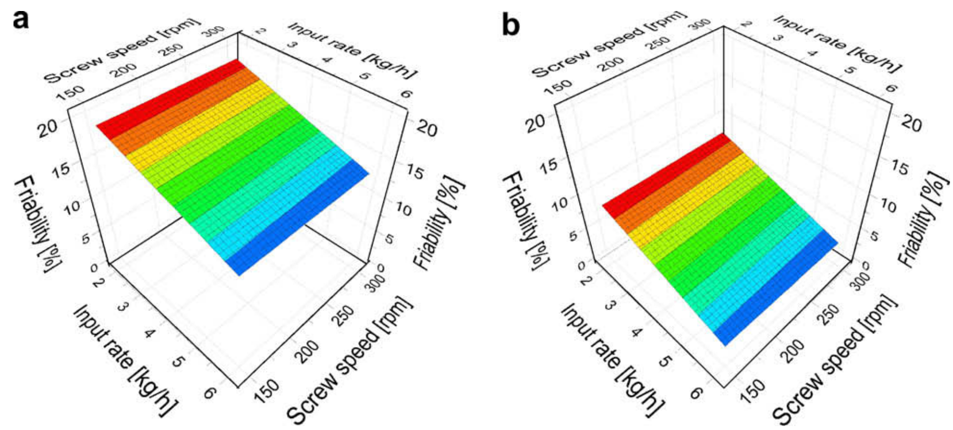


**Fig. 5.** (a) Surface plot for friability of dicalcium phosphate granules produced by the APV extruder ($R^2_{adj}$ = 0.876, $Q^2$ = 0.822). (b) Surface plot for friability of dicalcium phosphate granules produced by the Leistritz extruder ($R^2_{adj}$ = 0.876, $Q^2$ = 0.822).

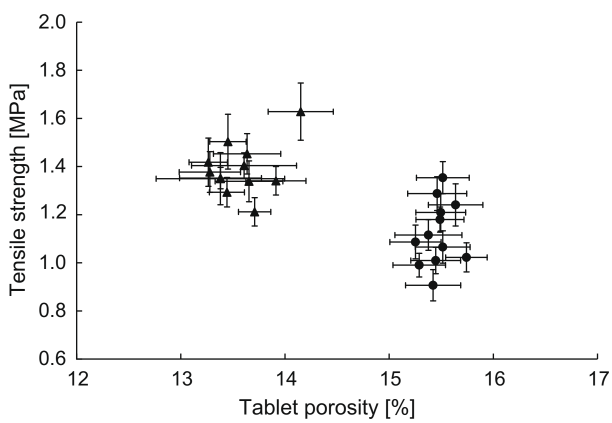


**Fig. 6.** Tablet tensile strength of dicalcium phosphate tablets ($n$ = 10, mean ± SD) (●, APV extruder, ▲, Leistritz extruder).

lower tablet porosities using granules processed on the Leistritz extruder. Tablets resulting from the APV extruder were less densified after compression at the same force level due to the lower mechanical pre-treatment during agglomeration. Although two clusters can be seen, a significant difference in tensile strengths cannot be observed (Fig. 6).

### 3.2. Granulation of lactose

#### 3.2.1. Particle size distribution

The amount of oversized agglomerates was significantly influenced by extruder type and total input rate (Fig. 7a and b). With the APV extruder almost no oversized agglomerates were produced. Due to the higher densification inside the barrel of the Leistritz extruder, a larger fraction of oversized agglomerates was found. For both the extruders a higher total input rate resulted in an increase of the amount of oversized agglomerates, as the higher filling degree in the extruder barrel induced more densification.

The cumulative distribution curves of the centre points (Fig. 8) confirm that the Leistritz extruder yielded coarser granules than the APV extruder. However, the difference is less pronounced than with dicalcium phosphate. As known from the literature [17] lactose possesses more moderate agglomeration behaviour than dicalcium phosphate, since it is not so sensitive towards shear or overwetting during granulation.

#### 3.2.2. Flowability

Flowability determination of lactose granules showed similar values as for dicalcium phosphate (Table 3). Due to the nearly complete agglomeration with a low amount of fines all granule batches showed easy flowing or free flowing behaviour. Significant differences in flow properties could not be detected since all $ff_c$ values were around 10.

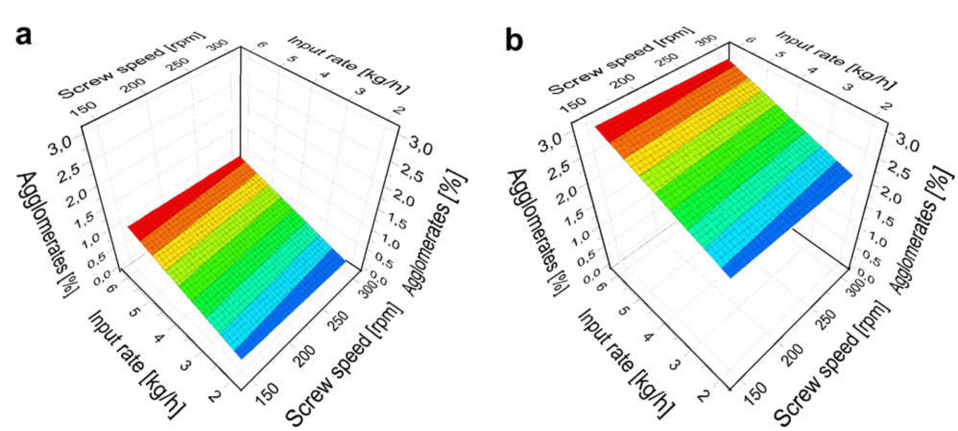


**Fig. 7.** (a) Surface plot for oversized agglomerates of lactose granules produced by the APV extruder (APV, $R^2_{adj}$ = 0.866, $Q^2$ = 0.818). b Surface plot for oversized agglomerates of lactose granules produced by the Leistritz extruder ($R^2_{adj}$ = 0.866, $Q^2$ = 0.818).

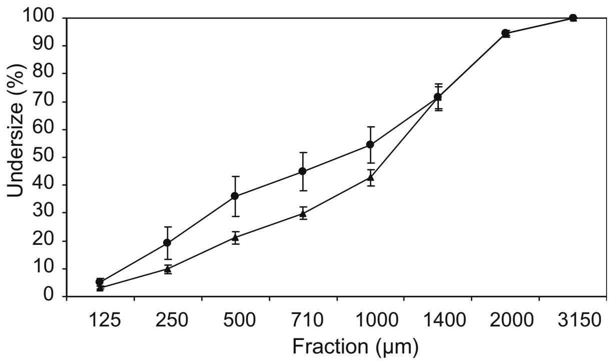


**Fig. 8.** Cumulative curves of the centre points (225 rpm, 4 kg/h) of lactose granules ($n = 4 \pm$ SD). ●, APV extruder; ▲, Leistritz extruder.

**Table 3**
Characterisation of lactose granules processed on the APV and Leistritz extruder using a full factorial design of experiments

| Experiment | Total input rate [kg/h] | Screw speed [rpm] | Fines [%] | Oversized agglomerates [%] | Friability [%] | Flowability ffc |
|---|---|---|---|---|---|---|
| APV1 | 6 | 300 | 4.9 | 0.8 | 3.6 | 11.7 |
| APV 2 | 4 | 225 | 7.0 | 0.5 | 4.3 | 12.8 |
| APV 3 | 4 | 150 | 6.0 | 0.9 | 4.3 | 12.8 |
| APV 4 | 2 | 300 | 5.7 | 0.5 | 3.3 | 11.7 |
| APV 5 | 2 | 150 | 4.8 | 0.3 | 3.5 | 12.2 |
| APV 6 | 6 | 150 | 3.5 | 2.1 | 2.5 | 13.0 |
| APV 7 | 6 | 225 | 3.7 | 0.8 | 3.7 | 14.8 |
| APV 8 | 2 | 225 | 4.7 | 0.4 | 3.1 | 13.1 |
| APV 9 | 4 | 225 | 4.2 | 0.2 | 3.2 | 13.5 |
| APV 10 | 4 | 300 | 5.5 | 0.2 | 5.0 | 12.3 |
| APV 11 | 4 | 225 | 5.1 | 0.3 | 3.4 | 10.4 |
| APV 12 | 4 | 225 | 4.4 | 0.3 | 3.7 | 14.8 |
| Leistritz 1 | 6 | 300 | 3.1 | 3.6 | 2.8 | 13.8 |
| Leistritz 2 | 4 | 225 | 3.2 | 2.4 | 3.3 | 9.7 |
| Leistritz 3 | 4 | 150 | 3.8 | 2.6 | 4.3 | 9.6 |
| Leistritz 4 | 2 | 300 | 2.7 | 2.7 | 2.8 | 9.5 |
| Leistritz 5 | 2 | 150 | 3.0 | 2.3 | 3.7 | 9.2 |
| Leistritz 6 | 6 | 150 | 2.4 | 2.7 | 3.8 | 7.5 |
| Leistritz 7 | 6 | 225 | 2.6 | 3.2 | 4.1 | 8.4 |
| Leistritz 8 | 2 | 225 | 3.4 | 2.0 | 4.9 | 8.9 |
| Leistritz 9 | 4 | 225 | 2.9 | 2.1 | 4.6 | 7.5 |
| Leistritz 10 | 4 | 300 | 3.1 | 2.8 | 4.6 | 8.8 |
| Leistritz 11 | 4 | 225 | 3.9 | 2.9 | 5.0 | 8.8 |
| Leistritz 12 | 4 | 225 | 2.8 | 2.1 | 4.9 | 8.9 |

*3.2.3. Tablet tensile strength*

Compression of lactose granules led to robust tablets with tensile strength values from 1.9 to 2 MPa (Leistritz) and 2.1 to 2.2 MPa (APV). Both tensile strength values and tablet porosities were comparable and showed no significant difference (Fig. 9).

## 4. Conclusion

Although both the extruders agglomerated dicalcium phosphate and lactose properly, the extruder type had the biggest impact on the granule properties. This effect was more pronounced for the water-insoluble material dicalcium phosphate. The results show that both the extruders used in this study are not simply interchangeable for a given formulation, but more research work should be done with geometrically similar extruder setups.

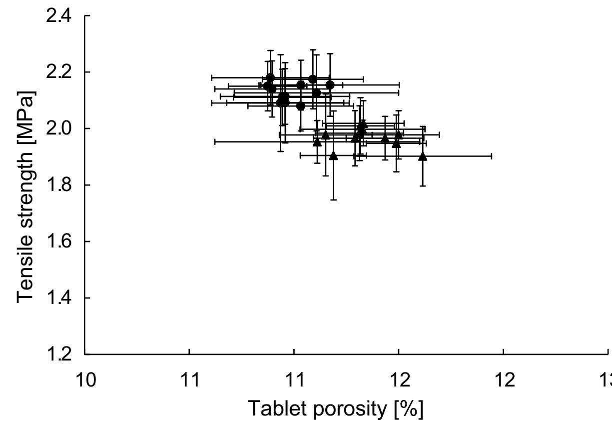


**Fig. 9.** Tablet tensile strength of lactose tablets ($n = 10$, mean ± SD) (●, APV extruder, ▲, Leistritz extruder).

## References

[1] H. Leuenberger, New trends in the production of pharmaceutical granules: batch versus continuous processing, Eur. J. Pharm. Biopharm. 52 (2001) 289–296.
[2] C. Vervaet, J.P. Remon, Continuous granulation in the pharmaceutical industry, Chem. Eng. Sci. 60 (2005) 3949–3957.
[3] M.J. Gamlen, C. Eardley, Continuous extrusion using a Baker Perkins MP50 (multipurpose) extruder, Drug Dev. Ind. Pharm. 12 (1986) 1701–1713.
[4] N.O. Lindberg, C. Tufvesson, P. Holm, L. Olbjer, Extrusion of an effervescent granulation with a twin screw extruder, Baker Perkins MPF 50D – influence on intragranular porosity and liquid saturation, Drug Dev. Ind. Pharm. 14 (1988) 1791–1798.
[5] R. Schroeder, K.J. Steffens, A new system for continuous wet granulation, Pharm. Ind. 64 (2002) 283–288.
[6] I. Ghebre-Sellasie, M. Plains, M.J. Mollan, N. Pathak, M. Lodaya, M. Fessehaie, Continuous production of pharmaceutical granulation (US 6,499, 984 B1), 2002.
[7] E.I. Keleb, A. Vermeire, C. Vervaet, J.P. Remon, Continuous twin screw extrusion for the wet granulation of lactose, Int. J. Pharm. 239 (2002) 69–80.
[8] B. Van Melkebeke, B. Vermeulen, C. Vervaet, J.P. Remon, Melt granulation using a twin-screw extruder: a case study, Int. J. Pharm. 326 (2006) 89–93.
[9] B. Van Melkebeke, C. Vervaet, J.P. Remon, Validation of a continuous granulation process using a twin-screw extruder, Int. J. Pharm. 356 (2008) 224–230.
[10] D. Djuric, P. Kleinebudde, Impact of screw elements on continuous granulation with a twin-screw extruder, J. Pharm. Sci., 2008, doi:10.1002/jps.21339.
[11] B.M. Hunter, A friability test for granules, J. Pharm. Pharmacol. 25 (1973) 111P.
[12] A.W. Jenike, Storage and flow of solids, Bulletin of the University of Utah No. 123. 1964, Salt Lake City, Engineering Experiment Station, University of Uta.
[13] D. Schulze, A. Wittmaier, Flow properties of highly dispersed powders at very small consolidation stresses, Chem. Eng. Technol. 26 (2003) 133–137.
[14] J. Albers, K. Knop, P. Kleinebudde, Brand-to-brand and batch-to-batch uniformity of microcrystalline cellulose in direct tableting with a pneumohydraulic tablet press, Pharm. Ind. 68 (2006) 1420–1428.
[15] A. Adolfsson, Ch. Nyström, Tablet strength, porosity, elasticity and solid state structure of tablets compressed at high loads, Int. J. Pharm. 132 (1996) 95–106.
[16] J.T. Fell, J.M. Newton, Determination of tablet strength by diametral-compression test, J. Pharm. Sci. 59 (1970) 688–691.
[17] P. Holm, O. Jungersen, T. Schaefer, H.G. Kristensen, Granulation in high speed mixers, Pharm. Ind. 45 (1983) 806–811.
[18] G.J.B. Horsthuis, J.A.H. Vanlaarhoven, R.C.B.M. Vanrooij, H. Vromans, Studies on upscaling parameters of the Gral high shear granulation process, Int. J. Pharm. 92 (1993) 143–150.
[19] J.S. Ramaker, M.A. Jelgersma, P. Vonk, N.W.F. Kossen, Scale-down of a high-shear pelletisation process: flow profile and growth kinetics, Int. J. Pharm. 166 (1998) 89–97.
[20] K. Zuurman, K.A. Riepma, G.K. Bolhuis, H. Vromans, C.F. Lerk, The relationship between bulk density and compatibility of lactose granulations, Int. J. Pharm. 102 (1994) 1–9.